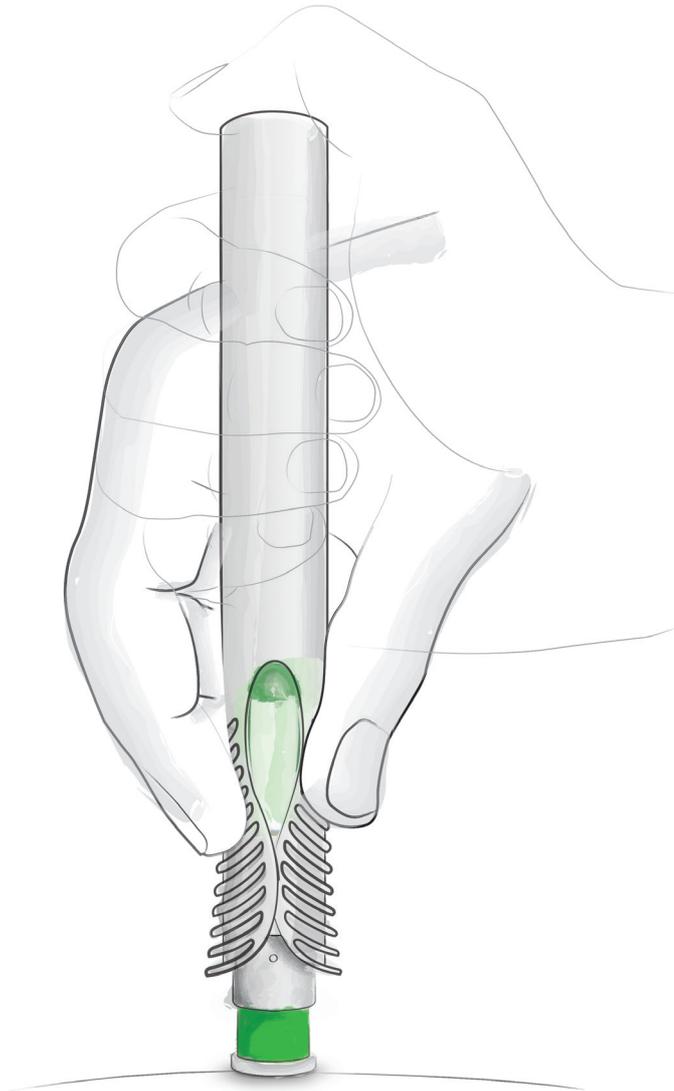


INJECTABLE DRUG DELIVERY: DEVICES FOCUS



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Injectable Drug Delivery: Devices Focus

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Front cover image: "Alternative grip options for the Amber auto-injector," supplied by SHL Group (see this issue pp 30).

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NEW HOME-BASED CARE MODELS CREATE CHALLENGES FOR PATIENTS WITH CHRONIC CONDITIONS

In this piece, Graham Reynolds, Vice-President, Marketing and Innovation, West Pharmaceutical Services, first takes a look at therapeutic compliance and shows how truly patient-centric delivery devices can be of benefit. In the context of chronic conditions, he emphasises the importance of an awareness of the patient's journey, and how needs change at various stages from diagnosis and throughout the treatment period.

Patients with chronic conditions are finding new freedom and comfort through self-care at home with injectable drug delivery systems, and will soon be offered new therapies delivered by wearable injectors. But these new home-based care paths pose challenges in ensuring compliance with drug therapies that can require life-long commitments, and often may not offer a perceived short-term benefit.

In fact, the World Health Organization reports that adherence rates for chronic conditions, such as diabetes or autoimmune diseases, are roughly 50% in developed countries. Non-compliance with daily drug

regimens can adversely impact the outcomes of patient therapy, and impose significant costs on healthcare providers that could be avoided. It also impacts pharmaceutical companies in numerous ways as well, including lost revenue.

What triggers patients diagnosed with chronic conditions such as diabetes, haemophilia, rheumatoid arthritis or multiple sclerosis to go off their medications? For one, emotions: anger, depression, denial, fear or anxiety triggered by their diagnosis or the realisation that they will be dependent on these medications for the rest of their lives. Another root cause can be con-

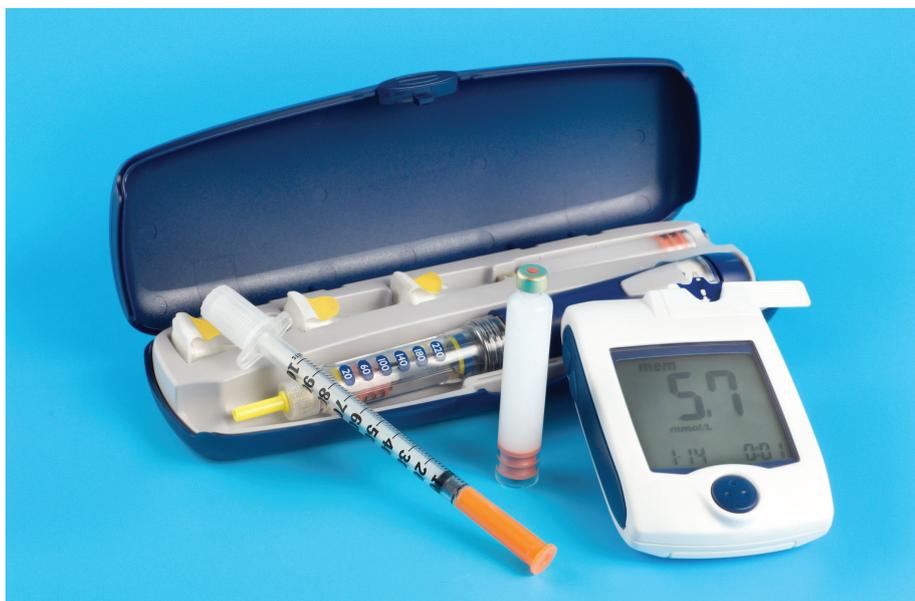


Figure 1: A variety of options exist for diabetes management and insulin delivery, including syringe systems, pen injectors and wearable insulin pumps.



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Figure 2: West's insulin pen cartridge components are used by the world's leading suppliers of diabetes therapies.

nected with education: learning the skills associated with self-care can be daunting, especially when it can get more difficult as the condition becomes more acute. Later, as the patient ages or degrades, lapses in therapy may occur due to the physical and emotional burdens of the condition.

CUSTOM DRUG DELIVERY SYSTEMS ENHANCE COMPLIANCE

For most patients, an easy-to-use, integrated delivery and administration system can be key to creating the routines that bring about compliance with care plans. Integrated systems combine the drug, its primary containment system and its delivery system. While many products do this reasonably well, a truly successful combination product

must also consider the needs of the end-user at a variety of stages during the patient journey. As an example, for a diabetes patient they may transition through a variety of injection systems, from a syringe to a pen, and ultimately to a wearable pump. In addition, their diagnostic method may change from a finger-prick to a continuous glucose monitoring technology (see Figure 1).

When they apply best-practice user-research methodology, pharma manufacturers can gain insight into a user's preferences and emotional requirements; those findings can translate into feature sets and design elements of the drug delivery system. Focusing on the relationship between the delivery system design and the patient interface, pharma manufacturers stand a better chance of satisfy-

"When they apply best-practice user-research methodology, pharma manufacturers can gain insight into a user's preferences and emotional requirements; those findings can translate into feature sets and design elements of the drug delivery system"

ing the emotional and physical needs of the intended user/patient throughout the course of treatment.

When drug delivery systems are intuitive and easy to use, they stand a better chance of encouraging adherence because the impact on daily routines becomes negligible. Conversely, delivery and administration systems deemed inconvenient or overly conspicuous can negatively affect a patient's emotional attitude and motivation to sustain adherent behaviour.

Patients also prefer a more discreet device that does not call undue attention to the delivery system and create distractions to others or feelings of stigmatisation. Such a shift from a product-centric focus to a patient-centric focus may help manufacturers design a product that encourages adherence – and brand loyalty – in crowded market segments.

QUALITY IS THE LINCHPIN OF BIOLOGIC DRUG CONTAINMENT

Many new biologics create significant challenges for containment systems, which can impact container and delivery system selection. Sensitivity to certain materials such as silicone oil, metal ions or extractables/leachables will drive the need for a container system that minimises adverse impact of containment materials over time (Figure 2).

Quality concerns regarding glass particles and delamination are driving increased interest in polymer-based systems. In addition, many newer biologics require higher concentrations, leading to higher viscosity and/or higher dosage volumes. In such cases the options include multiple doses of a smaller volume within 10 seconds with a syringe or auto-injector, or a prolonged injection of a higher volume through a wearable injector technology (Figure 3).



Figure 3: West's SmartDose® electronic wearable injector provides a solution for the challenge of delivering a large-volume dose of a drug product. Easily tailored to specific pharmaceutical customer needs, West's SmartDose technology, which uses Daikyo Crystal Zenith® prefilled cartridges, is designed for the delivery of viscous biologic drugs.



Figure 4: West's Mix2Vial® system is the ideal solution for one-piece preparation of powder drugs to be reconstituted by a diluent prefilled syringe.

Understanding all key elements of a drug delivery system provides the cornerstone that enables this system to achieve the goals of encouraging adherence in the home-care environment. The US FDA has provided recommendations for medical device design optimisation through human factors analysis, testing and validation.¹

ANOTHER CRITICAL DESIGN COMPONENT: HUMAN FACTORS

Human factors experts can help define and prioritise the needs of the intended users and determine what else needs to be learned about user and delivery system interaction. Common methods include qualitative,

To get the richest data, human factors experts must follow the patient on his or her journey – from diagnosis to end of therapy – and then translate the multitude of qualitative and quantitative data into features of a product that will not only provide a patient with an intuitive and easy to use delivery system, but also meet the emotions, needs and desires of the user at different stages of disease management.

SAFETY FEATURES: BUILD THEM INTO YOUR DELIVERY SYSTEM

Patient safety at home extends beyond the individual to the family and anyone involved in caregiving. When used, stored or disposed of incorrectly, delivery system containing a needle may cause a needlestick injury for caregivers and/or family members. The healthcare industry has seen advances in needlestick prevention thanks to legislation in both the US and Europe. However, such mandates are limited to the clinical environment.

For home-based care, needle-based systems that incorporate a safety mechanism – or those that are completely needle-free – can greatly reduce accidental needlesticks. Moreover, they reduce the spread of infectious disease, reduce costs associated with care, and help ensure the safety of those who come into contact with the system during disposal.

Patients start their journey with an initial diagnosis, but they travel a long road with a chronic condition. Pharmaceutical and delivery systems manufacturers must start the development journey with this in mind, and create systems and options that will not only help patients learn to care for their condition, but also comply with their prescribed treatment regimens throughout their course of care, with the goal of optimising patient outcomes.

REFERENCE

1. US FDA, "Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design". June 22, 2011 (www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm259748.htm).

"Many newer biologics require higher concentrations, leading to higher viscosity and/or higher dosage volumes.

In such cases the options include multiple doses of a smaller volume within 10 seconds with a syringe or auto-injector, or a prolonged injection of a higher volume through a wearable injector technology."

Drug manufacturers should seek a partner that can apply proprietary technologies, manufacturing excellence and patient understanding to their drug products and the products' packaging, delivery and administration systems. Such partnerships will help drug marketers offer successful, integrated solutions, benefitting manufacturers, clinicians and patients alike, while helping to ensure optimum adherence and improving patient outcomes (Figure 4).

quantitative and human factors/ergonomics analyses. Discovery research, usability testing, and directional and preference testing offer a strong framework for the development process.

It is also helpful for human factors experts to interview the user in the proper context or environment of use. Someone sitting in a conference room will have a different user experience than a stay-at-home mother who is also taking care of an aging parent.

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PROVIDING FULL-SERVICE SOLUTIONS FOR INJECTABLE DRUG DELIVERY

Here, Alan Shortall, Chairman and CEO, Unilife, provides an introduction to some significant trends in the pharma industry, such as the use of mobile electronics and smart phone apps, and the move of injectable medication delivery away from the clinical setting to wherever the user is, and describes some of the implications. He brings in the concept of the delivery device as a valuable brand differentiator in a market of similar therapeutic molecules to drive preference amongst increasingly medication brand-aware patients. He further highlights Unilife's portfolio of flexible, customisable device platforms, and the model of "Innovation within a Standard Footprint" which enables the development of innovative devices for pharma customers, without the need for them to retrofit established manufacturing and supply-chain processes.

Pharmaceutical and biotechnology companies continue to prioritise the development and lifecycle management of injectable biologics, drugs and vaccines. To help optimise the value of each molecule, target indication and patient population across their injectable portfolio, many companies are building deep relationships with a single preferred partner for injectable drug delivery systems that can provide full-service platform-based solutions for many, if not all, of their requirements.

THE RISE OF INJECTABLE THERAPIES

Injectable therapies account for some of the largest, fastest-growing and most valuable segments of the global drug portfolio. IMS Health data show that injectable products accounted for almost one-third of US drug sales in 2013, with sustained average annual growth rates of 10% since 2008. By comparison, oral products recorded flat to negative growth during the same period. Much of this demand is being driven by high-value biologics, such as monoclonal antibodies and peptides, which require injection due to their size and sensitivity. More than 900 biologics are in clinical development in the US alone, with most targeting industry growth areas such as

immuno-oncology, auto-immune diseases and rare diseases.

For many leading pharmaceutical and biotechnology companies, injectable biologics represent more than half of the clinical pipeline and are considered the most important drivers of future growth. These biologic-rich companies face two key challenges. First, they must manage, in parallel, the clinical development, registration and lifecycle management of a series of injectable therapies. Most of these injectable therapies are targeting well-defined patient populations, with many likely to be approved over time for multiple indications. Second, they must maximise the commercial success of each target molecule within a highly competitive global market that is in the midst of rapid change.

CONVERGING MARKET TRENDS FOR INJECTABLE DRUG DELIVERY

To minimise healthcare costs and improve quality of life, nations across the world are seeking to shift the place of care from healthcare facilities to wherever the patient happens to be during their normal day. According to Ernst and Young, half of all healthcare will take place outside of healthcare facilities within the decade. In many cases, the future place of healthcare will be normal environ-



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Figure 1: Unilife has created a broad proprietary portfolio across six product categories including (from left to right): prefilled syringes; reconstitution systems; wearable injectors; auto-injectors; ocular delivery systems; and novel delivery systems.

ments such as the home, workplace, school, café or gym, with the patient responsible for the administration of their therapy. With the typical frequency for a self-injectable biologic ranging from one week to every month or quarter, devices that contain and deliver a drug must be highly intuitive.

Due to the rise of biologics and the shift to patient self-injection, injectable drug delivery systems have never been more important to the overall success of an injectable therapy. Regulatory agencies such as the US FDA are requiring injectable therapies to be submitted for approval as drug-device combination products, with human factors studies required to validate safe and reliable administration by the target user group. The increasing influence of payers is also shifting the healthcare market from a volume-driven system to one focused on value-based healthcare outcomes. Today, the upfront cost of a drug is just one of a series of criteria being used to determine what brand of therapy will generate the best long-term return on investment.

Prescribers are seeking to select the brand of drug that can generate the best, most consistent rate of therapy compliance within the relevant target patient population. The level of acceptance for a device by a target user population across factors such as ease-of-use, safety, comfort and convenience now plays a key role in both therapy compliance and brand preference.

This trend will continue to accelerate over the next decade, as payers and providers seek greater access to real-time, cloud-based data

that can accurately assess how patients with a chronic disease adhere to their assigned drug regime. Where data indicates sub-optimal rates of adherence for the current medication, prescribers will be inclined (if not pressured by payers) to transfer to a rival brand. For pharmaceutical companies seeking to build long-term relationship with patients, the level to which a patient-centric device inspires brand loyalty for an applicable therapy will become critical.

Within this data-driven healthcare environment, drugs and devices will merge with electronics and software to resemble smart appliances such as an iPhone more closely. This new generation of smart drug delivery systems, such as wearable injectors and reusable auto-injectors, will come equipped with Bluetooth-enabled technologies and enable automatic synchronisation to a smart phone or tablet.

Patients are also becoming increasingly informed via social media and other information channels about their drug choices, leading them to become more influential in the decision regarding what brand of therapy they are prescribed. The new generation of brand-aware, technology-savvy patients desire therapies that can be safely, simply and conveniently administered with minimal disruption to their normal daily lives.

In the near future, it will be considered routine for many patients with a chronic disease to receive a reminder by their smart phone that it is time to take their medication, and for the smart phone to then issue

regular prompts until they have done so. In some cases, patients will be able to calculate the speed and depth of injection to minimise discomfort and have real-time access to data regarding the status of the injection until full dose delivery has been completed. The data generated during each injection can then be automatically disseminated via the cloud to authorised healthcare parties to help enhance patient care and optimise therapy compliance.

The value of biologics that are integrated with patient-preferred, brand-centric smart devices that can capture and disseminate protected data across the healthcare spectrum would be priceless. Where there is an established brand of therapy facing emerging competition from other branded or bio-similar rivals, such devices could potentially make all the difference to a pharmaceutical company seeking to protect market share.

ACCOMMODATING CUSTOMERS WITH LARGE INJECTABLE PORTFOLIOS

Despite the huge advantages, until recently, it has been difficult for a pharmaceutical company to pursue a device-based strategy that would optimise the approval, filling, containment, delivery and commercial success of each target therapy across their broad portfolio of injectable drugs. Traditionally, pharmaceutical companies simply launch a drug in a vial format, and then gradually introduce devices such as a prefilled syringe or auto-injector during the commercial life-

cycle. Device decisions have typically been made on a per-drug basis, with a handful of prospective suppliers invited to participate on a price-driven tender for a short-term, multi-source supply contract.

by a supplier to use a proprietary material for a component within the primary drug container. Questions of ownership and accountability may also arise when a pharmaceutical company sources related

also to provide critical expertise, knowledge and guidance to pharmaceutical customers to support the industrialisation of the drug-device combination.

These important value-adding services, which are provided by Unilife to provide customers with rapid industrialisation success, are enabled by the deep level of drug-device industrialisation expertise the company has built. The process of industrialisation between Unilife and the customer for both the device and drug-device combination typically starts very early in the product design process and ultimately manifests itself in:

- Robust products that can be manufactured reliably and efficiently with designs that can tolerate manufacturing tolerances and process capabilities
- Innovative solutions and designs within established standard geometries, processes, equipment, and capabilities of pharmaceutical industry

“For pharmaceutical companies seeking to build long-term relationship with patients, the level to which a patient-centric device inspires brand loyalty for an applicable therapy will become critical”

The fragmented nature of the injectable drug delivery systems market, as well as the entrenched, inflexible business models of some incumbent device companies, contributed to this situation. The majority of device companies have traditionally chosen to specialise in one, or a few, particular segments of the market such as disposable auto-injectors or ready-to-fill glass syringe barrels. Few companies were able to offer a broad selection of device technologies that could accommodate most, if not all, of a pharmaceutical company’s injectable therapy requirements. As a consequence, pharmaceutical companies were required to work with a variety of device and component suppliers.

While pharmaceutical companies have established processes to co-ordinate the supply of products from multiple vendors, the traditional supply process has also created certain challenges. One problem is the need to rely on commodity products that restrict opportunities for brand differentiation or device customisation. Quality variances might also occur between rival suppliers of the same component. Furthermore, a pharmaceutical company might be pressured

components, such as a prefilled syringe glass barrel and a disposable auto-injector, from separate suppliers. More often than not, in such cases, full accountability for the integration of multiple device components would fall onto the shoulders of the pharmaceutical company.

Furthermore, a device manufacturer that specialises in only one market segment, for example disposable auto-injectors, is likely to be naturally biased toward the selection of a product from that particular segment as opposed to other potential options such as reusable auto-injectors or wearable injectors. As a result of this lack of neutrality, a customer might be denied an opportunity to conduct a full and impartial review of all potential device technologies potentially available.

Over the last decade, Unilife has been at the forefront of the development of new partnership-based paradigms for the injectable drug delivery system industry that can provide pharmaceutical companies with greater choice and flexibility. The US-based, NASDAQ-listed company has consistently demonstrated its ability not only to manufacture complex devices commercially, but



Figure 3: The Ocu-Mix Duet™, an ocular delivery system with prefilled drugs in both chambers.

Figure 2: A range of product configurations with a multitude of customisation options are available within each product categories to address a customer’s specific drug, patient and commercial requirements.



- Human-factors-driven designs that directly address customer needs with customised features and ease of use that bolster both regulatory and commercial successes.

By pursuing customer-centric and patient-centric outcomes from day one, Unilife has become arguably the first company in its industry to create a comprehensive, market-driven portfolio that can accommodate the needs of any injectable biologic, drug or vaccine. The company's portfolio spans more than six distinct product categories (see Figure 1, previous page) including prefilled syringes, wearable injectors, auto-injectors, reconstitution delivery systems and ocular delivery systems, and encompasses more than 20 product platforms (Figure 2). Each of these platforms directly addresses identified unmet or emerging market needs and is the result of intensive, customer-centric R&D investment.

By creating such a broad portfolio of product platforms, along with a streamlined business structure with strong industry knowledge and deep scientific expertise, Unilife is able to serve as a preferred full-service solutions provider for a customer across either single- or multiple-device categories.

Pharmaceutical customers can gain attractive economies of scope by building a deep relationship with a dedicated long-term partner, such as Unilife, that can efficiently support a multitude of their immediate and future requirements.

Such is the breadth of Unilife's portfolio and capacity for innovation; it is common for a customer to be provided with multiple technology choices within the same market segment.



Figure 4: Innovation within a Standard Footprint.

The development of both single-barrel and double-barrel technologies for drug reconstitution is one example of Unilife's prowess in this area. Furthermore, the depth of the Unilife portfolio enables it to service customer requirements fully across a range of administration routes including subcutaneous, intramuscular, intravenous and

intravitreal injection. Unilife is perhaps the first company to provide systems that can be leveraged by a customer irrespective of whether the target drug is to be utilised in a liquid-stable or lyophilised form.

Unilife is equally well positioned to meet customer requirements for any dose volume, with technologies developed to contain and deliver everything from small doses measured in microliters as low as 10 uL to large volumes as high as 50 mL or more. Within the 1-3 mL dose volume range, which is becoming a sweet spot for many biologics, Unilife can provide a multitude of product choices, including prefilled syringes with integrated, automatic needle retraction, smart reusable auto-injectors that can control the speed of injection and provide needle-free disposal, dual-chamber systems for the automatic reconstitution or mixing of combination therapies (Figure 3), and a broad platform of wearable injectors. As a result, Unilife



Figure 5: A selection of some of the customisation options available within the Unifill platform of prefilled syringes.



is able to provide a customer with neutral support regarding the various product options that may be available.

MITIGATING RISK VIA INNOVATION WITHIN A STANDARD FOOTPRINT

A broad, flexible array of injectable drug delivery systems such as those just described would be largely redundant if they required pharmaceutical companies to retrofit or replace their established manufacturing and

dozens of approved and pipeline biologics reside within a pharmaceutical company's pipeline, the importance of a platform-based device approach can become even more paramount.

At the heart of any robust device platform is the capacity for a pharmaceutical customer to be able to select their perfect product configuration from among a broad range of customisation options. For every platform across its portfolio, Unilife has created a vast pool of features that can be leveraged by a customer (Figure 5).

“Unilife empowers customers to leverage the innovative, customisable features and functionality of its products fully in order to generate powerful brand differentiation against brand-name, generic or biosimilar rivals and to build or protect market share.”

supply chain processes. Increasingly, pharmaceutical companies recognise that only platform-based devices can provide them with the right balance between flexibility and uniformity. Unilife is one of the first companies to provide its customers with sophisticated platform-based delivery systems that utilise standard filling processes and materials, yet are customisable to address the specific requirements of individual target molecules and patient populations. Unilife calls this service, which allows a customer to utilise one platform technology for an entire family of drugs, “Innovation within a Standard Footprint” (Figure 4).

By having access to modular, platform-based device solutions, which are essentially the same base model product but can be easily reconfigured for each specific drug, pharmaceutical companies can rely on standard equipment to fill and package their drugs, streamline their supply chain and manufacturing processes and mitigate risk in general. Furthermore, it allows them to create a distinctive visual brand identity for each applicable drug in their portfolio.

ADDRESSING CUSTOMER NEEDS FOR EVERY MOLECULE

Because one biologic can be approved across several indications and patient populations, Unilife recognises that no rigid device offering can truly accommodate the intricate clinical, commercial and patient requirements that can be involved. When

retraction, customer options include needle length and gauge, luer connections, barrel volume, elastomers and coatings, dose markings, barrel materials, silicisation and product branding. These options enable Unilife to create an endless array of configurations off the same base of prefilled syringe technology that will pair the right device with the right therapy and patient population.

The LISA™ platform of smart disposable auto-injectors represents another case study in device customisation. In addition to a range of ergonomic shapes and sizes, Unilife has developed a series of options that can be tailored to the specific needs of an individual therapy and its target patient population. Options include the heating of the molecule to room temperature prior to an injection, the ability for a patient to control the speed or depth of each injection, and the pairing of the device with Bluetooth connectivity as well as a related app.

When the respective customisation options of both the Unifill® syringes and the LISA™ auto-injector platforms are combined, a pharmaceutical customer becomes fully empowered to drive user preference across all segments of a patient population.



As just one example, the Unifill® category of ready-to-fill (prefilled) syringes includes over a dozen customisation options. In addition to automatic, user-controlled needle

Figure 6: The Unifill Finesse Standard syringe, using the Unilife logo to show how customer brand logos and dose information can be incorporated onto the band of the barrel.

GENERATING COMPETITIVE BRAND DIFFERENTIATION

With so many injectable drugs approved and under clinical development that will target a defined number of chronic diseases, the ability of a pharmaceutical company to build a differentiation strategy based on clinical performance alone is diminishing. Across many chronic diseases, the likelihood of commercial success is becoming directly proportional to the level of device differentiation that an injectable therapy can generate compared to the competition. A review of marketing strategies for leading insulin brands, where proprietary pens are today utilised as a primary differentiation tool, highlights the growing importance of this market trend.

Unilife empowers customers to leverage the innovative, customisable features and functionality of its products fully in order to generate powerful brand differentiation against brand-name, generic or biosimilar rivals and to build or protect market share. The elegance and visual distinctiveness of all Unilife products are central to this strategy. Core advantages of Unilife products compared with equivalent commodity devices can include minimal steps of use, optimal protection against needlestick injuries, convenient portability and disposal and a streamlined filling process.

Unilife provides a customer with additional options to maximise user preference and brand differentiation for a therapy within each target indication or patient population. The shapes and sizes of products from platforms, such as wearable injectors and auto-injectors, can be tailored to specific brand and patient population requirements in any number of ways. Brand logos and dose information can also be incorporated onto the branding band of the barrel for syringe-based products such as Unifill® syringes (Figure 6) and ocular delivery systems.

When a customer seeks to attain some level of exclusive access to the look, feel or functionality of a product platform within a particular drug class or indication to maximise brand differentiation, Unilife has the flexibility to discuss options that could support the interests of both parties.

PROVIDING A FLEXIBLE, ROBUST SUPPLY CHAIN WITH LONG-TERM CONTINUITY OF SUPPLY

Another factor that indicates how Unilife is helping to redefine the industry in favour of its pharmaceutical customers is the provision

of a flexible, robust supply chain, as well as an assurance for long-term continuity of supply. Although many device companies can struggle with their supply chain and making it fit the needs of their customers, Unilife has addressed this in the most effective way. It has formed partnerships with many leading, established material and equipment suppliers, CMOS and global production specialists to mitigate risk and maximise customer preference.

As a manufacturer of injectable drug delivery systems, Unilife is able to buy-in all components and materials from suppliers. For its incoming supply chain of components

“Core advantages of Unilife products compared with equivalent commodity devices can include minimal steps of use, optimal protection against needlestick injuries, convenient portability and disposal and a streamlined filling process”

and standard materials, Unilife has partnered with best-in-class suppliers, most of which are already vetted and trusted by pharmaceutical customers. Each of these suppliers has global operations and is able to supply from multiple geographies around the world. Unilife works with each customer to select preferred materials or components from among a selection of qualified suppliers. The company also provides full transparency in the management and documentation of its suppliers in accordance with US FDA requirements.

In addition to Unilife’s own large, state-of-the-art facility in the US state of Pennsylvania, the company can provide customers with alternative sites of production and supply. Again, Unilife has partnered with best-in-class suppliers that are already fully vetted and trusted by many pharmaceutical companies.

Unilife’s global partnership with Flextronics is one recent example of the company’s diversified manufacturing and supply-chain strategy. As one of the finest manufacturers in the world, Flextronics provides an alternative source of production and supply for Unilife’s proprietary products from a multitude of global production sites. The partnership not only enhances Unilife’s own supply chain, but maximises efficiencies by leveraging the production, capacity, and rapid scale-up capability of Flextronics.

Given the importance of Unilife’s proprietary devices in the development, approval and commercial success of the drug-device combination product, the company can provide customers with an assurance for long-term continuity of sup-

ply. This assurance can often span periods of between ten and fifteen years. Unilife may also provide a commitment to continued innovation on behalf of the customer during the term of the commercial partnership, so that the customer can continue to stay ahead of the competition.

Before the signing of the first commercial supply agreement between a pharmaceutical company and a full-service device solutions provider such as Unilife, it can take significant upfront effort to complete the due diligence. However, once the first supply agreement has been signed and a level of

trust has been developed between both parties, the prior due diligence can be leveraged and amortised on future supply agreements for additional molecule or device categories.

SERVING CUSTOMERS WITH SPEED, AGILITY & RELIABILITY

Unlike many incumbent device companies that operate under a matrix business structure, Unilife utilises cross-functional teams with deep scientific expertise that are dedicated to each customer. Highly-experienced project leaders are fully empowered to make immediate decisions to serve customers with speed and agility. Combined with a robust quality management system that has been audited regularly by multiple regulatory agencies, notified bodies and customers, Unilife’s business structure is aimed at providing customers with everything they want, as well as anything they need.

These and other customer benefits have allowed Unilife to attain a reputation amongst a multitude of global pharmaceutical companies as the lowest-risk and highest-quality supplier. The number of companies that hold this view continues to grow. Innovation, customer centricity with urgency, world-class experts and highest quality with lowest risk define the essence of Unilife. As pharmaceutical companies continue to shift towards a platform-based device strategy for use with large portfolios of injectable therapies, Unilife is well positioned to serve their long-term requirements.



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Wearable Injectors



Prefilled Syringes Reconstitution Systems



Auto-Injectors



Ocular Systems



Novel Systems





DRUG DELIVERY SYSTEMS: READY TO USE FOR HIGHEST PATIENT COMFORT

Micro-infusion – a new trend in drug delivery? This and other questions are discussed by Ludwig Weibel, Chief Executive Officer, and Hans Peter Manser, Business Director, both of Weibel CDS AG. A novel and innovative approach is presented offering all stakeholders – pharmaceutical companies, healthcare personnel as well as patients – numerous advantages.

Safer, easier and faster drug delivery – Weibel CDS AG, Switzerland, develops and produces innovative, user friendly, application-oriented primary packaging and devices.

INJECTABLE DRUG ADMINISTRATION – MARKET VIEW

Only one third of injectable drugs are injected, whereas all others are administered by infusion. These two thirds of the cake are

patients use small pumps which are either carried in a special holster on a belt or patched to the body. In rare cases the pump may even be implanted.

The most familiar use of this latter category is for insulin, where pump systems are widely accepted. Unfortunately, all systems available today require patients to transfer the drug from a container (for example, a vial) into the pump by using a syringe. Self-medication is heavily dependent on the ability of the patients to prepare and manipulate the injection device. For any patients with reduced manual dexterity, such as those with Parkinson's disease and requiring apomorphine, this can be a major issue.

New systems are being developed, but most still rely on a tube as a connection between pump and catheter.

“Weibel CDS has developed DrugDeliverySystems, which are ready to use, and no longer require the patient to transfer the drug into the system”

traditionally infused via infusion bags and sets (see Figure 1). Not only is the handling of infusions time-consuming and cumbersome, patients often also lose mobility and are usually confined to bed.

Valuable time of healthcare personnel, as well as high costs for time spent in hospitals, is outweighing the actual cost of drugs by far, thus increasing the total cost of treatment dramatically.

Alternatively, drugs are administered by infusion pumps. Here two different solutions are available. Hospitalised patients are given their treatment via infusion pumps based on 50 mL syringes with the same effect on mobility and confinement to bed as for infusion bags. Mobile



Figure 1: Traditional infusion sets.



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Figure 2: Small yet incorporating all functions.

MICRO-INFUSION – A NEW TREND IN DRUG DELIVERY?

Subcutaneous Infusion

The positive feedback from diabetics in using micro-infusion pumps subcutaneously has prompted the pharmaceutical industry to evaluate such systems for other drugs requiring repeated daily or even hourly SC injections, such as apomorphine for Parkinson's disease, or interferon beta for multiple sclerosis. But also for diabetics the end of the rope has not been reached as one of the major elements still need to be implemented – ready to use, prefilled systems are required to really mark a break through.

“Ready to use, prefilled drug delivery systems are required to open up a new era in drug administration”

Intravenous Infusion

Patient mobility and changes in drug administration will require new drug delivery systems that allow for total freedom to move as well as long-term treatment. Studies suggest in some cases a better drug acceptance and, more importantly, improved long term results if cytostatic drugs, for example, are administered starting with a bolus injection at the hospital followed by a long-term basal injection. The big challenge for such systems is again to be ready to use as well as prefilled, since handling by the patient may lead to dangerous situations due to the toxicity of the drug. In addition the container size may no longer be adequate if only around 1-3 mL. Large-volume containers up to 30 mL will be needed creating a huge challenge as the size of the device itself



Figure 3: Available for all 3 mL cartridges.

should still be small. Especially as glass containers holding 30 mL have diameters of up to 30 mm.

NOVEL DRUGDELIVERYSYSTEMS BY WEIBEL CDS AG

Weibel CDS has developed DrugDeliverySystems, which are ready to use, and no longer require the patient to transfer the drug into the system. Two versions are available, one for standard 3 mL cartridges as well as one using Weibel's MiniBagSystems, scalable from 1-30 mL.

CARTRIDGE-BASED DRUGDELIVERYSYSTEMS

Designed to accept standard 3 mL insulin cartridges of all insulin manufacturers, the cartridge-based DrugDeliverySystems are barely larger than the cartridge itself (see Figure 2). The system is extremely small yet still incorporates all functions including a unique pump system, a needle insertion system, a battery, a drive and an electronic control unit. The pump system is powerful, guaranteeing that it will overcome the break-loose forces and maintain the smooth gliding of the rubber stopper throughout the injection.

The cartridge may be pre-assembled by the pharmaceutical company or alternatively a solution is available offering the patient the option to choose the insulin supplier themselves (Figure 3).

The device is patched to the body, often the abdomen, and may be operated via an external control unit allowing the patient discreet use.

MINIBAGSYSTEMS-BASED DRUGDELIVERYSYSTEMS

Weibel's MiniBagSystems are a revolutionary concept providing a platform for



Figure 4: The MiniBagSystems-based DrugDelivery System.

various drug delivery systems (Figure 4). MiniBagSystems are designed with a unique port to enable filling and discharging, thus limiting overdosing to an absolute minimum. Multilayer foil has been chosen as the base material to provide the lowest levels of gas (including water vapour) permeability, close to those of glass. Long-term stability studies with protein-based drugs have shown positive results at >1.5 years, and still ongoing.

Size is a big advantage of MiniBagSystems as they remain flat, even for versions holding 30 mL (Figure 5). Combined with a unique pump system, a needle insertion system, a battery, a drive and an electronic control unit, the device is available for subcutaneous infusions. The automatic needle insertion system includes a soft cannula and the steel needle is permanently withdrawn.

For intravenous infusion, replacing today's gravimetric systems and larger pump systems, the device is available with a tube and cannula. Again patched to the body, the system offers patients total freedom to move.

RE-USABLE VERSUS FULLY INTEGRATED SOLUTIONS

A re-usable unit containing the drive, battery and the electronic parts allow for a highly economic footprint. Yet, as these parts will be used for one year or



Figure 5: Size comparison up to 30 mL.

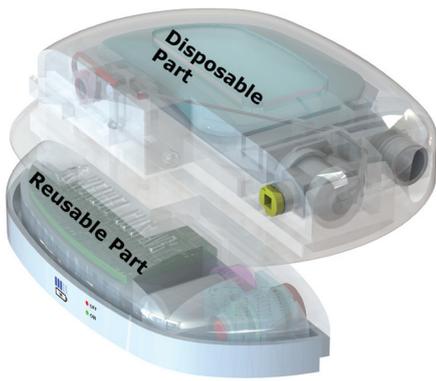


Figure 6: Re-usable and disposable parts.

more and are not discarded after every infusion, more durable and expensive components can be chosen. Additional components, such as a pressure sensor, can be added to offer controlled and guaranteed system reliability.

The disposable part includes the drug container, pump and the needle insertion system as all parts in contact with the drug or blood need to be discarded (Figure 6). Thanks to the soft cannula and retracted steel needle the risk of needle stick injuries is eliminated.

Market acceptance, however, may demand for a fully integrated solution. For such components are available with a guaranteed life time over e.g. a certain number of turns as for the drive.

Weibel CDS offers all DrugDeliverySystems in re-usable / disposable or fully integrated versions as finally

needles including a passive safety device.

- The **Reconstyringe®** product family is first in offering a fully automated reconstitution of lyophilised drugs. The drug is contained in its original vial, the solvent in the MiniBagSystem. With a spring mechanism and holder plates the content of the MiniBagSystem is emptied into the vial. Like

“The system is extremely small yet still incorporates all functions including a unique pump system, a needle insertion system, a battery, a drive and an electronic control unit.”

the market and individual customers will decide on the solution chosen – re-usable / disposable or fully integrated.

Besides DrugDeliverySystems, Weibel CDS supplies injection devices such as:

- The **SuperCapSyringe®** product family upgrades your vial practically to a pre-filled syringe. Based on a modular design, the syringe is fully adaptable to your application needs. It is supplied in different sizes and, as a novelty, with staked

a Swiss watch, it runs through the full reconstitution cycle. Finally, the drug is drawn into the SuperCapSyringe® for injection.

(Both the **SuperCapSyringe®** and the **Reconstyringe®** were discussed in greater detail in [ONdrugDelivery Magazine, 2015, Issue 55, pp 66-67.](#))

International patents pending. SuperCapSyringe® and Reconstyringe® are registered trademarks of Weibel CDS AG, Switzerland.

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Container Closure Device System Solutions

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ENABLING DEVICE INNOVATION THROUGH COMPONENT CUSTOMISATION

In this article, Susan M. Dounce, PhD, Senior Manager, Business Development & Innovation – Injection Systems, Datwyler Sealing Solutions, and Rick Bente, Vice-President, Advanced Drug Delivery Systems, Unilife Corporation, outline Datwyler's offering in the area of customised elastomeric components, in particular for devices containing biologic products. The authors go on to provide Datwyler's collaboration with Unilife for the elastomeric components for its wearable high-volume injection device platform as an example of the successful integration of numerous components into devices, made possible by an increased level of co-operation right along the supply chain.

With the continued growth in the therapeutic biologics industry, there are more drug delivery challenges than ever before. Proteins are inherently susceptible to enzymatic degradation and therefore, in the absence of significant technological advances, therapeutic proteins must be delivered by injection. At the same time, with respect to the parenteral industry, biologic drugs, without question, have the most unmet packaging / delivery needs and therefore the most opportunities for innovation.

As such, there is an increased momentum towards bringing new delivery devices to market which safely and reliably address these challenges and simultaneously optimise the patient experience.

The challenges around the delivery of biologic drugs are largely due to the size and stability of the molecules. As an example, whereas the most comfortable patient experience may be self-administration in a home setting, many biologics are currently administered by intravenous infusion in a healthcare setting. In many cases, this is due to the simple fact that the size of the drug molecules make concentration into a 1-3 mL delivery volume difficult and in some cases impossible. To put things in perspective, a monoclonal antibody with a molecular weight of around 150 kDa is roughly 150 to 1000 times larger than a small-molecule drug. With such large mol-

ecules, as concentration increases, so does formulation viscosity and this can translate into larger dose volumes.

Since self-administration can reduce healthcare costs and increase patient satisfaction and compliance, there is a drive to transition drug administration out of the hospital and directly into the hands of patients – especially for chronic disease states. For biologic drugs, this may require new forms of delivery like a wearable injector system which can administer larger dose volumes over extended periods of time.

Another attribute of biologic drugs which creates delivery challenges is their comparative instability relative to small-molecule drugs. During shipping and storage, biologics can be prone to aggregation, chemical changes like oxidation or de-amidation, and conformational changes. For this reason, it is common for biologics to be stored in a lyophilised form. Although this may be an effective way to handle stability issues, lyophilised products are usually packaged in vials and must be reconstituted at the time of administration by a many-step process which can be complicated and time-consuming.

Reconstitution syringes, which can transform the delivery of a lyophilised drug into a single-step, intuitive and comfortable process, represent a significant advancement in patient-friendly delivery of lyophilised drugs.



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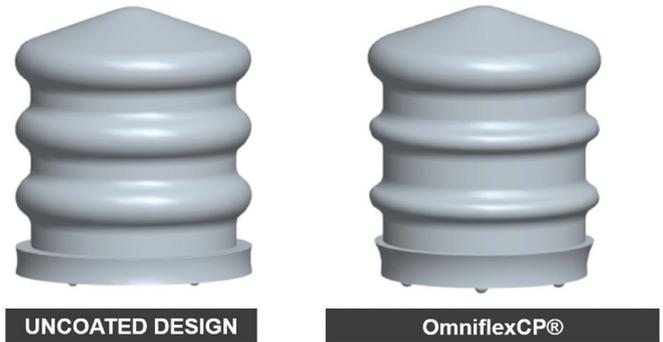
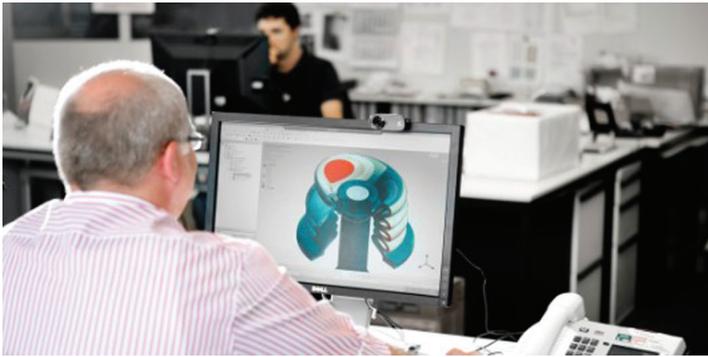


Figure 1: Engineering Expertise – small design changes can significantly impact the performance of a component or the ability to manufacture it. Here, engineers have modified an ISO standard plunger design (left) into a form that gives highly consistent glide forces in a syringe (right).

While such new drug delivery devices like wearable injectors and reconstitution syringes present solutions to some of the unmet needs of biologic drug delivery, they have additional functional features beyond the traditional prefilled syringe and therefore require the seamless integration of dozens of components. Combined with ever increasing regulatory scrutiny, it is this added device complexity that is changing the climate of drug delivery device innovation. Relationships along the entire supply chain are becoming increasingly collaborative – from raw material suppliers to component manufacturers to device integrators to combination product manufacturers.

Also, component suppliers such as Datwyler are experiencing increased demands for customisation. Key to the performance of the integral device is the function of every component and often times, customisation of a single component such as an elastomeric closure, can be a key enabler of device innovation.

SUPPORTING ELASTOMER COMPONENT CUSTOMISATION FOR NOVEL DRUG DELIVERY

With drug delivery device designs becoming more complex, there is an ever increasing demand on each component within the device. Every component, including elastomeric closures, must perform to a high standard and must be effectively integrated with the other device components. By focusing on the core capabilities of engineering, material development and simulation, and quality processing, Datwyler is able to deliver the highest quality, most innovative, customised elastomeric closures to its partners. The seamless interdisciplinary co-operation within Datwyler and the focus on customer collaboration make Datwyler the preferred partner for co-engineering customised solutions.

ENGINEERING EXPERTISE

The mission of the Datwyler engineering team is to drive the smooth and timely transition of products from concept to prototype to mass production - not only for product lines that are proprietary to Datwyler, but also for customer-specific developments. Very often, Datwyler customers are also partners in co-engineering solutions. Tooling Engineering Manager Koen Maes states: “Our customers tell us that what sets Datwyler apart is our flexibility and our timely response. Beyond that, our engineers have a deep understanding of the interaction between elastomer design and processability.”

Indeed, Datwyler engineers are uniquely positioned to identify future production challenges at the concept stage. When starting a new project with a partner, it is common for the initial product design to be tailored to the particular application, but it may not necessarily be optimised for manufacturing. Some design changes can have a significant impact on performance (as in Figure 1) or the ability to scale-up production. “It might not look like a big

MATERIAL EXPERTISE & SIMULATION

Datwyler continues to lead the industry when it comes to developing the cleanest and best performing elastomer compounds and coatings. As the scrutiny around leachables and particulates from parenteral packaging components continues to escalate, Datwyler material developers advance the industry standards in elastomeric closure cleanliness by a three-part approach:

1. to develop next-generation elastomer compositions that are inherently cleaner
2. to understand and manage the raw materials used in the compounds and coatings
3. to develop and optimise low-particulating, lubricious barrier coatings such as Omniflex.

Datwyler’s proprietary Omniflex coating which significantly reduces subvisible particle levels, is inherently well-suited for creating custom designs that are barrier coated. “The flexibility and scalability of our Omniflex technology makes it the only technology that offers a very short iteration loop for customised coated product

“Relationships along the entire supply chain are becoming increasingly collaborative – from raw material suppliers to component manufacturers to device integrators to combination product manufacturers”

deal but sometimes a minor alteration to a radius of curvature or a cavity diameter can make all the difference when it comes to industrialisation,” says An Vanheel, Project Manager. This expertise is critical to optimising customer-specific designs and Datwyler’s open collaboration is one key to co-engineering success.

development and hence offers, in the end, a speed-to-market benefit,” says Dr Bram Jongen, Head of Material Development. “Datwyler is equipped to coat a few hundred products up to full-blown production of millions per year.”

Combining Datwyler’s best-in-class materials with customised, optimised

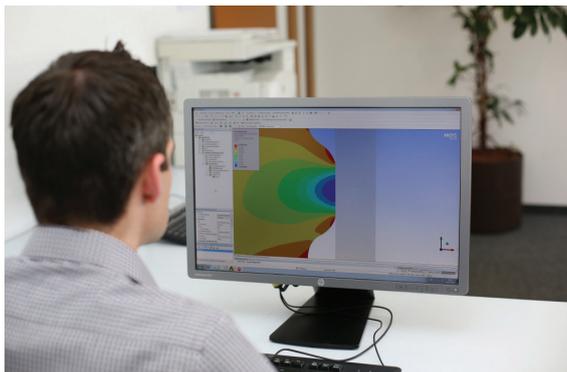
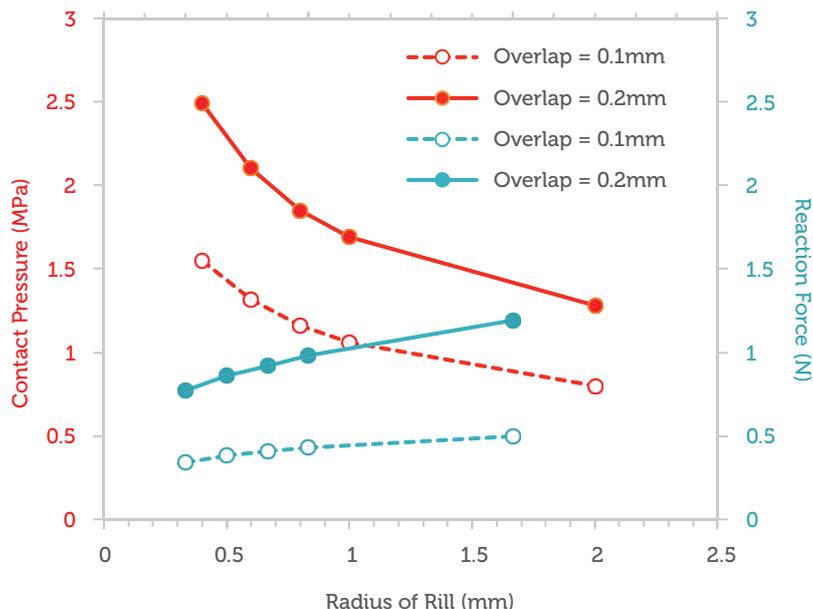


Figure 2: Material Expertise & Simulation – Datwyler continues to develop the industry’s cleanest and best performing elastomer compounds and coatings and Datwyler’s material expertise is complemented by simulation capabilities. Here, experts in Finite Element Analysis simulation construct a qualitative model to depict the influence of syringe barrel and plunger rill diameters on contact pressures and reaction forces.



designs leads to products with outstanding performance. Finite element analysis (FEA) facilitates a fundamental understanding of the properties and functionalities of products and provides a basis for improving product performance. “The keys to building reliable FEA models with predictive power are the use of the most accurate physical and mechanical input parameters, and the alignment of the simulation results with well-understood experimental data”, says Rudolf Randler, Head of Material Development for New Products & Simulation. “This involves high quality measurements for the determination of the material properties of Datwyler elastomers and also requires the design and execution of well-controlled, statistically sound testing.” The Datwyler simulation team uses qualitative and quantitative FEA results to understand better how material properties and design changes can impact product processability or performance (as in Figure 2), and the team is available to aid in the optimisation of customised co-engineering solutions.

PROCESSING QUALITY

FirstLine® is Datwyler’s state-of-the-art manufacturing facility (Figure 3) located in Alken, Belgium which is dedicated to the production of high quality pharmaceutical closures. Today, primary packaging component manufacturing is considered to be an extension of the drug manufacturing process itself and the FirstLine® facility was designed to meet the evolving standards of the parenteral industry. The facility design, process flow, gowning protocols, personnel and material flow, camera inspection, and automation all result in the lowest endotoxin, bioburden, particulate, and defect levels available in the industry. The production of custom-designed elastomer products for pharmaceutical packaging can be located within the FirstLine® facility upon request.

By focusing on and excelling at these core capabilities, Datwyler is able to deliver the highest quality elastomeric closures for new drug delivery devices. Flexibility, customer focus, and interdisciplinary cooperation make Datwyler

the preferred partner for collaborative developments.

CASE STUDY IN ELASTOMER DEVELOPMENT: UNILIFE WEARABLE INJECTOR PLATFORM

A growing multitude of pharmaceutical and biotechnology companies have large portfolios of biologics, such as monoclonal antibodies, that require the subcutaneous self-administration of large dose volumes over periods longer than is suitable for the use of hand-held devices. To accommodate the specific drug and patient needs of each molecule in the portfolio, many pharmaceutical companies are seeking to select one platform-based wearable injector technology that is simple to customise, commercialise and use.

Unilife, a US based designer, developer and supplier of injectable drug delivery systems, has created a broad, flexible portfolio of wearable injectors (see Figure 4) that allows pharmaceutical customers to bring to market each molecule with minimal risk and maximum user preference. In addition,



Figure 3: Processing Quality – FirstLine® is Datwyler’s state-of-the-art manufacturing facility for elastomeric closures designed to provide the lowest endotoxin, bioburden, particulate, and defect levels available in the industry.



Figure 4: The Unilife Wearable Injector Platform – Unilife has created a broad, flexible portfolio of wearable injectors that allows pharmaceutical customers to bring each molecule to market with minimal risk and maximum user preference.

Unilife Requirement	Datwyler Solution
Chemical compatibility with biologic drugs	Material Expertise – Omniflex fluoropolymer coating technology for superior chemical compatibility and the elimination of silicone-oil-based subvisible particles.
Low subvisible particle levels	
No new production processes	Engineering Expertise – Fast, flexible, customer-centered design engineering for rapid transition from prototype to production of custom designs. Processing Quality – State of the art processes and production facilities with turnkey solutions to accommodate custom designs. Processing Quality – State of the art processes and production facilities with turnkey solutions to accommodate custom designs.
Less than 6 months to validated production runs for custom designs	

Figure 5: Four key programme requirements for Datwyler elastomeric closures in the Unilife wearable injector platform.

tion to the company’s wearable injectors being prefilled, pre-assembled and ready-to-inject, they can be fully customisable to address specific drug and patient requirements including dose volume, duration rate, drug viscosity and Bluetooth connectivity. Like all of its platforms, Unilife also works with customers to select standard primary container materials and components from a range of preferred suppliers.

As part of its customer-centric strategy to leverage well understood materials and ensure systems are supplied ready for seamless integration with approved filling and packaging processes, Unilife entered into a collaborative development programme with Datwyler to design and manufacture customised elastomeric components for the Unilife wearable injector platform. Unilife’s device and primary container expertise and Datwyler’s deep understanding of elastomers have together resulted in a new septum and plunger system which meets the exacting specifications of the Unilife design and provides the value of Datwyler’s bromobutyl elastomer and Omniflex fluoropolymer coating technologies. The system is validated and available for use in commercial and stability programmes.

Key Requirements for Elastomeric Closures in the Unilife Wearable Injector

In entering into the collaborative partnership, Unilife identified a number of key programme requirements for elastomeric closures in the wearable injector system. Four of these are shown in Figure 5 together with Datwyler’s solutions.

Both the custom designed plunger and septum are coated by Datwyler’s proprietary Omniflex inert fluoropolymer spray coating technology. This enables the elastomeric closures to meet the first two key programme requirements. The Omniflex fluoropolymer coating is the first coating to simultaneously provide barrier properties and to eliminate the closure as a source of silicone-oil-based subvisible particles. As a consequence of the coating’s chemical composition and method of application, Omniflex Coated Plungers (OmniflexCP®) not only have barrier properties that result in superior chemical compatibility but have the added benefits of a significant reduction in subvisible particle levels and highly consistent delivery forces.

The other two programme requirements were the use of existing processes and scaling up within six months to ensure speed to mar-

“Key to the performance of the integral device is the function of every component and customisation of a single component such as an elastomeric closure, can be a key enabler of device innovation.”

ket with minimum risk to the combination product manufacturer. Although the product designs are customised, the septum and plunger production, coating, washing, and sterilisation are standard, turnkey processes.

Key Attributes of the Plunger and Septum

The overall functional performance and chemical compatibility of the Unilife wearable injector are influenced by the Datwyler elastomer components. The proprietary septum and plunger (as in Figure 6) that are used in the Unilife wearable injector platform have been developed using the Datwyler FM257 / FM259 bromobutyl elastomer platform.

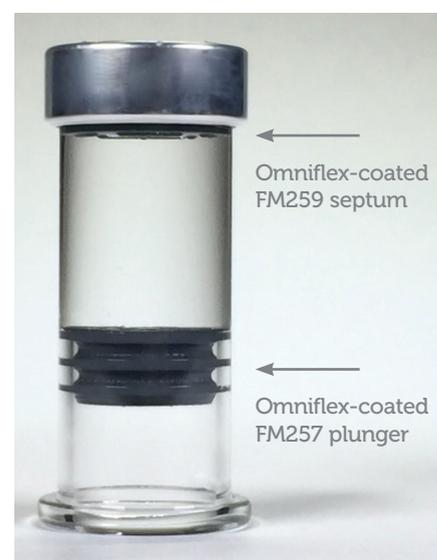


Figure 6: Datwyler Elastomeric Closures for the Unilife Wearable Injector Platform – The collaborative program between Datwyler and Unilife has resulted in a new septum and plunger system designed to meet the demanding specifications of the Unilife wearable injector platform. The customised elastomeric components are coated with the Omniflex fluoropolymer coating technology which results in low extractable levels, low subvisible particle levels and highly consistent delivery forces.

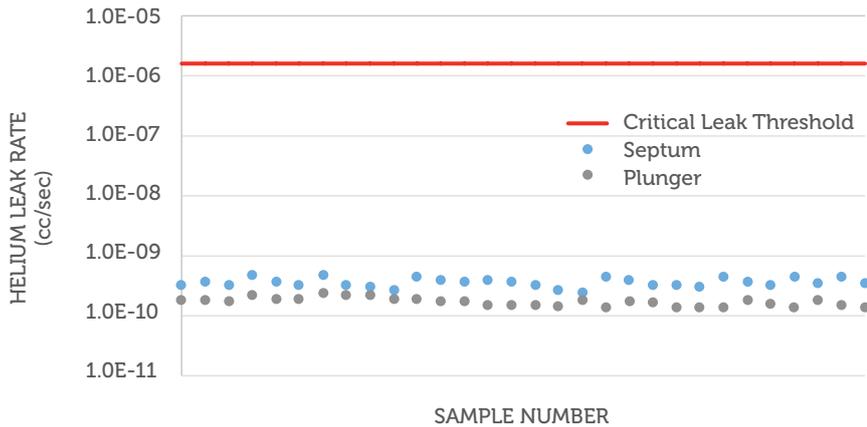


Figure 7: Container closure integrity: helium leak test results from 30 different septa samples (blue) and plunger samples (grey) assembled in the glass barrel. The leak rates are more than three orders of magnitude lower than the critical leak threshold (red line) defined by Kirsch et al.

“The overall functional performance and chemical compatibility of the Unilife wearable injector are influenced by the Datwyler elastomer components”

With the same base formulation ingredients, the FM257 rubber is designed to be harder and well-suited to plunger applications and the FM259 rubber is designed to be softer and shows exceptional fragmentation and resealing properties. Lab-scale Omniflex coating capabilities enabled rapid prototyping of early design iterations prior to scale-up to full production. Some of the key chemical and functional properties of the injector platform which are influenced by the elastomeric closures are discussed below.

Container Closure Integrity

Container closure integrity is the most basic requirement of an elastomeric closure for parenteral packaging. Helium leak testing on each closure used in the wearable injector, as shown in Figure 7, revealed results of $3.6 \times 10^{-10} \text{ cm}^3/\text{s}$ for the septum and $1.7 \times 10^{-10} \text{ cm}^3/\text{s}$ for the plunger assembled in the glass barrel. These values are more than three orders of magnitude lower than the critical helium leak rate considered to be correlated to microbial ingress ($1.6 \times 10^{-6} \text{ std cm}^3/\text{s}$) (Kirsch et al, PDA J Pharm Sci Tech, 1997, Vol 51, pp 195-207).

Low Dead Volume

Especially for biologic drugs which can cost thousands of dollars per dose, ensuring a low residual volume is an essential attribute of any injection device. The proprietary custom designs of the wearable injector’s plunger and septum enable the residual volume to be less than 100 μL , with nominal values ranging between 30-50 μL .

Consistent Delivery Forces

Consistent delivery forces are an important factor in minimising the variability in injection times. Due to both the absence of silicone oil and to the optimised plunger design which eliminates the trim edge, the Omniflex coated plunger has highly consistent delivery forces from three perspectives: 1) consistent forces as a function of displacement (i.e. no stick-slip behaviour)

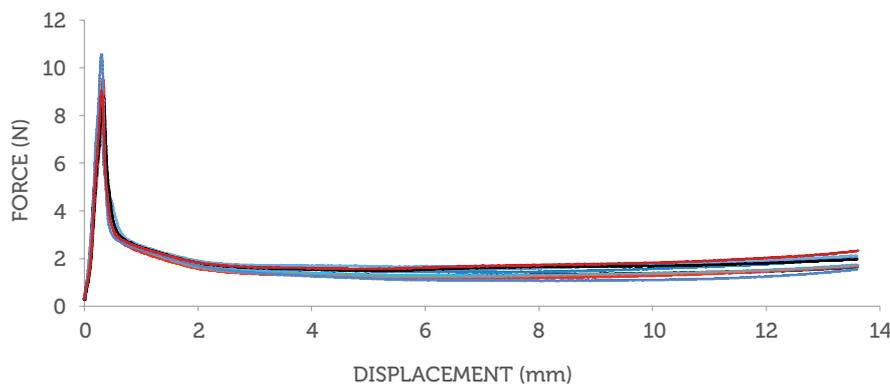


Figure 8: Delivery force profiles from ten different empty Unilife wearable injector samples. The highly consistent profiles are attributable to the Omniflex coating technology along with the optimised plunger design.

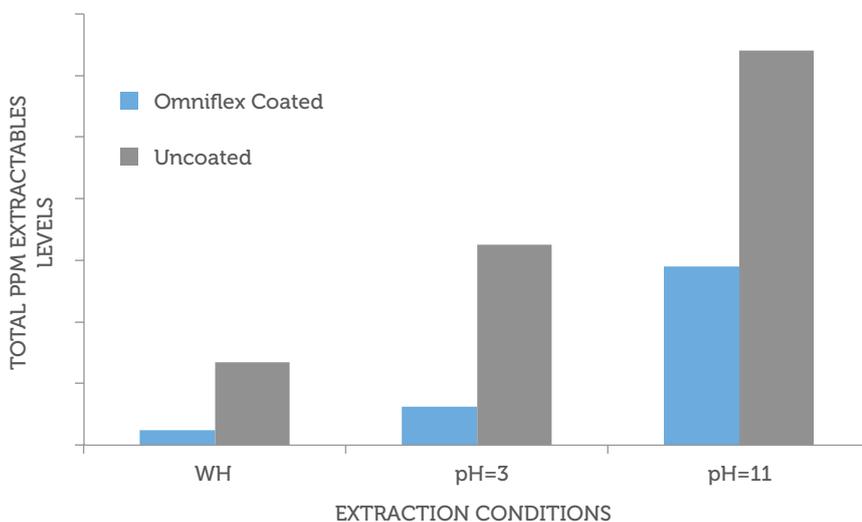


Figure 8. Relative elastomer extractable levels from an uncoated FM257 bromobutyl plunger (gray bars) as compared with Omniflex coated plunger (blue bars).

CUSTOMIZED SEALING SOLUTIONS FOR INNOVATIONS IN DRUG DELIVERY



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- 2) consistent forces from plunger to plunger
- 3) consistent glide forces with aging.

Figure 8 shows the force profiles for ten different empty wearable injector samples. The break-loose forces are typically less than 13 N and glide forces are less than 2 N.

Low Extractables

An advantage of the Omniflex spray coating process is that, in contrast to most film coatings, the entire surface of the bromobutyl closure that is in contact with the container walls and drug product, is barrier coated. As Figure 9 shows, the Omniflex coating is designed both to reduce the number and levels of extractable species from the base rubber including, especially, metal ions.

Elimination of Silicone-Oil-Based Subvisible Particles from the Elastomers

One of the largest sources of subvisible particles in prefilled syringes is silicone oil and studies have shown that the plunger can be a larger source of free silicone than compared to the barrel. (Felsevalyi et al, J Pharm Sci, 2012, Vol 101(12), p 4569.) The Omniflex coating is lubricious and does not require

siliconisation. As such, and as demonstrated by Felsevalyi et al, there is an absence of silicone-oil-based subvisible particles migrating from an Omniflex-coated elastomer and an overall reduction in particle levels of up to 95% versus components siliconised with a low viscosity oil.

No Coring

The septum designed for the Unilife wearable injector utilises the Datwyler FM259 bromobutyl compound in combination with the Omniflex coating. This rubber has a hardness of 39°ShoreA which enables excellent fragmentation and resealing properties. Furthermore, the Omniflex coating stays intact upon puncturing without tearing or wrinkling as may be experienced with a traditional film coating. The septum easi-

“The successful integration of the many components in these devices requires an increased level of co-operation along the entire supply chain”

ly meets the coring requirements of ISO 11608-3 (Needle-based injection systems for medical use – Requirements and test methods – Part 3 – Finished containers.)

SUMMARY

Devices like wearable injectors and reconstitution syringes (the subject of another on-going Datwyler-Unilife collaboration) represent significant innovations in the delivery of biologic drugs and are well-positioned to improve the patient experience. The successful integration of the many components in these devices requires an increased level of co-operation along the entire supply chain. Flexibility, customer focus, and interdisciplinary co-operation make Datwyler the preferred partner for collaborative developments.

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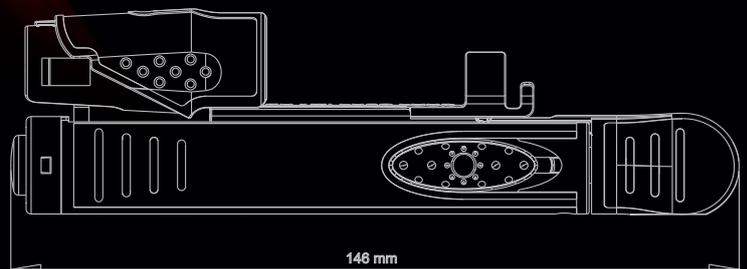
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INTERVIEW: JOCHEN RATJEN, SHL GROUP

As the momentum of self-administrated injection trends continue to increase, auto injector devices are no longer a foreign concept to many patients and device designs have since shifted towards a user-centric approach. The application of human factors and usability engineering is thus necessitated to minimise user-related risks, enhance ease-of-use and, ultimately, allowing them to use the device safely and effectively.

Early involvement of targeted patient groups in user studies during the research and development stages helps engineers not only to understand patient dynamics better, but also to ensure patients' needs are fully integrated into the design of the device. For example, patients with rheumatoid arthritis (RA) may have serious dexterity issues that hinder their ability to uncap or grip a device and properly administer the injection. Thus, a device with customised uncapping or grip options and an exterior that provides additional friction is an example that can prove to be an enhancement for this patient group.

Here, SHL Group's Director of Industrial Design, Jochen Ratjen, shares his insights when approaching the design and development of user-centric auto injectors.

Q: What are some of the key industrial design considerations for an auto injector?

A: As a device partner to biopharmaceutical companies in the design of autoinjectors, communication is key, especially during the early stages of the design process. It is important for us to understand who our targeted users are, what kind of treatment they require, what environment the auto injector will be used in and any associated limitations. These could range from dexterity issues or impaired vision as a result of chronic diseases to simple, intuitive devices that the patient feels comfortable self-administering. Other essential considerations include storage of the device, expected delivery timelines and design requirements, such as whether or not the device should be based on an existing platform or created as a completely new system.

Q: Why is human factors engineering (HFE) important for medical devices like auto injectors?

A: Auto injectors are intended to assist the end-user with the injection process and are most often self-administered by the patients themselves (as opposed to trained health-care professionals). Consequently, applying HFE principles is crucial as incorporated physical and psychological characteristics minimise user-related risks and optimise user compliance.

Q: How do you apply HFE and usability engineering to an auto injector?

A: HFE and usability engineering are applied throughout the entire product development

process and assist us with key design decisions; this is certainly not a factor for consideration solely at the end of the project. Depending on the nature and stage of the project, various usability tools are applied to the process, including but not limited to user-performance studies, interviews, on-site visits, failure mode effects analysis (FMEA), review of existing ergonomic research, and design guidance.

We further aim to increase user empathy with the goal of improving our understand-

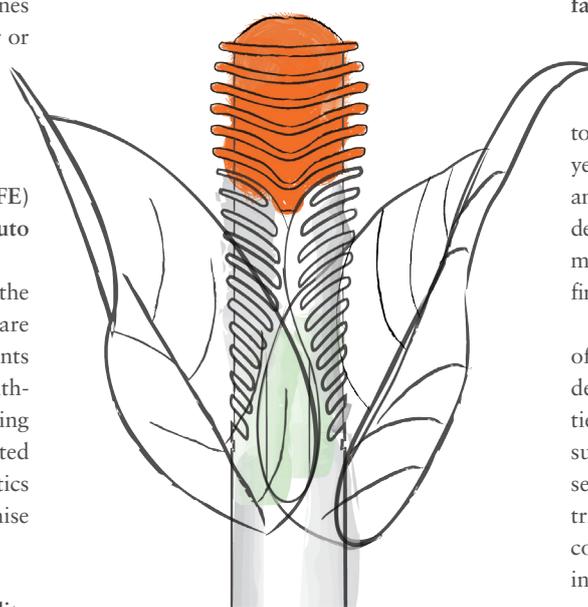


Figure 1: The surfaces surrounding the Amber™ Auto Injector's viewing window, inspired by overlapping leaves.

ing of real users' needs. This is accomplished using various approaches, such as sharing our insights from internal user studies with colleagues, or simply showing an online usage video uploaded by the user— all with the goal to gain better understanding of real users' needs and reality.

Ultimately, we strive to broaden our knowledge beyond identifying factors such as the force required to operate a device or the most comfortable grip – we want to understand the user's emotional context. Indeed, while an auto injector may be simple to use and the cap easy to remove, it is an obsolete device if the user is afraid to use it.

Q: How do you balance clients' user requirement specifications (URSs) and the ideal user-centric design?

A: Our biopharmaceutical clients' strengths lie in their injectable drugs and targeted patient groups, while SHL excels in the design, development and manufacturing of the secondary packaging device component of an auto injector. As such, an important part of my job is helping our partners to understand the design concepts we have created, the usability programs we have performed, and sharing our valuable experience from past projects. By doing so, we collectively ensure a balance is met between the URSs and user-centric design considerations.

Q: What impact does designing for manufacturability (DFM) have on a device such as an auto injector?

A: DFM was in fact one of the main reasons SHL took the strategic decision to establish an in-house design department 14 years ago. This enabled close collaboration and instant communication between industrial design engineers, production teams and project managers. The result is a faster track towards a finalised product for mass production.

Today, one of the valuable products SHL offers is the in-house availability of key design services and manufacturing capabilities for the development of medical devices such as auto injectors. This ranges from services including but not limited to industrial design, regulatory affairs, and quality control systems; to capabilities such as tooling, molding, assembly, and final assembly.

Q: Where do you get your design inspirations from?

A: This differs across the team and is



Figure 2: SHL's range of auto-injector products.

dependent on the individual. Personally, I find inspiration in non-medical fields. Bionics, for example, is an application that is especially intriguing for me as nature never ceases to surprise us. In fact, the design of the surfaces surrounding the Amber™ Auto Injector's viewing window was inspired by overlapping leaves which adds an organic element and steers away from the look and feel of a typical medical device (Figure 1). Furthermore, I like to explore all sorts of hand-held tools, especially when I travel, as this allows me to explore solution variations across different cultures.

Q: What does your team do to stay innovative?

A: I believe my team is very privileged to be working in the medical device field, especially in the design and development of self-injection devices like auto injectors, the purpose of which is to improve the

patient's treatment experience and consequently their quality of life. By always bearing in mind that what we do has the potential to help others, we are motivated to remain innovative in the design and

unprecedented design concepts. Our aim is to never idle in the present; a model which I believe will keep us at the forefront of pioneering the development of drug delivery devices.

"DFM was in fact one of the main reasons SHL took the strategic decision to establish an in-house design department 14 years ago. This enabled close collaboration and instant communication between industrial design engineers, production teams and project managers"

development of next-generation devices. In addition, as a company of Swedish heritage with a strong native culture, we are empowered to take creative initiatives and have the flexibility to experiment with

Q: Can you give us some examples of devices that embody user-centric designs?

A: Integrating user needs has always been discussed, evaluated and prioritised in the development of drug delivery devices. As such, many commercially-available auto injector products have evolved and improved and now show promising user-centric designs, including the range from SHL (Figure 2).

A great example is the Emerade® – an intuitive two-step intramuscular adrenaline auto injector (AAI) for the treatment of anaphylaxis (Figure 3). The design of the Emerade® is the result of a collaborative effort between SHL and Medeca Pharma (Uppsala, Sweden), a pharmaceutical company specialising in allergy therapies.

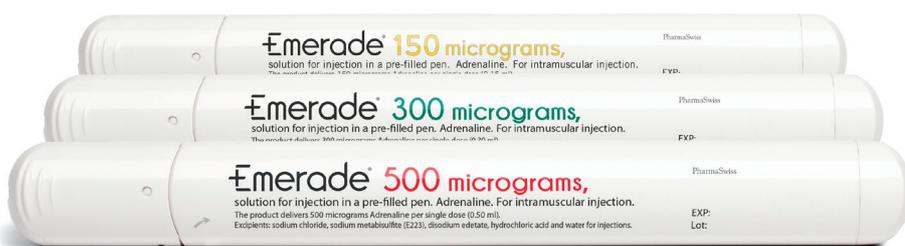


Figure 3: Emerade®, an intuitive two-step intramuscular adrenaline auto injector for the treatment of anaphylaxis.

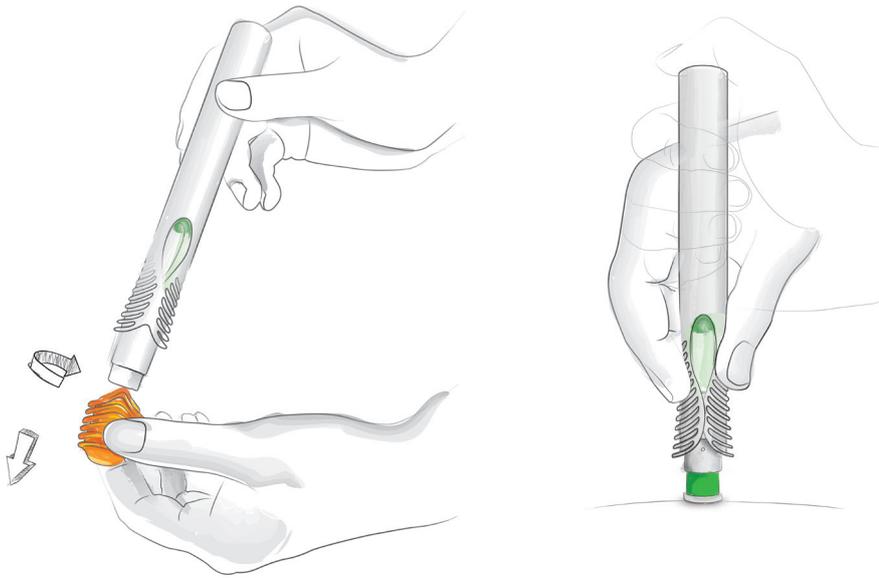


Figure 4: The Amber™ auto injector can be operated in just two simple steps: uncap and inject.

By incorporating Medeca Pharma's years of experience with clinical allergy specialists and the patients themselves, along with SHL's expertise in design and manufacturing, the Emerade® auto injector truly reflects the end-user's needs and has revolutionised the AAI market. The device features a two-step operation, intuitive industrial design, a longer needle and three dosage options. To showcase this device's user-centric design further, a usability study on accuracy of use in a simulated emergency showed that all participants were able to successfully administer the injection in accordance with the label's instructions.

Another example is SHL's internal device, the Amber™ auto injector – that I mentioned briefly previously – which features a unique, ergonomic design that embodies various grip options both during cap removal and on administration. In addition, unique surface extrusions surrounding

needle and a range of audible, visual and tactile feedback mechanisms.

Q: What do you consider an upcoming trend in the industrial design of auto injectors?

A: This is an industry where long development cycles and time-consuming product approval processes can make trends difficult to recognise. However, I do believe a user-centric approach will remain the basis for the industrial design of auto injectors. In the short term, we will continue to see aesthetically-pleasing devices with good usability aimed at different therapeutic areas. Five years from now, I believe we will see a greater number of unadorned, disposable devices with even more simplified performances. These could potentially have the ability to connect to smart communication systems, for improved compliance while reducing costs.

“Five years from now, I believe we will see a greater number of unadorned, disposable devices with even more simplified performances. These could potentially have the ability to connect to smart communication systems, for improved compliance while reducing costs”

the cap and viewing window extend the area of friction for improved handling. Utilising SHL's Pushclick™ technology, the Amber™ auto injector can be operated in just two simple steps: uncap and inject (Figure 4); and integrates essential safety features, including a permanently hidden

Q: What other methods can be provided to enhance the user experience of an auto injector?

A: While we strive to introduce the most innovative and user-centric device solutions, we understand that even the most intuitive device cannot overcome a patient's

anxiety when faced with their first self-administered injection. In order to lessen the impact of this psychological barrier, we recommend the use of needle-free trainers that replicate both the look and feel of the actual device. Trainers can prove to be very effective and provide users with an opportunity to practice handling the device without the fear of incorrect administration and should thus be taken into consideration by biopharmaceutical companies at an early stage in the project's lifecycle.

Aside from SHL's comprehensive range of in-house manufacturing capabilities, the company has invested significantly in R&D in recent years, expanding their design and innovation teams in Sweden, Florida, US, and Taiwan. This is in large part to better support our customers with breakthrough devices that provide their products with a strong competitive edge while simultaneously meeting previously unrealised user needs.

SHL designs, develops, and manufactures a diverse range of drug delivery devices to address existing and upcoming injectable needs, including auto injectors, pen injectors, and inhalers. Requirements include but are not limited to accommodating various primary containers as well as increased agent viscosities or volumes. With the goal of improving patient compliance, SHL's comprehensive portfolio offers devices with simple two-step operations, ultra-compact designs, ergonomic exteriors, innovative feedback systems and more.



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COMPANY PROFILE: KAHLE AUTOMATION



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COMPANY PROFILE: **HASELMEIER****User Focus**

At Haselmeier, our mission is to create products enabling a convenient and comfortable experience. This is why patient feedback is integrated early in our device designs. Early concepts are prototyped for testing and Human Factors studies to capture the handling needs and skills of potential users. This knowledge is integrated into the device design to provide successful administration of the drug product and a positive user experience.

Haselmeier offers a range of early-stage activities:

- Think-tank discussions and paper concepts
- Detailed product concepts and industrial designs
- Detailed user handling review and risk-analysis
- Prototyping of initial concepts up to functional devices
- User focus groups and human factors studies for concept and prototype evaluations
- Detailed user requirements and product design specifications based on selected concept.

**Bridge to Market**

Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements. At Haselmeier we provide integrated design, development and industrialisation services to help you bridge your serial product into the market. Our qualified design control process, certified quality system, regulatory expertise, solid network of partners and strong manufacturing operations are all designed to achieve

your expectations. Together we enable a smooth market introduction for your commercial drug delivery device.

Haselmeier's commercial development and industrialisation services include:

- Concept transfer into detailed User Requirements and Product Design Specifications
- A certified Design Control Process and Quality System
- Design verification, product and process validation processes

- A strong network of sub-suppliers and manufacturing partners
- Continuous Engineering and product improvement programme
- Innovation meetings to identify next product generation.

PLATFORM & PRODUCTS

The Haselmeier Axis-D Pen System (Figure 1) is a disposable, variable-dose injection device designed for the use with

"Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements"

- Regulatory expertise to support your approval strategy
- Controlled design-to-manufacturing transfer, verification and validation.

**Manufacturing & Lifecycle Partner**

We understand that each customer has individual and specific requirements for their product. Regardless of your requirements, Haselmeier applies the highest quality standard for manufacturing your drug delivery device to ensure a reliable and reproducible manufacturing and quality process. We work continuously with our customers to identify product improvements at all stages of the product's lifecycle to provide a safe and state-of-the-art drug delivery device.

Haselmeier provides flexible, reliable, manufacturing and lifecycle management:

- Certified and modern production facilities and manufacturing processes
- Qualified and well trained personnel

a 3 mL cartridge. The elegant and compact Axis-D Pen System is available as a high quality plastic version.

- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale.

The Haselmeier i-pen (Figure 2) is a reusable, variable dose injection device for use with a standard 3 mL cartridge. The

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COMPANY PROFILE: **HASELMEIER**

“We understand that each customer has individual and specific requirements for their product”

i-pen features an elegant non-medical design which is the result of extensive research and patient testing.

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body.

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

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components

The Softpen (Figure 4) is a fully automatic, reusable injection device featuring Haselmeier’s patented hidden needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution.

- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3ml cartridge.

The Haselmeier disposable Penlet (Figure 5) is a fully automatic, fixed dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue, which is followed by delivery of the solution.

- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection.



Figure 1: The Axis-D Pen System – disposable, variable-dose injection device designed for the use with a 3 mL cartridge.



Figure 2: The i-pen – reusable, variable-dose injection device for use with a standard 3 mL cartridge.



Figure 3: The i-pen² is a reusable, variable-dose injection device for use with a standard 3 mL cartridge.



Figure 4: The Softpen – a fully automatic, reusable injection device featuring Haselmeier’s patented hidden needle design.



Figure 5: The Penlet is a fully automatic, fixed-dose injection device

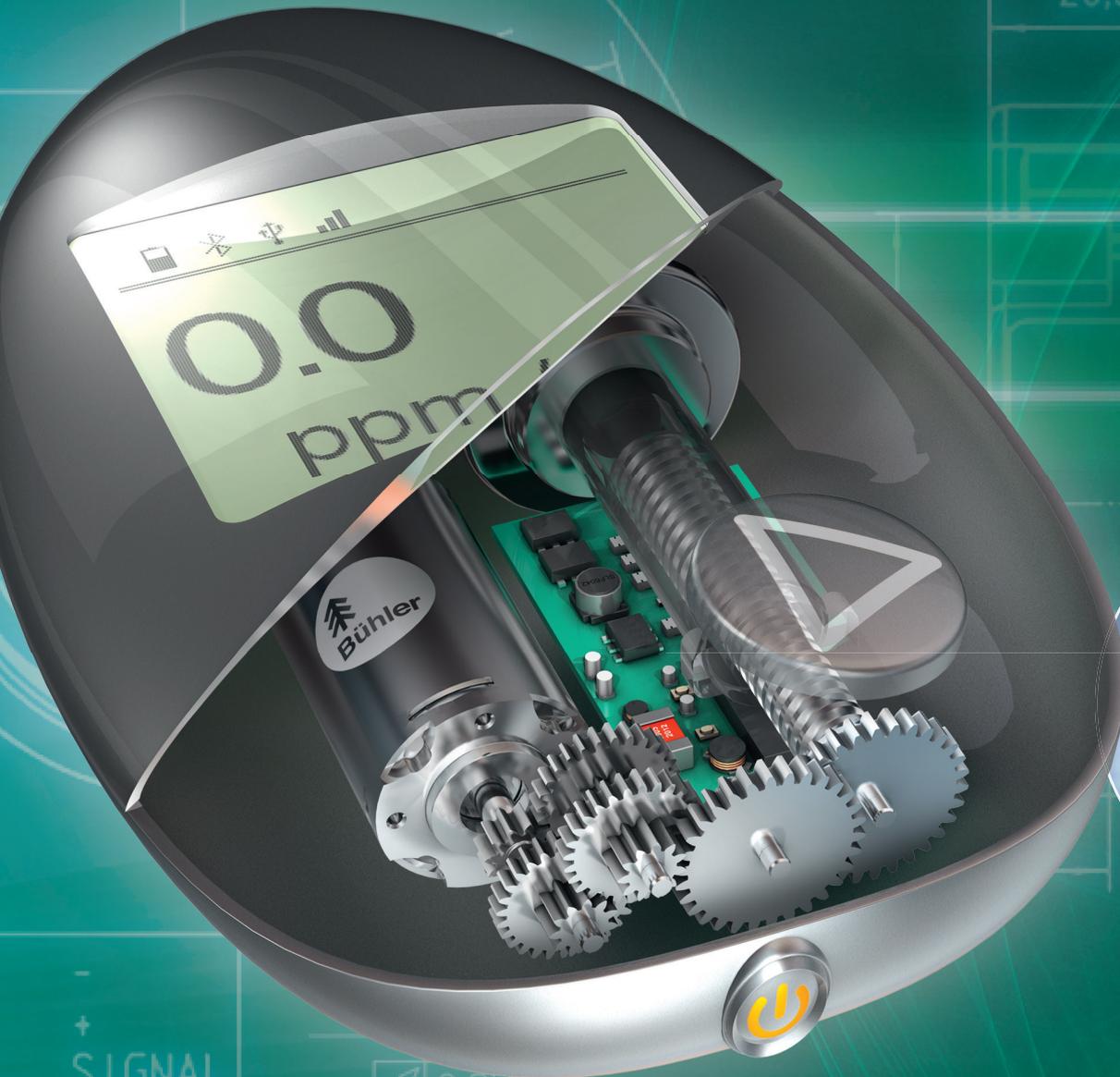


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Partnerships Built on Innovation

SCALABLE AUTOMATION FOR DRUG DELIVERY DEVICES

Today's medical device and pharma industry assembly concepts can be complex. Here, Bill Welch, Chief Technology Officer, Phillips-Medisize, outlines why, therefore, the company provides a comprehensive assembly concept, tailored to customers' needs. Scalability begins with early DFM/DFA philosophy integrated into the product development process.

It is commonly estimated that 80% of a product's cost and quality is determined during the first 20% of the product development timeline. As such, whether the commercialisation strategy involves in-house manufacturing or the use of a contract manufacturing organisation (CMO), early integration

design conforms to the guidelines for the manufacturing process to be used. This is especially critical in drug delivery devices, since plastics are the most common material for mechanical components. Further, component-level DFM forms the backbone of the assembly process – regardless of the planned level of automation – since the process capability at the component level is necessary to reduce variation in the assembly process.

“Successful DFM/DFA needs to be an underlying philosophy truly integrated into the product development process. It cannot be viewed as a “checklist”, step, or phase to be completed on the individual components after the drug delivery mechanism design is nearly complete”

Similarly, DFA is done concurrently with product design, with quality, cost, and risk of the assembly in mind. At the component level, this includes addition of features to make part handling, positioning, orientation, and inclusion into the assembly or sub-assembly. Component-level DFA ensures a mistake-proofing plan is established, which is also necessary

of a strong design for manufacture (DFM) and design for assembly (DFA) philosophy is critical to the device quality, cost and risk during clinical builds and commercial launch. A strong DFM/DFA philosophy ingrained within the product development process ensures manufacturing quality, cost, and risk objectives are met, without losing sight of HFE and the end-user device needs.

In a more general sense, DFx refers to “design for x”, in which “x” may be any desirable attribute. At the component level, DFM, or the more specific design for mouldability for injection moulded components, refers to ensuring the product

to reduce variation in the assembly process.

Additional benefits are gained by concurrent DFM/DFA throughout the product development process, for example to reduce part count and eliminate high-risk assembly operations. Multimaterial, or multishot, moulding is one approach to combining components that eliminate complex assembly operations and provide an elegant solution to design problems such as sealing to prevent moisture intrusion. Early DFM/DFA team collaboration can then evaluate the return on investment of the upfront mould tooling costs to reduce assembly equipment and labour costs, prior to finalising the design.



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BOX 1: FIVE LEVELS OR CLASSIFICATIONS OF ASSEMBLY

In order to facilitate development of a manufacturing strategy, it is useful to leverage a high-level common language and terminology for tooling and assembly classifications. Such classifications are not intended to replace the actual specifications, but simply to ensure all team members can understand and agree in concept as to the initial, interim, and final approaches to be taken to meet engineering, clinical and commercial volume requirements.

Achieving conceptual agreement and alignment as rapidly as possible allows the tooling and automation engineering specialists to develop the detailed specifications right the first time, thereby eliminating rework that increases resources needs and timeline.

The table below shows the five classes Phillips-Medisize uses to describe different levels and types of assembly, and examples of Class II and III assembly lines are shown in Figure 1.

	Step Change Required	Step Change Required	Scalable Process		Prototype Process
DMC Classification	Class I	Class II	Class III	Class IV	Class V
Relative Description	CAM Driven, multi-up, fully integrated, high speed automation. Human precense required for monitoring only. Self diagnostic with built in compliance and integrity checks.	Rotary Indexing Table or Integrated Linear System, with automated part feeding/conveyance. Single or multi-up capable. Fully automated work cell. Limited human interaction.	Scalable Manumation with multiple station and multiple operators.	Manumation with a single operator station.	Manual Operation that may include hand press, special tooling, and part fixtures.
Types of Use	Automated Production	Automated Production	Combination of Full / Semi- Automated	Semi-Automated	Manual Operation
QA Requirements	Automated Inspection & DAQ	Automated Inspection & DAQ	Some Automated Inspection, No DAQ	Manual Inspection	Manual Inspection
Product Handling	Automated Conveyance	Automated Conveyance	Conveyor or Robot	Conveyor / Manual Transfer	Manual Transfer
Capacity	~ 20MM EAU	~ 5MM EAU	~ 1MM EAU	~ 0.50MM EAU	~ 0.10MM EAU
Capability*	Established Global Provider	Established Global or Regional Assembly Line Provider	Established Regional Assembly Line Provider	Regional or Local Assembly Line Provider	Regional or Local Assembly Line Provider
Cycle Time	1 PPS	10 PPM	5 PPM	5 PPM	2 PPM
	e.g. injection pens	e.g. safety syringes	e.g. filters	e.g. insulin pumps	e.g. IV-Sets

*Requires ASL Grading

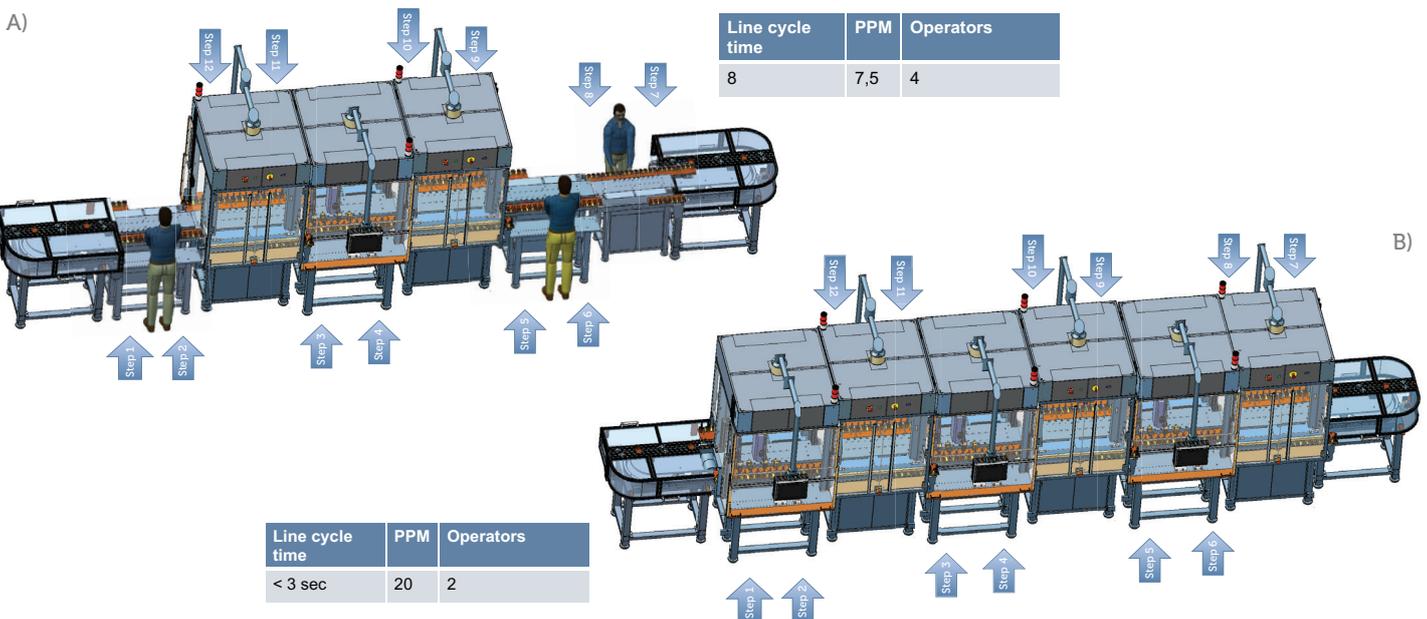


Figure 1: Examples of different classes of assembly line with A (top) showing a Class III line, partially automated with manual stations achieving 7.5 parts per minute (PPM) and B (bottom) showing a fully automated Class II line achieving 20 PPM.

While DFM/DFA must start at the component level to facilitate future scalability, the application of DFAA (Design for Automated Assembly) is also applied concurrently by the DFM/DFA team. DFAA is the next level, designing assembly processes in which components are oriented, handled, assembled, and transported through an assembly process without manual intervention.

- DFAA focuses solely on the automated assembly process, which is defined as “automated” only if the process does not require human interaction
- DFAA application makes interim manual assembly processes to support builds prior to automation build and validation easier. A device that is easy to assemble manually will lend itself to automated assembly. Component-level DFA alone does not develop processes suitable for automated assembly
- DFAA requires specialised automation engineering involvement in the beginning phases of the development process to ensure automated assembly is taken into consideration in parallel with other DFx.

Box 2 summarises ten often overlooked DFA/DFAA guidelines for drug delivery devices.

In summary, successful DFM/DFA needs to be an underlying philosophy truly integrated into the product development pro-

cess. It cannot be viewed as a “checklist”, step, or phase to be completed on the individual components after the drug delivery mechanism design is nearly complete. While at the component level an understanding of the DFM guidelines for the intended manufacturing processes is key, the greatest benefit comes from looking beyond component-level DFM/DFA to find system- or sub-system level solutions that enhance device performance while meeting human factors, quality, cost, and risk requirements.

SCALABILITY TO MEET END-VOLUME REQUIREMENTS

Increasing volume and varying production on a single system platform? Feasible! Scalability is the process to develop the manufacturing scale from the initial low-volume methods to the desired end-state volumes. In the case of a specialised, niche drug delivery device this may mean progressing from low-volume, 3D-printed components assembled by skilled technicians to a “manumation” assembly process conducted by a trained operator. In the case of a commonly used drug delivery devices, this typically means developing processes to support first engineering builds, then clinical supply, and finally a fully automated or high-speed automation process, supported first by developmental, single-cavity tooling and then incrementally higher multi-cavity tools.

Flexibility, while related to scalability, has its own definition as it relates to two primary concepts:

1. Ability to re-use assembly equipment modules when progressing from one scale level to the next, in order both to prove-out initial assembly concepts at lower scale, and save time and cost by leveraging that same equipment
2. Ability to use all or most of an entire base flexible assembly line to produce multiple, similar devices. In the case of pens and auto-injectors, this typically means matching up a device product platform with an assembly platform, with changes being primarily in the components presented to the line following a controlled line clearance and changeover process.

As with DFM/DFA, scalability considerations must be looked at concurrently with product development as part of a device manufacturing concept which is a device-specific plan to scale component and assembly production capabilities to a desired end-state, typically with iterations for both components and assembly to meet engineering, clinical, and commercial volume demand.

A well-constructed device manufacturing concept will not only consider the volume, costs, and timing of device needs, but also the regulatory requirements, risks, and geographic considerations with each iteration

BOX 2: TEN BASIC DFA AND DFAA GUIDELINES

While not all-inclusive, shown below are ten basic and often overlooked DFA and DFAA guidelines for drug delivery devices:

1. Ensure component-level DFM is applied to provide a stable and capable supply to the assembly process
2. Simplify the design and reduce the number of components, utilising techniques such as multi-material moulding for plastic components
3. Standardise and use common components and materials, both within and across drug delivery device assemblies, to minimise tooling, validation, and supply chain management costs
4. Ensure component-level DFA is applied for stable and capable orientation, handling, and placement
5. Minimise the use of fasteners, flexible components, interconnections, and adhesive / lubricant dispensing operations
6. Design mistake-proofing, part presence checking, in-line quality controls, and segregation of failed or rejected components, into the assembly process starting with initial builds
7. Design for robust assembly by minimising complex orientations and axes of assembly, beginning with components with suitable “lead-in” taper and location features
8. Manage final assembly cost and risk by strategic selection of sub-assemblies and modules in the assembly process, and

ensuring high-value components and sub-assemblies are known to be of acceptable quality before integration into the next level of build

9. Design for flexible assembly to minimise time and cost associated with equipment, validation, and change-overs:
 - a. Design components to use the same or similar bowl feeding, pallets, or other methods to introduce to the base flexible assembly line.
 - b. Design components and assembly sequence to use the same or similar assembly and joining methods already included in the base flexible assembly line.
 - c. Develop a standard set of product requirements to be subsequently inspected or tested on the base flexible assembly line
10. Design for high-speed, automated assembly:
 - a. Use components that can be fed without tangling. In the case of springs, consider making the springs as part of the device assembly process
 - b. Pre-orient the components when presented to the line to reduce cycle time
 - c. Integrate finished device handling, packaging, and palletisation into device assembly and facility planning, since high-volume devices require purpose-built infrastructure beyond the assembly equipment itself.

of the scale-up plan. It provides clearly structured, modularly designed assembly lines which can be extended at any time, allowing fast retooling times. Essentially, the device manufacturing concept provides

ing the single-track configuration.

Equipment and tooling supplier selection is an important factor of the device manufacturing concept, and consistent with DFM/DFA the suppliers should have early

“A well-constructed device manufacturing concept ... provides clearly structured, modularly designed assembly lines which can be extended at any time, allowing fast retooling times”

the “roadmap” to progress from initial, limited control engineering builds to the validated end-stage scale, meeting all quality system and regulatory requirements.

Core to the device manufacturing concept is a strong assembly systems foundation, starting with the earliest manual builds to ensure the manual process is feasible for scaling:

- Early manual builds need to establish the assembly sequence, fixturing, component orientation, and assembly operations that will be carried forward to subsequent scaling iterations
- Proper manual assembly is an enabler for higher level automation. Conversely, as mentioned above, a DFAA analysis may lead to a more robust manual assembly
- Collect and analyse reject / scrap data to reduce variation with each subsequent scaling iteration. It is imperative to ensure proof of concept has been achieved for each process before making further scaling investment
- The user requirements specification (URS) for a manual process needs to set the stage for the URS on the desired end-stage automation level. In some cases, it is helpful to draft the URS for the high volume automation first, and ensure as much as possible can be learned from the manual process.

In terms of flexibility, the re-use of assembly platform equipment is typically limited. For example, a core single-track assembly process cannot cost effectively become a four-track system such as that used for a typical high volume pen, but a single-track line platform may be scaled from manumation to semi-automation to full automation with upgrades to component feeding, orientation, assembly, and inspection / test operations which maintain-

involvement. While ideally the same suppliers can be used for all iterations of the same equipment and tooling, in many cases this is not feasible or practical due to the technical focus, timing requirements, or global support capabilities of the supplier. For example, a quick-turn tooling shop and local equipment builder may be necessary to maintain timelines for single-cavity moulds and manual assembly fixtures, but they do not have high-volume capabilities or a global service network. In such cases, it is imperative that the manufacturing unit or CMO possess the project management, tooling engineering, and automation engineering skills to develop suitable URS and ensure any learning from initial stages is carried over to subsequent scaling iterations.

It is critical to focus the URS on its intent, which is to define clearly and precisely what the equipment should do, and state any constraints. It is a requirements document, and not intended to be a technical document defining the system itself. Given that the URS will drive the validation requirements, it is recommended to take a modified “specific, measurable, achievable, realistic, and testable) SMART approach to URS development.

IMPORTANCE OF GAMP

The Good Automated Manufacturing Practice (GAMP) standard provides practical guidance to meet current regulatory requirements through efficient and effective use of industry practices. Given its purpose to facilitate interpretation of regulatory requirements and establish a common language and terminology, it can be tailored to a number of system types. The core principal of GAMP is that quality must be built into the manufacturing process and should not simply be measured after the product is made. Following GAMP ensures that pro-

cess quality is a consideration when designing and fabricating automated assemblies and equipment.

GAMPs Key Concepts:

- Product and Process Understanding
- Using a Life Cycle Approach
- Scalable Life Cycle Activities
- Science Based Quality Risk Management
- Leverage Supplier Involvement

So what does this mean for automation and Phillips-Medisize customers? It means that our customers in the medical device, pharmaceutical, and life sciences industries are assured that our machines are designed and built under a quality management system. It begins with a URS for the machine, from which a functional requirement and a design specification is created. Those documents are the basis for the traceability matrix for the formal testing milestones of internal acceptance, factory acceptance, and site acceptance. Phillips-Medisize automation processes are GAMP-5 compliant, providing our customers the quality of service they require.

SUMMARY

Scalability for drug delivery devices begins with concurrent engineering via DFM/DFA and development of a device manufacturing concept. Use of common definitions for classifications of tooling and assembly equipment can be used to align the team on the concept, and enable the tooling and automation engineers to then specify, via the URS, the process requirements and select the appropriate suppliers for each scaling iteration. Therefore, the manufacturing unit or CMO must have the capabilities to provide effective DFM/DFA and development of a device manufacturing concept, in addition to capabilities for the project management and technical execution of the plan.

Phillips-Medisize has a long experience in managing different kinds of assembly concepts, from low-volume (smart assembly) through high-volume (high-speed automation) and is able to find the optimal assembly concept by looking at costs, volume and ramp-up schedule to meet the targets within budget, time and specification. Strategically-located resource centres support global manufacturing operations, and the companies’ global footprint allows flexibility in production while optimising capacity.

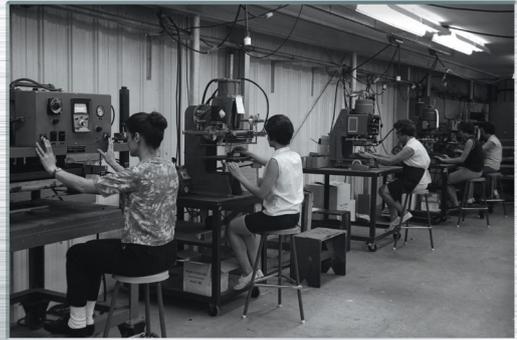
ONdrugDelivery 2015 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
June 2015	Novel Oral Delivery Systems	Now Closed
July 2015	Wearable Bolus Injectors	June 1st
October 2015	Prefilled Syringes	September 7th
November 2015	Pulmonary & Nasal Drug Delivery	October 5th
December 2015	Delivering Biotherapeutics	November 9th
January 2016	Ophthalmic Drug Delivery	December 14th
February 2016	Prefilled Syringes	January 11th
March 2016	Transdermal Delivery & Microneedles	February 8th
April 2016	Pulmonary & Nasal Drug Delivery	March 7th
May 2016	Injectable Drug Delivery: Devices Focus	April 4th

At Phillips-Medisize We're All About Process



This



Not This

We know process is the absolute key to assuring that we deliver upon our customers' expectations, **the first time and every time**. That's why our people are all about process. In fact, our process requirements apply not only to manufacturing and quality SOPs, but also to our customer facing operations such as Program Management and Design and Development engagements, ensuring our customers benefit from a repeatable and scalable model.

So, when you work with Phillips-Medisize, you can be certain we'll exceed your highest expectations **the first time and every time**.

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AUTOMATION FROM ZAHORANSKY WITH OWN AUTOMATIC NEEDLE- FEEDING SYSTEM FOR PRODUCTION OF READY-TO-FILL PREFILLABLE SYRINGES

In this article, Harry Pruner, Freelance Journalist, Pruner Marketing Services, describes the automated assembly equipment offered by ZAHORANSKY AG for the production of ready-to-fill, prefillable syringes.

As a supplier of automation equipment for the manufacture of drug delivery systems, ZAHORANSKY provides the Z.BLIZZARD system for the glueless production of staked-needle syringes (Figure 1). It combines complete needle isolation, the injection mould and the automation into a single unit.

Z.BLIZZARD is an integrated automation solution in modular design, allowing the isolation and glueless over-moulding of cannulas. The Z.BLIZZARD system features both the needle feeding system (Z.NFS) (see Figure 2) and the injection moulding machine with mould (Figure 3). The integrated Z.NFS is also modular in structure, with the effect that different

design variations of cannulas can be processed within the specification. The Z.NFS is capable of handling needles, cannulas and lancet devices in various lengths and diameters. Optionally, even needles and cannulas with ground or shaped sections can so be aligned automatically and then carried to downstream processing.

ZAHORANSKY offers needle isolation systems (Figure 4) capable of singularising between four and currently 32 needles or cannulas with as much as 12 cycles per minute. Diameters range from 0.2 mm upwards, lengths of as much as 40 mm are handled properly. There are plans for more model sizes to enlarge the delivery range.



Figure 1: The Z.BLIZZARD system for the glueless production of staked-needle syringes.

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Z.NFS SYSTEM, IDEAL NEEDLE ISOLATION FOR MEDIUM BATCH SIZES

The market already offers a number of different solutions for needle isolation, but many of these systems have been designed for producing very large unit quantities. With its new Z.NFS unit, ZAHORANSKY closes the downward gap for delivering as many as 400 cannulas per minute, covering the general tendency in the industry toward smaller batch sizes and higher redundancies and toward multiple units for smaller volumes.

The new Z.NFS system allows the quick conversion to similar products or the flexible production in the event of breakdowns without causing delivery delays or keeping stocks high as a safeguard. The new Z.NFS system has been designed such that it can be used smoothly for inserting needles in automation equipment, moulds or injection moulding machines.

FIVE STEPS TO NEEDLE ISOLATION

Generally speaking, the full function sequence of the isolation process right through to overmoulding can be divided into five steps. The first step involves mounting the filled magazine, followed by splitting off and separating the needles from the magazine by gripping or vacuum pickup. The next step is the visual check for “all needles available”. Finally, the needles are fed for overmoulding or further processing using a gripper head with a linear robot or an alternative automation component of the injection moulding machine or a downstream automation device.



Figure 2: The Z.NFS – ZAHORANSKY Needle Feeding System.

The five steps in detail are:

1. Needle Magazine Filling

There are several options for filling the compact and transport-safe magazines. Either customers themselves fill the magazine or they have it filled by their needle supplier. The magazine is used internally or externally as a reusable transport unit, with the design of the magazine guaranteeing the safe transport of the needles to the point of processing.

Keeping a second ready-filled magazine in stock in the Z.NFS unit is another advantage, allowing the fast mechanical or manual changeover. The ideal variant

– virtually without any downtimes – is ZAHORANSKY’s optional automatic magazine changing device where as many as two ready-filled magazines are installed additionally in the Z.NFS system that are changed automatically. This has the added advantage that the operator does not touch the needles, with the effect that contact contamination by personnel is largely ruled out.

2. Needle Isolation

To isolate the needles, a partition slide equipped with the desired number of notches matching the design and size of the needles passes underneath the loaded magazine by means of a left-right movement, placing a needle in every notch.

This movement is servo-electrical and can therefore be controlled with SPC device.

Once the final position is reached, the needles are either taken by mechanical grippers or released for vacuuming through stainless steel tubes. The isolation process is now repeated by the partition slide moving in the opposite direction until it is located in front of the second vacuuming or gripper station.

The isolation from the magazine follows the first-in-first-out principle (FIFO) which ensures the best possible batch processing of the needles. This would be a substantial advantage if the batch needed to be tracked at some point later. Production in medical category 1 and 2, but also in category 3 is possible.

3. Visual Completion Check

A sensor mounted to the left and right of the feeder magazine checks the needles in transit to ensure that they are complete. While moving in the direction of the final position, it also checks if the required number of needles is available. Once the partition slide moves back, a check is made to ensure that all the needles have been duly removed for further processing.

4. Transporting Isolated Needles

There are two equivalent options for carrying to the syringes’ cavities – rearward suction or mechanically gripping the separated cannulas.

The needles separated by the partition slide are vacuumed off at the same time. To do so, a transfer station with the tubes leading to the gripper head or the transfer unit docks against the separated needles. For the vacuuming process, a gripper head docks at the other end of the tube, triggers a suction impulse and sucks up the needles without damaging the tips or the grinded section. The resulting vacuum positions the



Figure 3: Cannula mounted in b-side of injection mould.

needles against the corresponding stop in the gripper head. The cannulas are gripped directly at the partition slide, with one gripper head located at each end position of the partition slide removing the cannulas and taking these to the transfer position required for further processing, from where they are taken off aligned in the proper position. Every part making contact with the product is subject to the stringent US FDA and GMP regulations and is corrosion resistant and designed compatible with the product.

5. Handover of Loaded Gripper Head to Injection Mould

Before insertion, checks are carried out at various points to make sure that the following injection moulding process proceeds without any rejects. In line with the number of cavities in the injection mould, the cannulas are aligned and transferred to a handling system which first checks whether they are in place and in the correct position.

A two-axes linear unit hands over the cannulas placed on a holding plate into the mould cavities on the ejector side. There, they are already exactly positioned matching the mould inserts. Parallel to the insertion phase in the mould half on the closing side, the already injected parts are at the same time removed on the nozzle side mould half via a six-axes robot. This substantially reduces the cycle time, as feed-in and removal take place at the same time.

The injection mould used is a ZAHORANSKY patented Stack Mould System. The special features of this patented system are the two parting lines, allowing cannulas to be inserted and to remove ready overmoulded cannulas at the same time.

Injection is done by utilising an Ewikon (Frankenberg, Germany) hot runner system with needle valve gate. The material used is a high-grade technical polymer, mostly cyclo-olefin copolymer (COC) or cyclo-olefin polymer (COP).

The cavity inserts are heated, while the rest of the mould is cooled normally. To do so, the inserts are thermally separated from the mould in order to minimise the energy loss and to accomplish a thermal equilibrium in the system quickly.

EASY PRODUCTION CHANGEOVER

In designing the system, ZAHORANSKY engineers also focused on the easy, quick and cost-effective refitting during a production changeover. During a product change, essential components of the Z.NFS system



Figure 4: Detailed view of needle isolation.

can be used again for a later use. Especially in the production of smaller and medium batch sizes, this flexibility offers substantial cost benefits compared with rigid systems designed only for a single product.

ADDITIONAL STEPS AND FUNCTIONALITY

Additional external automation equipment makes the system even more convenient. After the isolated cannulas are handed over to a gripper head, the needles are delivered either to an injection moulding machine for direct machining or to another automation equipment item. A system for bending the needles for higher retention forces, beading the blunt end for better piercing strength, or aligning the grinded cannula tips, for example, are conceivable downstream processing steps.

Depending on application, the machined needles are servo-motor removed, fed-in and placed back in position either by a six-axes robot or a linear handling unit. If the needles are carried into the injection mould directly for overmoulding, a linear axis is used. Before being transported further into the downstream unit – in most cases an injection moulding machine – the needles are normally checked for completeness. If the insertion gripper is not completely filled, the machine operator, or the previously specified procedures in the system control unit, decide whether the missing needle should be replenished or whether the complete content of the gripper head should be discarded. Another option involves an intermediate station to make the fully automated orientation of the polished needles.

Laser devices check both the feed-in of the needles and the overmoulded needles for completeness. The finished syringe bodies can then be siliconised in an integrated follow-up station to improve the sliding property of the needles. Other operational steps could possibly include placing a protective cap on top or a subsequent X-ray test to ensure that the integrity of the tip of the syringe is guaranteed and that the overmoulded zone complies with requirements.

This step is followed by automatic packaging in standardized or customer-specific trays, ensuring that particle contamination caused by hand contact is prevented or at least minimized throughout the whole of the process chain.

ABOUT ZAHORANSKY

ZAHORANSKY AG is a full-range supplier in machinery and production lines, sophisticated, innovative injection moulds and automation equipment. The company operates with over 600 associates at production sites in Germany, Spain, China, India and the US.

System Technology offers across-system solutions for injection-related automation. These systems are based on injection moulds by ZAHORANSKY AG and on established systems from different modules of automation. Intelligent and injection-related automation solutions can be composed with these modules.

System Technology serves the areas of industrial automation and medical devices, with pre-configured solutions provided for medical engineering. Z.BLIZZARD, for example, is an integral solution for making prefilled syringes as primary pharmaceutical packaging.

Automation solutions from the **toolkit**

- System modules for automating manufacturing processes around injection molding
- can be combined individually
- for high-availability systems



Z.NFS



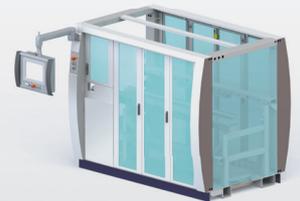
Z.BLIZZARD



Z.ZYKLON



Z.SIROC



Z.MISTRAL

Starting from a toolkit of preconfigured automation modules, we work with you to develop a flexible solution for manufacturing your plastic products for industry, consumer goods, and medical technology. Efficient, and cost-effective. We will be happy to advise you.
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BIOCORP

BEYOND TREATMENT

DEVELOPING CONNECTED DEVICES TO IMPROVE THE INTEGRATED STANDARD OF CARE

Here, Eric Dessertenne, Head of Commercial Operations and Business Development, and Edouard Poisson, Business Developer, both of Biocorp, introduce mHealth – the growing field of devices and apps that use mobile communications for healthcare – describe the importance of integrating medical devices with software in order to achieve the best results, and present their mHealth product, DataPen, a subcutaneous injection device that is connected with a mobile app using Bluetooth. The authors outline the various advantages that such a system brings, describe how they ensure security is maintained, and update us on the development status of the project.

INTRODUCTION

During the last decade, numerous studies on health information technology have underlined the positive impact of *eHealth* and *mHealth* on the healthcare system and patients' health. *eHealth* is the transfer of health resources and health care by electronic means. The term *mHealth* covers all devices and/or apps using mobile communications for health services. A review of the recent literature on the benefits of health information technology shows predominantly positive results with 92% of 154 included studies being positive or mixed-positive.¹

These innovations are fuelled by healthcare sector needs and smartphone industry growth. Globally, there is a strong demand for new solutions to treat the rising number of people with chronic conditions and manage efficiently the growing healthcare expenses. Meanwhile, the booming smartphone industry is helping the spread of *mHealth* technologies, with more than one billion smartphone users worldwide in 2014.

Mobile health applications offer several opportunities such as lower healthcare costs, improved treatment outcomes and enhanced point-of-care delivery. Stakeholders from the entire healthcare industry have strong expectations concern-

ing *mHealth* technologies:

1. Physicians strongly believe mobile health systems can help them give more informed clinical decisions and increase their patients' engagement
2. Patients favour medical treatments aligned more closely with the fluidity of their daily life
3. Payers face growing hospitalisation costs and need new processes to lower expenses
4. Pharmaceutical companies expect improved point-of-care delivery can bring new added value to their treatments.

THE IMPORTANCE OF MEDICAL DEVICE-SOFTWARE INTEGRATION

The rapid expansion and broad applicability of health-oriented software products have made it more complex to differentiate applications in one category, dedicated to mobile integrated therapies, from those in another, the lifestyle and information apps. The largest share of mobile health apps available today for download belong to the second category with apps that aim to inform users or help them improve their general health but do not target specific therapeutic areas (e.g. fitness, medical reference and wellness). These *mHealth* applications may be combined with wearable technology but are not integrated to a treatment. The



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Figure 1: Biocorp's DataPen, a reusable injection pen connected to a smartphone app.

mHealth apps from the first category help patients suffering from particular conditions in different possible ways (e.g. medical condition management, remote consultation and monitoring, compliance, etc). The *mHealth* apps belonging to this category, which are the focus of our study and also the focus of the US FDA's regulatory oversight, may have a significant impact on treatments and on the overall healthcare system.

However, these mobile applications often encounter the same obstacle: patients do not use them enough. Their retention rates are too low, mainly due to convenience issues for patients who already put a lot of effort into their treatments. Even mobile health apps recommended or prescribed by healthcare professionals meet moderate success, with 20% of patients using them and only 9.5% on a regular basis.² This issue greatly limits the benefits associated with *mHealth* technologies and their impact on patients' treatments.

Passive monitoring provides the solution to this hurdle. Once the medical mobile

software is directly integrated with the drug delivery device, the monitoring process becomes fully automated. This device-software integration improves greatly point-of-care delivery and ensures the patient uses the mobile health app to its full extent. Furthermore, in order for this integrated system to be effective, it is necessary to keep both the device and the software easy-to-use and intuitive for the patient.

INTRODUCTION TO THE DATAPEN

The DataPen is a system composed of a reusable injection pen and a mobile app, connected by Bluetooth 4.0 (see Figure 1). This fully integrated system aims to help patients administer their medication, manage their treatment and share essential data with their physicians or relatives. The DataPen is used for subcutaneous delivery. The proof-of-concept has been developed for insulin therapy in diabetes mellitus, as real-time management is extremely important for this chronic condition.

"Passive monitoring provides the solution to this hurdle. Once the medical mobile software is directly integrated with the drug delivery device, the monitoring process becomes fully automated"

The device itself is easy to use and allows patients to deliver their treatment accurately and comfortably. There are only two steps prior to injection, to input the blood glucose level measured beforehand and to input the insulin dose to inject. The user can then proceed to the insulin delivery by attaching a new needle to the pen, priming and injecting the drug. All the different steps are indicated by colour LEDs to ensure patient follows the right process (Figure 2). The data is then sent automatically to the mobile app and stored in a secure database.

The device is compatible with standard 3 ml cartridges and with standard pen needles. The design and user interface of the DataPen are similar to those of existing pens in order to allow patients to switch easily from their traditional insulin delivery device to Biocorp's connected pen. Its weight (55 g without cartridge) and its size (16.8 cm) are also close to other reusable pens available. The device is fully independent during the injection process. Its internal memory can store up to three weeks of data (for insulin treatment, 3-4 injections per day), if it is not close to the smartphone or if the mobile phone does not have internet connection.

The mobile app associated with the device brings additional functionalities to help the patient, including reminders and



Figure 2: The DataPen uses a colour LED to help the patient go through the injection process.

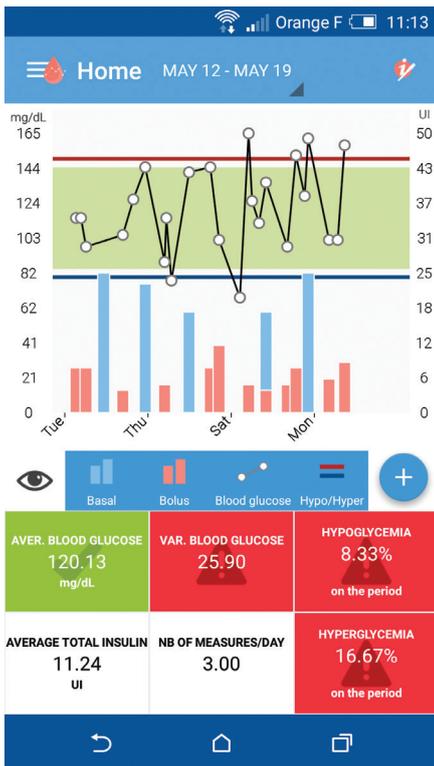


Figure 3: The patients can review quickly all their data thanks to a customisable dashboard. (demo version shown here)

alerts. Biocorp has focused its software development on three aspects:

- An intuitive user interface: patients prefer easy-to-use applications that require very little training
- Comprehensive visualisation dashboard (shown in Figure 3): physicians and patients need easy and quick access to the recorded data

“The DataPen is composed of a reusable injection pen and a mobile app, connected by Bluetooth 4.0. This fully integrated system aims to help patients administer their medication, manage their treatment and share essential data with their physicians or relatives”

- Data security: as detailed further below, health data security is crucial to develop patient-wise and even pharmaceutical lab-wise applications.

A DEVICE TO IMPROVE THERAPEUTIC COMPLIANCE

Therapeutic compliance can diminish complication risks and improve treatment outcome. A recent study estimated the effect of 100% treatment compliance in diabetes mellitus treatment with positive results: direct risk for diabetes-related kidney disease, stroke, heart disease and amputation were reduced by 13.6% for fully compliant patients.³

However, lack of therapeutic compliance is common, especially for patients suffering from chronic conditions. These diseases require burdensome treatments for a long period – often life-long, after the initial diagnosis – that patients have trouble following. For instance, the average compliance rate for Type 1 diabetes patients in the US is 70%.⁴ It is even lower for other conditions such as multiple sclerosis with an average compliance rate of only 40% worldwide.⁵

These low rates impact treatment outcome and patients’ health on the short- and long-term, and also have financial consequences for both healthcare systems and pharmaceutical companies. In the US, associated avoidable healthcare costs are estimated to amount to US\$100-300 billion (£65-195 billion) per year.⁶ Globally, associated annual pharmaceutical revenue loss is estimated to be \$564 billion.

There are several factors explaining general lack of compliance:⁶

- Patient-centred factors: patient-prescriber relationship, forgetfulness, demographic and psychosocial factors, etc.
- Therapy-related factors: treatment complexity, medication side effects, etc.
- Healthcare system factors: lack of accessibility, long waiting time, difficulty in getting prescriptions filled, etc.
- Social and economic factors: inability to take time off work, cost and income, etc.
- Disease factors: disease symptoms, severity of the disease.

The DataPen contributes to an improved therapeutic compliance by influencing

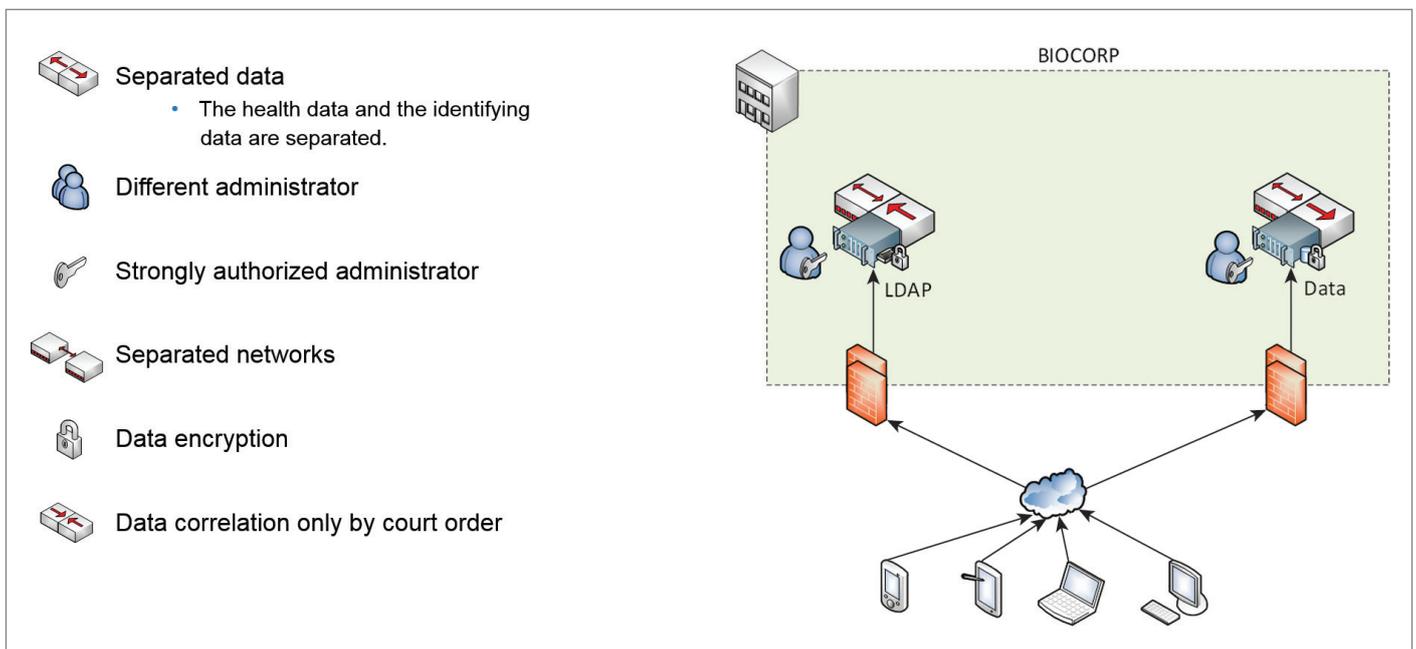


Figure 4: Data anonymisation: one of the security layers developed by Biocorp to protect patient data.

patient-centred factors. First of all, patients have real-time access to information about their treatment and can better understand the benefits associated with good therapeutic compliance. Secondly, the DataPen helps create and maintain behavioural habits enhancing compliance. Both the device and the mobile application are extremely intuitive to ensure the patient uses the system regularly. Thirdly, the reminders and alerts avoid forgetfulness, especially if the patient's family is involved. This is particularly important for diseases such as diabetes for which non-taken medication can lead to major health issues and hospitalisation.

The connected device also improves the patient-prescriber relationship. The physician receives essential information about the patient's health and treatment, and can make more informed clinical decisions. Due to the integration of the software with the device, all of the data is recorded and managed automatically, making it much easier for physicians to provide accurate follow-up.

Finally, the DataPen contributes to the development of a "personalised medicine". Monitoring extended Phase IV trials can help define specific groups of patients. These patient pools can then be treated more accurately.

THE IMPORTANCE OF DATA SECURITY

Mobile health is still a fresh and emerging field and all the stakes and opportunities are not clearly identified yet. The literature available on the subject has, however, underlined the importance of data security. In the 2015 Data Breach Investigations Report, Verizon reported 234 incidents concerning health data security and 141 of data theft amongst them. Health data security requires greater efforts in order to protect patient confidentiality. The purpose of implementing high data security is two-fold:

- Push cautious patients to use *mHealth* systems without restraint
- Use anonymous data more freely.

Bluetooth 4.0, used by the DataPen to transmit data to the associated app, is low energy consuming but brings moderate protection. The software R&D division at Biocorp, expert in data encryption and security, has added several layers of protection (see Figure 4).

First of all, each DataPen is associated with an app with an individual code that the patient enters before first-use. After this code has been successfully entered, the DataPen is linked to the patient's user

account, meaning he can access his treatment information on any mobile device provided it is connected to the internet. In consequence, the data is not stored directly on the smartphone but on a database that the user account has access to. The database is a certified tier III with very high security, optimal availability and performance.

Secondly, the data is encrypted at the beginning of the data transfer process.

"The connected device also improves the patient-prescriber relationship"

Biocorp has patented an encryption system that adds more security to the Bluetooth 4.0 communication process.

Finally, the data is fully anonymised. Even though the data is encrypted and kept secure, this last layer of protection ensures that the patient data is kept confidential. User personal information and health data are two separate flows of information, kept into two different networks. Only the patient concerned can choose to de-anonymise his personal data, a process which requires two separate authorised administrators.

Most companies in the *mHealth* industry do not develop this complex infrastructure to support their software products. However, such systems are necessary today to implement mobile integrated treatments and provide comprehensive solutions. The structure developed by Biocorp grants optimal data security and has the capacity to process several billions of transaction.

DEVELOPMENT STATUS

The DataPen was presented for the first time at Pharmapack Europe 2015 in Paris, France in February, and was awarded in the "Exhibitor Innovation" category. The device has not yet been approved by the regulatory authorities. Discussions with pharmaceutical companies for various therapeutic areas are ongoing. Biocorp continues to strengthen its position as the pioneer in connected drug delivery and will announce new products over the next few months.

ABOUT BIOCORP

Biocorp is a company specialised in the development and manufacturing of medical devices. Biocorp develops innovative primary packaging for the pharmaceutical indus-

try such as reconstitution sets and alternative to crimp caps. Biocorp also develops leading-edge passive safety systems for syringes and drug delivery devices. Biocorp has a unique double-expertise, making it a pioneer in digital health: a device R&D team and a software R&D team work hand-in-hand to develop highly integrated devices that help patients manage their treatment and improve their therapeutic compliance.

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BIOCORP

PIONEER IN CONNECTED HEALTH

The DataPen: be smart about your injection

- Improve therapeutic compliance
- Increase treatment efficiency
- Inject with high precision



Analytical insights



Data sharing



Treatment history



Stock management

The DataPen has not yet been approved by regulatory authorities

BIOCORP

BEYOND TREATMENT

DEVELOPING AND MANUFACTURING
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