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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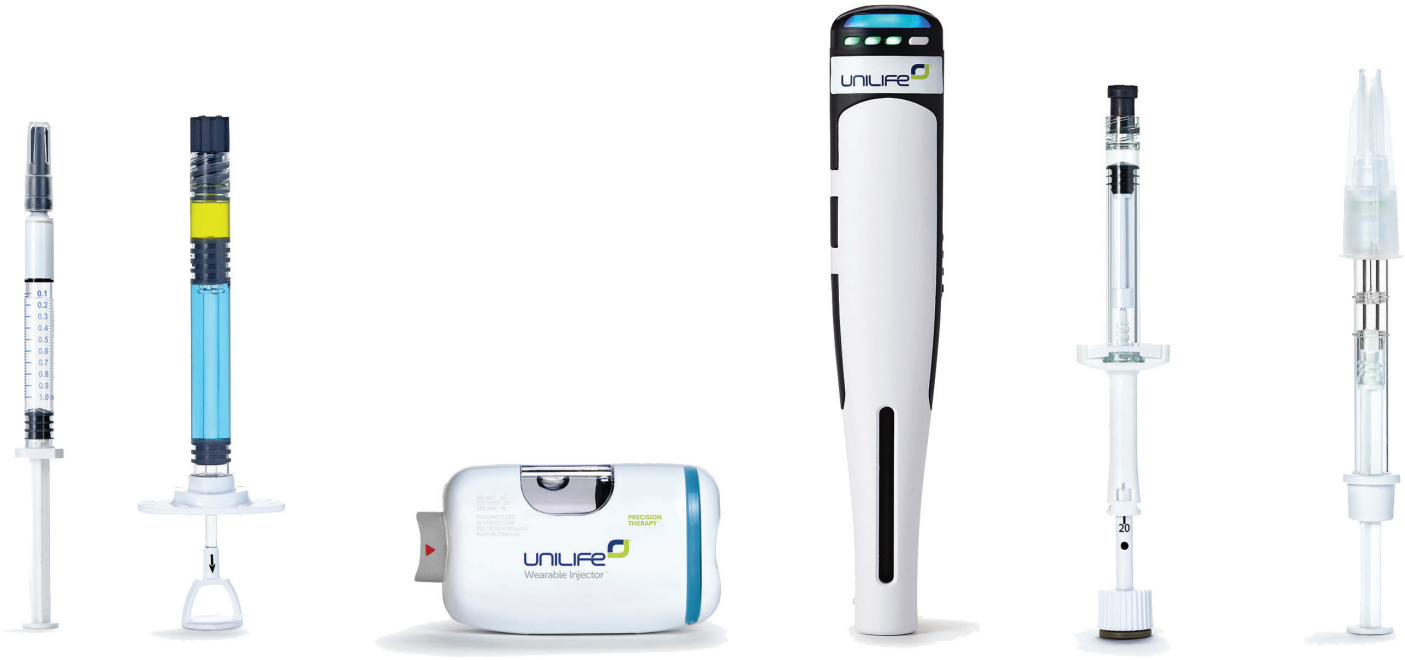


Figure 1: Unilife has created a broad proprietary portfolio across six product categories including (from left to right): prefilled syringes; reconstitution systems; wearable injectors; auto-injectors; ocular delivery systems; and novel delivery systems.

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 biosimilar 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

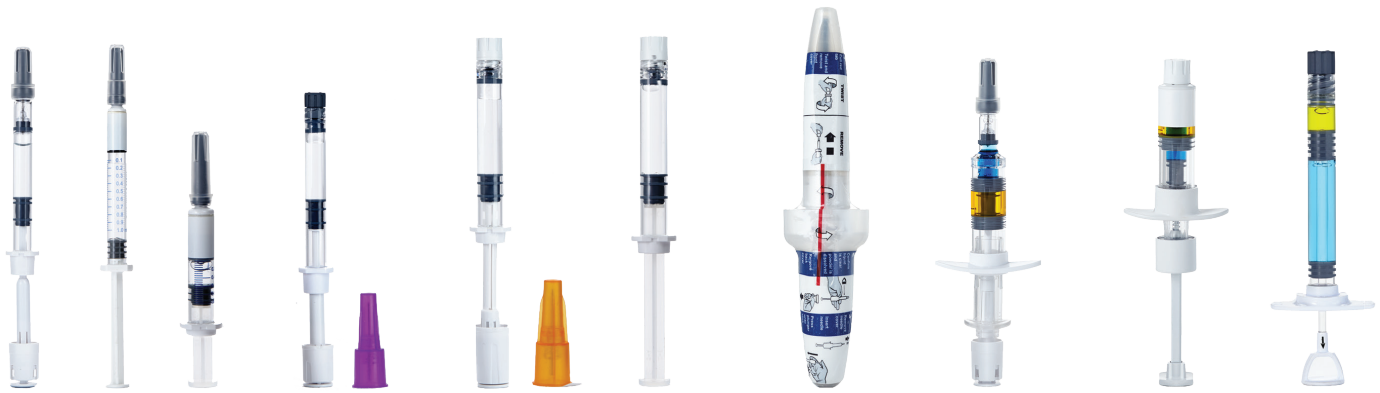
components, such as a prefilled syringe glass barrel and a disposable auto-injector, from separate suppliers. More often than not, in such cases, full accountability for the integration of multiple device components would fall onto the shoulders of the pharmaceutical company.

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

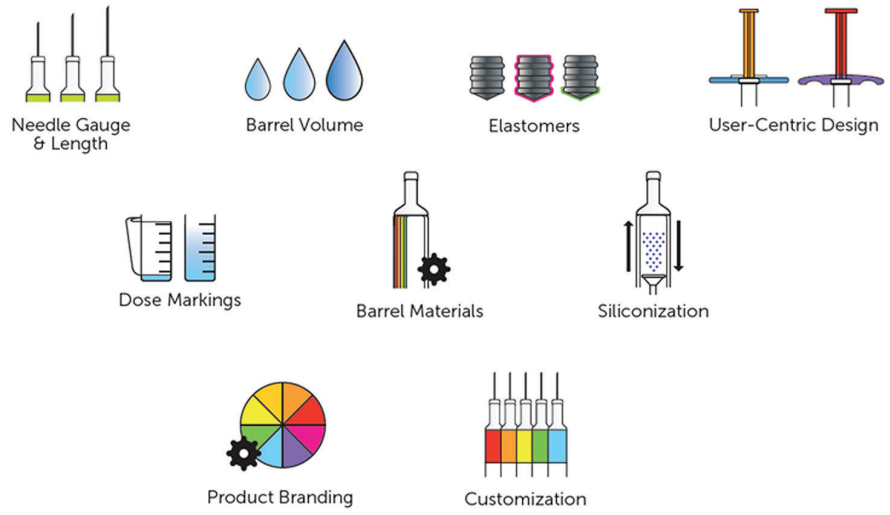
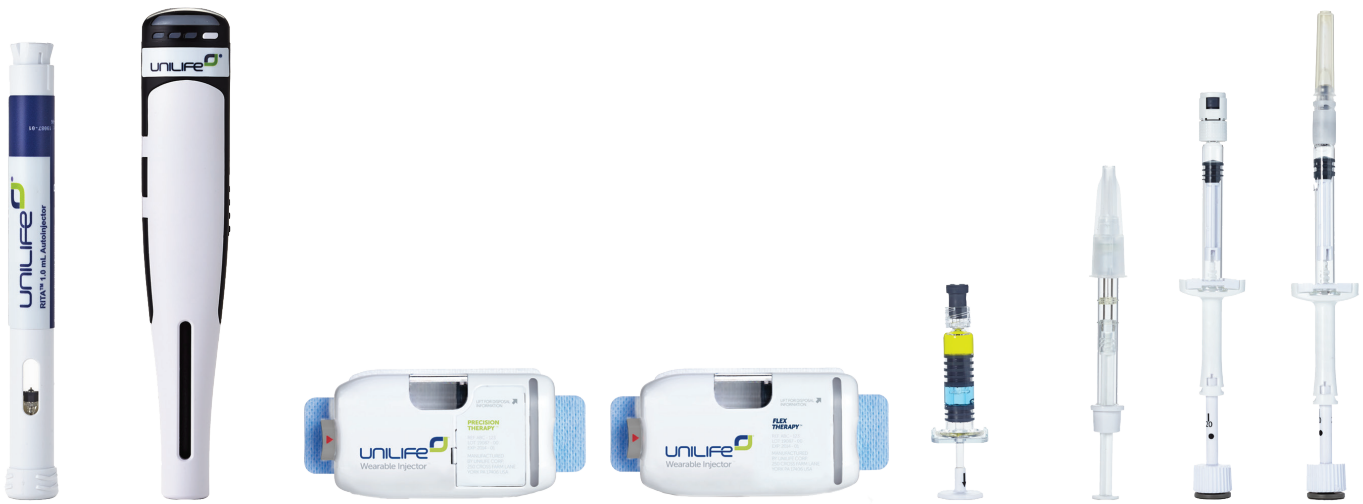


Figure 5: A selection of some of the customisation options available within the Unifill platform of prefilled syringes.



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 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 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."

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 retraction, customer options include needle length and gauge, luer connections, barrel volume, elastomers and coatings, dose markings, barrel materials, siliconisation 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 temperate 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.

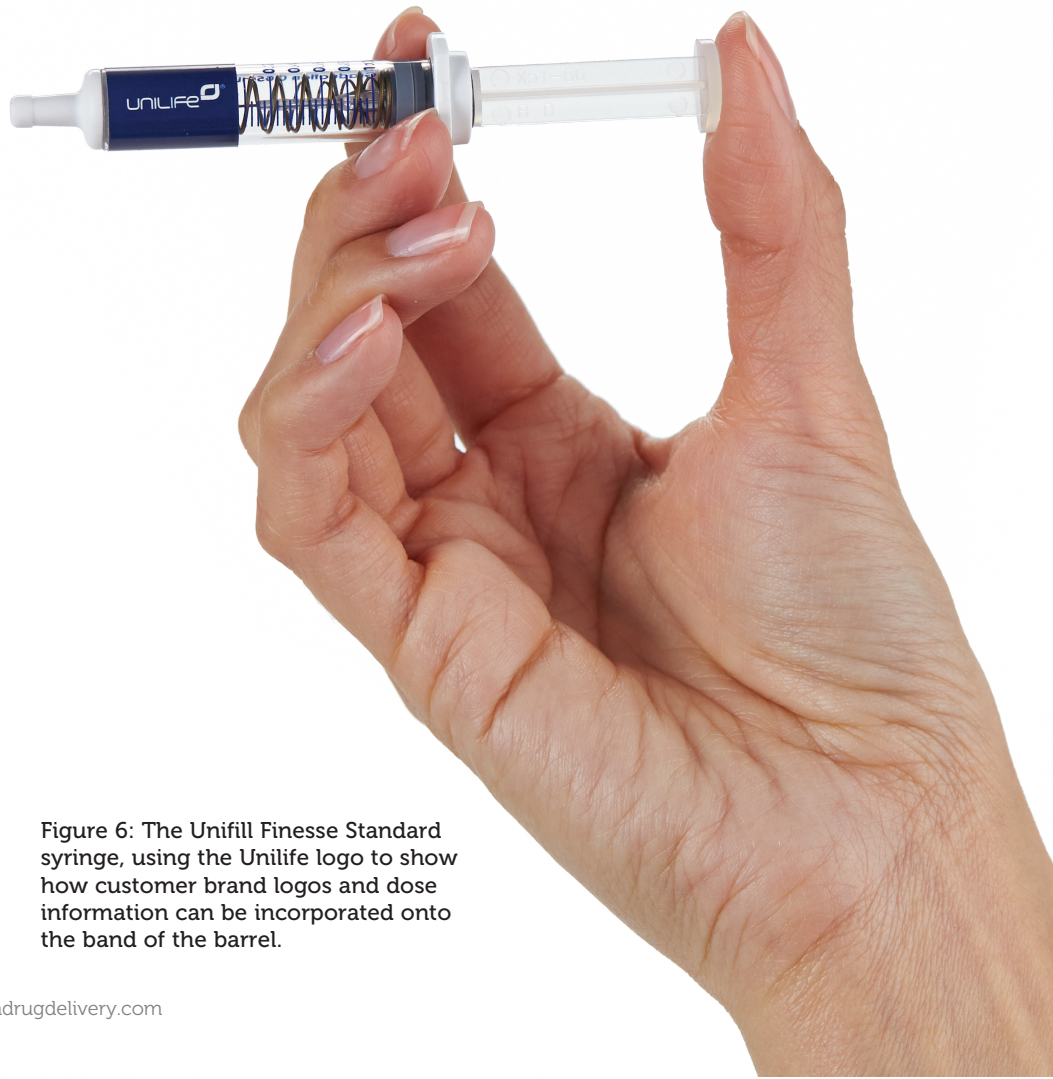


Figure 6: The Unifill Finesse Standard syringe, using the Unilife logo to show how customer brand logos and dose information can be incorporated onto the band of the barrel.

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 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 supply. 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.

"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"

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.

UNILIFE®

Deliver Brilliance

Wearable Injectors

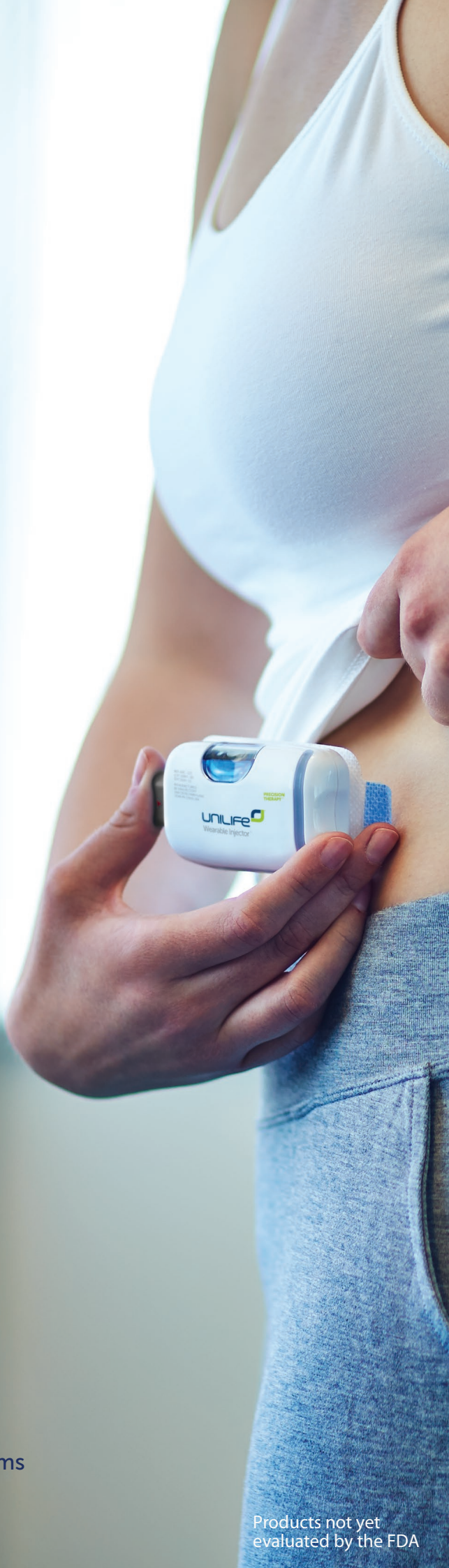
Prefilled Syringes

Reconstitution Systems

Auto-Injectors

Ocular Systems

Novel Systems



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Products not yet evaluated by the FDA