INJECTABLE DRUG DELIVERY

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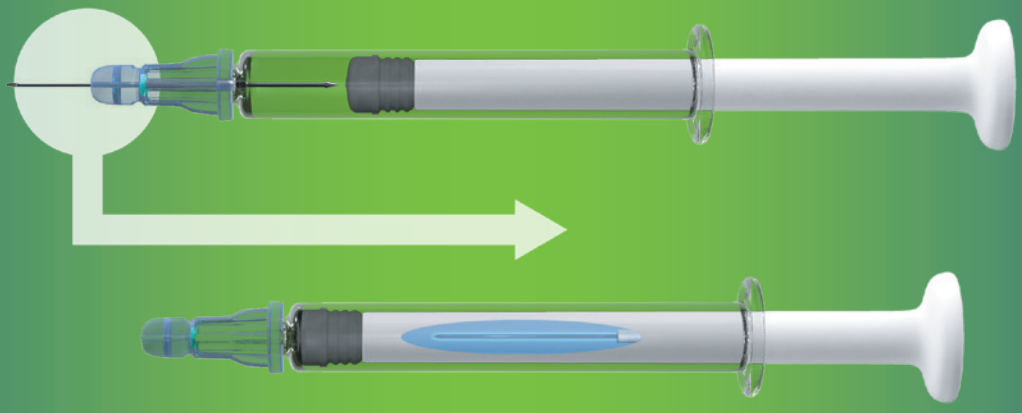

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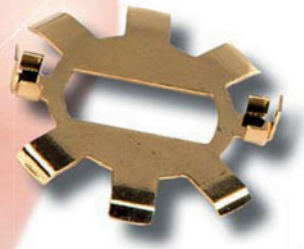

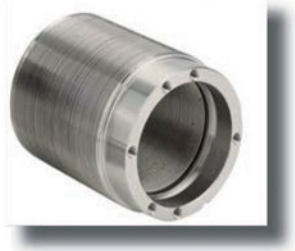

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INJECTABLE DRUG DELIVERY

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

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ENABLING SUBCUTANEOUS DELIVERY OF BIOLOGICS

Subcutaneous delivery of monoclonal antibodies is typically limited by viscosity-associated syringe forces and poor stability. Here, Elektrofi introduces Elektroject™, a gentle process for the production of ultra-high concentration protein formulations, that maintains a syringeable format and excellent protein stability, making the switch from intravenous to subcutaneous delivery viable for numerous biotherapeutics, including monoclonal antibodies.

Monoclonal antibodies (mAbs) are expected to reach combined global sales of US$150 billion (£116 billion) by 2022 thanks to healthy development pipelines. In recent years, biosimilars and mAbs with similar drug targets have also entered the market, creating a highly competitive landscape and compelling biopharmaceutical companies to differentiate their products.[1] Since their initial introduction to the market in 1986, mAb therapies have had tremendous impact, but have yet to reach their full potential, largely because of hurdles in drug delivery.

Solving delivery challenges will be key to enabling mAb therapeutics to reach their full potential. To achieve optimal therapeutic effect, antibodies often require doses as high as 1 g. These antibodies are conventionally administered by high-volume intravenous (IV) infusions that can last up to eight hours under carefully monitored conditions.[2] Such infusions are inconvenient and often financially inaccessible for the patient. Additionally, they can limit the number of patients that hospitals and infusion centers can treat.

Subcutaneous (SC) injections of biologics are preferable to IV infusions as they decrease the burden on healthcare providers and payers by requiring much less time and offering a lower risk of complications (infection, infusion reaction, etc.). For patients, they also offer the opportunity for self-administration and favourably alter the economic landscape: SC mAb drugs are much more affordable as they obviate the high mark-ups typical of long-duration IV infusions.[3]

> "Since their initial introduction to the market in 1986, mAb therapies have had tremendous impact, but have yet to reach their full potential largely because of hurdles in drug delivery."

This preference for SC delivery is reflected in the market as an increasing number of mAb therapeutics have been released in an SC form in recent years.[3] For many mAbs, however, the high concentrations (>100 mg/mL) needed to reach appropriate doses within the volume limit of standard SC injections – 1.0 to 2.25 mL – are typically intractable on account of high viscosity-associated syringe force or protein instability.[4] High syringe forces make SC delivery virtually impossible, constraining drug manufacturers to either provide IV

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infusions or administer lower doses more frequently. Elektrofi has overcome these delivery challenges (see Table 1).

ELEKTROJECT™ DIRECTLY ADDRESSES SC MAB DELIVERY CHALLENGES

With large-molecule biologics such as mAbs, protein instability and high viscosities result from intermolecular interactions in solution.[4] High viscosities make it difficult to handle and inject the drug. Protein instability reduces the effective dose as less of the protein is therapeutically useful and can potentially form aggregates which may harm the patient.

Strategies for solving these problems include:

- addition of excipients to reduce the prevalence of intermolecular interactions
- administration using on-body injectors to infuse a large volume of low-concentration drug over a prolonged period
- use of hyaluronidase to enable high-volume SC injections.

However, these methods still have not achieved high concentrations without compromising on stability and may require relatively complex administration procedures (i.e. the addition of hyaluronidase still requires a nurse to keep a needle in the patient for 5-6 minutes), which preclude the potential for self-administration.

> "Compared with aqueous mAbs, Elektroject™ suspensions achieve much lower viscosities at high concentrations."

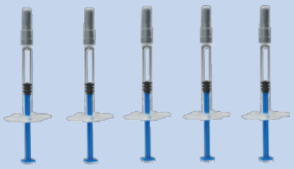
	Conventional Delivery		Next-Generation Delivery
Delivery Format	**Intravenous (IV)** 	**Subcutaneous (SC)** 	**Electroject™ (SC)** 
Delivery Time	Hours	Seconds	Seconds
Delivery Frequecy	Low frequency	High frequency	Low frequency
Dose	Full	Low	Full
Concentration	Low concentration	Low concentration	High concentration
Volume	High volume	Low volume	Low volume

Table 1: Elektroject™ directly addresses challenges in mAb delivery.

Elektrofi has developed a next-generation microparticle-based suspension formulation, Elektroject™, which directly addresses the current challenges of SC mAb delivery by enabling ultra-high concentrations (>400 mg/mL) of protein, while maintaining a syringeable format and excellent protein stability.

The Elektroject™ manufacturing process is inherently scalable and can be run aseptically at low temperature. This novel droplet formation and drying process yields dense, spherical microparticles without compromising protein quality (see Figure 1a). The solid microparticles limit the intermolecular interactions responsible for high viscosities and instabilities in aqueous formulations (see Figures 2b and c).

The particles are suspended in a liquid carrier vehicle to prevent dissolution until injection. This suspension can be filled in a prefilled syringe format, eliminating the need for complex, error-prone reconstitution procedures. The highly dispersible nature of the microparticles enables easy resuspension by gentle shaking, allowing for a patient-friendly SC injection. Within the subcutaneous space, the proteins comprising the microparticles readily return to their original monomeric state enabling full bioavailability.

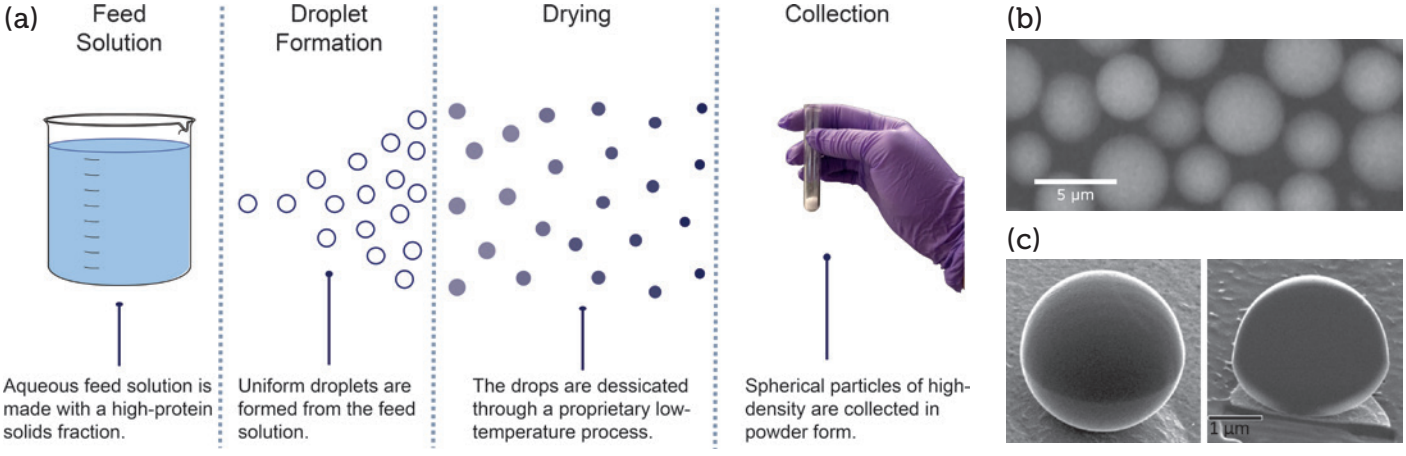


Figure 1: Elektroject™ microparticle production process (a), microparticles (b), and a cross section of a single microparticle demonstrating non-porous morphology (c).

Compared with other microparticle formation methods, Elektroject™ formulations:

- do not compromise on protein quality
- achieve higher protein loading
- exhibit tightly controlled particle size and shape.

Altogether, this allows the mAbs to be delivered in a prefilled syringe format and allows SC injection to become the standard of drug delivery for mAbs.

HIGH-CONCENTRATION, SYRINGEABLE SUSPENSIONS

Viscosity plays an important role in the handling and administration of injectable products. For suspension products, higher viscosities can prevent settling of the suspension. But when the viscosity is too high, it may be too difficult to deliver the drug through a 27-gauge needle because it takes much more force to actuate the syringe. The alternatives, such as using a wider needle or requiring longer injection times, reduce patient compliance with their treatment. Although there is no exact limit on viscosity, since it depends on the patient population and the syringe components, common targets are 20 and 50 cP.

Microparticle size and dispersity also impact syringeability. Microparticles are often recommended to be at least 3-10 times smaller than the inner diameter of the needle. Even if a small fraction of the particle population is larger than that, they may clog the needle and cause the whole dosage to go to waste.[5,6]

Compared with aqueous mAbs, Elektroject™ suspensions achieve much lower viscosities at high concentrations (Figure 2a). The tight particle size distribution control afforded by the Elektroject™ microparticle production process allows for the use of smaller needles without the risk of clogging (Figure 1b).

Compared with other particle production techniques, such as spray drying, atmospheric spray freeze drying, or polymer-based microspheres, Elektroject™ can make solid, dense microparticles with high protein loading under gentle conditions. While other particle production techniques use high temperatures, which can damage the protein, the Elektroject™ platform operates at low temperatures. Protein loading plays a role in the effective concentration-viscosity relationship. The lower the protein loading, the lower the effective protein concentration, which shifts the suspension curve to the left in Figure 2a. The more excipient is loaded into the solid fraction, the higher the viscosity at any given protein dose. Elektroject™ can achieve protein loadings greater than 90% while maintaining stability of the protein, whereas other microparticle technologies require relatively large fractions of stabilisers or protectants.

Elektroject™ microparticles are produced to fit through 27-30-gauge needles without needle clogging events. When in a syringe, the Elektroject™ suspensions take up to

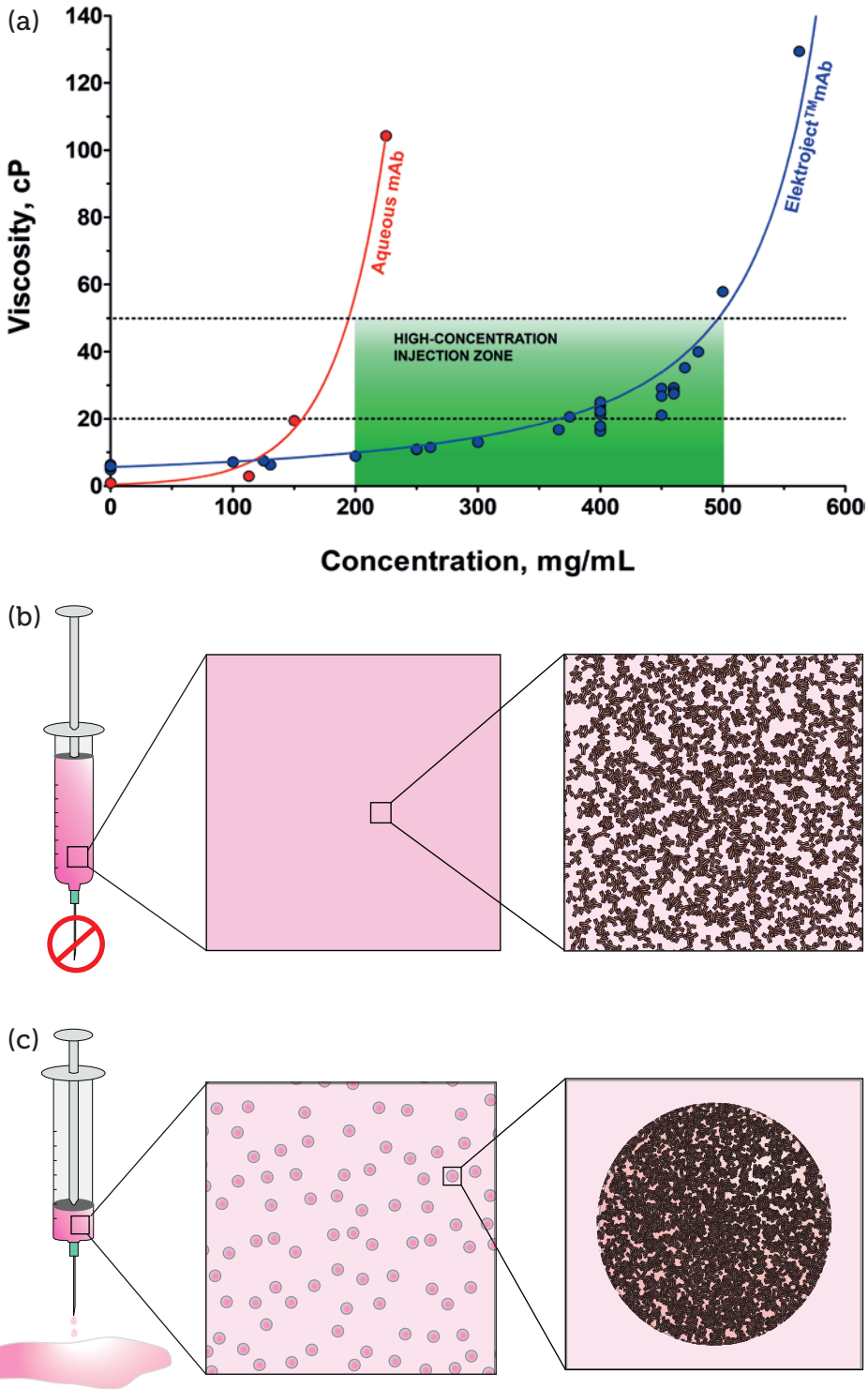


Figure 2: Elektroject™ enables high concentrations of biologics at low viscosity. Graph's x-axis shows protein concentration for aqueous mAb and particle concentration for Elektroject™ mAb (a). Intermolecular forces drive viscosity and protein degradation at high viscosity (b). Elektroject™ formulations physically reorganise protein solutions into reversible suspensions to reduce viscosity (c).

Drug Property	Experiment	Risk of Error
Delivery-relevant measurements	Viscosity	Higher concentrations with lower viscosity
	Syringeability	Lower syringe forces at higher concentrations
Molecule structure	Size exclusion chromatography	Preservation of monomers and improved storage stability
	Subvisible particle (SvP) analysis	Preservation of low SvP count and improved storage stability
	Cation exchange chromatography	Preservation of charge variants and improved storage stability
	Circular dichroism	Preservation of secondary structure and storage stability
	Differential scanning fluorimetry	Preservation of melting temperature and storage stability
Molecular function	Cell-based binding assays	Preserved cellular binding activity and storage stability
	Cell-based functional assays	Preserved functional activity and storage stability
***In vivo* function**	Pharmacokinetic profile	Statistically indistinguishable
	Tumour xenograft efficacy	Statistically equivalent efficacy

Table 2: Summary of Elektroject™ capabilities.

two hours to sediment and can be easily resuspended with gentle shaking. With these suspensions, protein concentrations of protein concentrations in excess of 400 mg/mL below 50 cP are possible, enabling the possibility of SC delivery. All this can be done without compromising molecule stability.

MAINTAINING MOLECULE STRUCTURE

Elektroject's gentle particle formation conditions allow for a variety of molecules to be formed into microparticles, including fragile molecules such as mAbs and fusion proteins. Unlike other techniques, Elektroject™ does not require high temperature conditions. Elektroject™ has demonstrated high preservation of mAb structure and functional bioactivity throughout the manufacturing process.

Once the suspension mixes with aqueous media, complete dissolution occurs within seconds to minutes, mitigating any immunological risks posed by particles persisting in the subcutaneous space.

Compared with an equal dose of aqueous mAb, Elektroject™ mAb demonstrated similar pharmacokinetic profile (AUC, C_{max}, and T_{max}) and efficacy (tumour growth reduction) in an animal model. Table 2 contains a list of highlighted drug properties comparing Elektroject™ particles with aqueous drug.

"Elektrofi's next-generation delivery platform, Elektroject™, improves accessibility by enabling the SC delivery of most protein therapeutics at full dose and without compromise on protein quality."

CONCLUSION

Patient-friendly products will continue to define the future of biologics. Although mAb therapeutics already comprise a large part of the biopharmaceutical landscape by market share, patient accessibility remains a problem. Elektrofi's next-generation delivery platform, Elektroject™, improves accessibility by enabling the SC delivery of most protein therapeutics at full dose and without compromise on protein quality.

ABOUT THE COMPANY

Elektrofi is a biotechnology company working on transforming the delivery of biologics. It envisions a patient-centric future where all protein therapeutics can be conveniently administered to patients in small-volume syringe injections instead of large-volume IV infusions or frequent injections. Elektrofi's gentle platform technology, Elektroject™, enables the transformation to high-dose SC delivery without compromise on product quality for a wide range of biologics.

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COMPANY SHOWCASE: Cristal Therapeutics

Over the past year, Cristal Therapeutics has transitioned from a research-stage start-up based on a nanoparticle technology platform, to a fully fledged, clinical-stage business with a promising pipeline of proprietary drug candidates. This diverse pipeline together with the proprietary nanoparticle platform, CriPec®, presents a broad range of promising late- and early-stage partnering opportunities for companies active in the oncology space.

The CriPec® platform (Figure 1) forms the backbone for the company's R&D efforts. CriPec® is built using tailormade, proprietary polymers that Cristal Therapeutics' expert team of scientists apply to create nanomedicines that transiently entrap a pharmaceutical payload. The resulting CriPec® nanomedicines improve therapeutic performance by shielding the drug from healthy tissues and increasing its exposure to the target tissue.

The drug payload is entrapped in the core of the CriPec® nanoparticles using proprietary, covalent linkers that prevent it from escaping the particles and being exposed to healthy cells. The high stability of CriPec® nanomedicines allows them to circulate in the bloodstream for much longer than the native drug molecule can achieve. This long circulation combined with the small size of CriPec® facilitates accumulation in tumour or chronically inflamed tissue via a phenomenon known as the Enhanced Permeation and Retention (EPR) effect. This is the observation that blood vessels in tumours and chronically inflamed tissues are more "leaky" than those in healthy tissue, allowing very small particles like CriPec® to escape through the gaps in the vessel wall and into the tumour interstitial space.

Release of the payload from CriPec® nanomedicines is driven purely by chemical hydrolysis. The rate and site of release can be customised dependent on the needs of the specific payload to further increase tumour targeting and local sustained exposure. This results in a higher ratio of the administered drug reaching its target and in turn a lower ratio being exposed to healthy tissue. This drives an enhanced efficacy and safety profile resulting in a substantially improved therapeutic index.

Cristal Therapeutics' lead CriPec® nanomedicine programme, CPC634, employs the taxane docetaxel. Whilst docetaxel is an essential standard-of-care treatment across a wide variety of solid tumours, the native drug suffers significantly from various toxicities that limit its use and efficacy in many patients. CriPec® has the unique ability to address these shortcomings

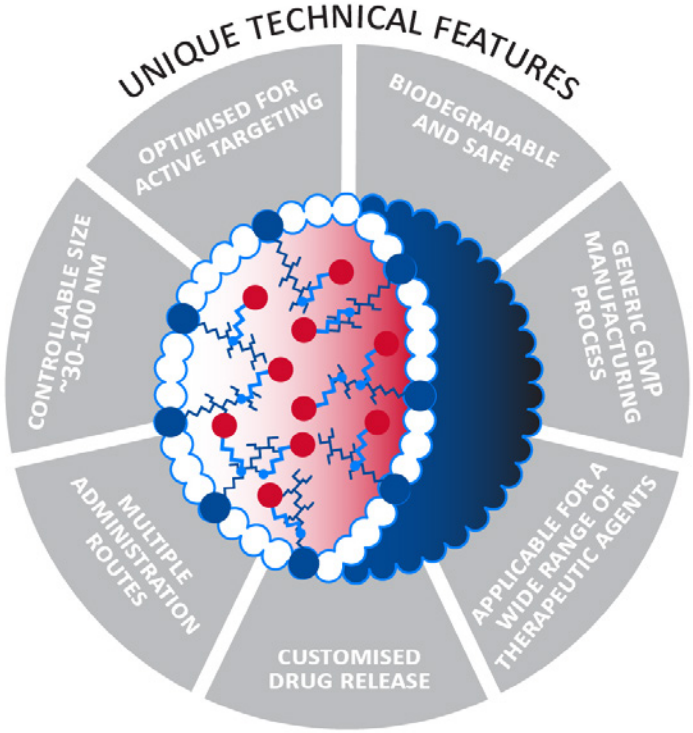

Figure 1: Tuneability of CriPec® platform – CriPec® nanomedicines can be fully tweaked dependent on the indication and the API(s), respectively.

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whilst further enhancing the efficacy of docetaxel to provide a vital treatment option for patients, validating the potential of this technology.

Cristal Therapeutics also has several preclinical candidates in its diverse portfolio utilising multiple therapeutic modalities, such as oligonucleotides and peptides, and targeting various tumour types.

CLINICAL EVALUATION

CPC634 was successfully evaluated in a Phase I clinical trial. The data demonstrated that CPC634 is safe and well tolerated at potentially therapeutic doses and has a significantly better pharmacokinetic profile compared with conventional docetaxel. These early-phase results support the basis of tumour targeting via the EPR effect to provide an improved treatment for patients with a variety of solid tumours.

An abstract on this study, "A phase I dose-finding and pharmacokinetics study of CPC634 (nanoparticle entrapped docetaxel) in patients with advanced solid tumours" (poster #3026), will be presented at the American Society of Clinical Oncology (ASCO) Annual Meeting (May 31-June 4, 2019, Chicago, IL, US).

Based on the promising early signs of efficacy in Phase I, CPC634 was advanced to a Phase II trial in October 2018, which is currently ongoing. The trial is evaluating safety, tolerability and efficacy in a well-defined patient population with platinum-resistant ovarian cancer, an indication with no effective therapies currently, and very poor survival rates.

Cristal Therapeutics intends to find a partner to expand the CPC634 development programme to further solid tumours including prostate, breast and lung cancers. Several of these additional target indications are especially prevalent in Asia and the emerging market of China. As a result, the company is proactively seeking partners with proven expertise in successful drug development and commercialisation in Asia.

In addition to the ongoing Phase II trial, Cristal Therapeutics is developing a radiolabelled CPC634 to enable non-invasive visualisation of the nanomedicine in patients (Figure 2). This radiolabelled CPC634, known as CPC205, is being tested in a clinical study to demonstrate its tumour accumulation in patients, and provides the basis for the potential future development of a companion diagnostic. An abstract on this study, "First-in-human imaging of nanoparticle entrapped docetaxel (CPC634) in patients with advanced solid tumours using 89Zr-Df-CPC634 positron emission tomography / computed tomography (PET/CT)" (poster #3093), will also be presented at ASCO 2019.

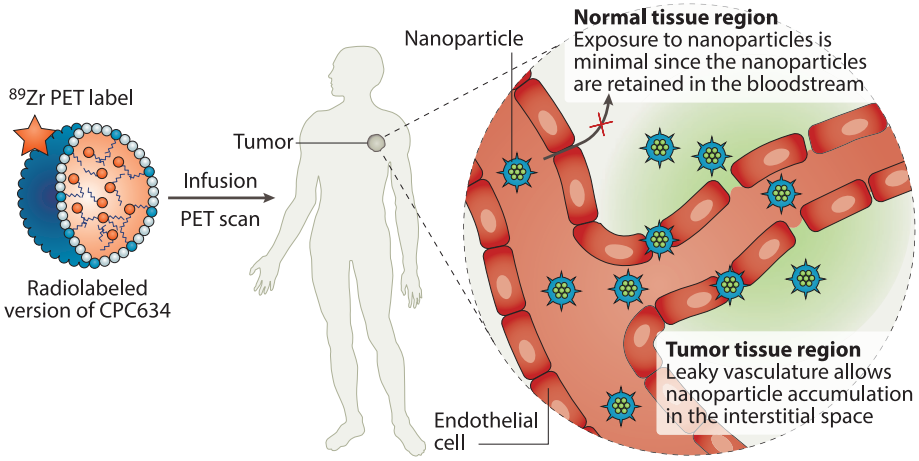

Figure 2: Clinical visualisation of tumour uptake. The radiolabelled CPC634 carries an 89Zr PET label enabling non-invasive imaging by PET/CT scans.

"Several of these additional target indications are especially prevalent in Asia and the emerging market of China. As a result, the company is proactively seeking partners with proven expertise in successful drug development and commercialisation in Asia."

BROAD APPLICABILITY CRIPEC®

Utilising docetaxel enables Cristal Therapeutics to develop its lead candidate in an efficient way with an attractive cost and risk profile that simultaneously demonstrates the benefit of CPC634, and validates the potential of the CriPec® platform as a whole, for other therapeutic payloads.

CriPec® is an extremely versatile platform that enables the entrapment of a wide variety of therapeutic modalities including small molecules, peptides and oligonucleotides. Payloads can be entrapped as monotherapies, as is the case for CPC634, or as synergistic combinations to provide further therapeutic benefit.

This broad applicability is driven by Cristal Therapeutics' ability to customise various aspects of the platform to the specific requirements of particular drugs and diseases. This can be achieved by tailoring the size of the nanoparticles between 30 and 100 nm, tailoring the linker used to entrap the drug, or by using targeting ligands on the surface of the particles to provide even more specific delivery to cancer cells.

PARTNERING WITH CRISTAL THERAPEUTICS

Cristal Therapeutics has several ongoing collaborations with large pharma and biotech companies working on a range of therapeutic modalities and diseases. To capitalise on the full potential of CriPec® the company seeks further partners developing (immuno-)oncology and other drugs that can benefit from CriPec® tumour targeting.

Cristal Therapeutics collaborates by first conducting a joint proof-of-concept study to allow partners to test their compounds in combination with CriPec®, followed by a licensing deal on the CriPec® platform and mutual further development.

Partners will benefit from collaborating with an experienced company with proven expertise in the nanomedicine field, a strong intellectual property portfolio, and an established good manufacturing practice (GMP) site that allows straightforward manufacturing at clinical scale. These foundations make Cristal Therapeutics the ideal partner for swift development of tumour targeted nanomedicines.

Through these collaborations together with its own diverse pipeline, Cristal Therapeutics is a dynamic, development-stage enterprise with the expertise to take cancer therapies and other treatments to the next level by allowing drugs to realise their full potential.

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A NEW MULTI-COMPENDIA MODIFIED BETA-CYCLODEXTRIN, KLEPTOSE® HPB-LB PARENTERAL GRADE

In this article, Elham Blouet, PhD, Global Market Manager Injectable, Dialysis and Specialty APIs, Roquette, introduces the latest addition to the company's range of beta-cyclodextrins, and outlines the benefits it brings.

Roquette, a leader in beta-cyclodextrins (KLEPTOSE®), recently expanded its range by launching KLEPTOSE® HPB-LB – a new grade of modified cyclodextrin: hydroxypropyl-beta cyclodextrin (HPβCD) as an excipient grade for use in parenteral applications. Meeting the highest global purity standards and following the principles of GMP, KLEPTOSE® HPB-LB parenteral grade will facilitate the registration of pharmaceutical products in multiple target markets.

Increased interest in cyclodextrins (CDs) in recent years has led to a strong market demand, and several new pharmaceutical products containing beta-cyclodextrins or their derivatives have reached the market successfully. To meet the specific needs of the pharmaceutical industry, Roquette now offers a wide range of KLEPTOSE® products: beta-cyclodextrins and HPβCDs.

> "It is the ability to form inclusion compounds through molecular encapsulation that gives HPßCD its interest as a formulation aid."

ONE SOLUTION FOR GLOBAL COMPLIANCE

KLEPTOSE® HPB-LB parenteral grade is a multi-compendia product that complies with the European Pharmacopoeia (EP) and US Pharmacopeia (USP) – and has standards that not only comply with but are even higher than those of the Chinese pharmacopoeia. Part of the wider KLEPTOSE® product range, KLEPTOSE® HPB-LB supports local and global pharmaceutical manufacturers in overcoming registration filing challenges in China, as well as the rest of the world, without the need to develop multiple drug solutions. This can accelerate speed to market and provide a competitive advantage.

A VERSATILE EXCIPIENT

Both native and modified CDs have the ability to form inclusion compounds through molecular encapsulation with a wide range of organic molecules. This ability makes CDs and their derivatives valuable as formulation aids.

They are used to increase the aqueous solubility of poorly soluble drugs and so avoid the use of organic solvents. Their use is also of great interest for improving the physical and chemical stability of drugs (protection against light, oxidation, etc.), for enhancing local tolerance of drugs and

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for any other applications where inclusion compounds would enable innovative solutions. Oral, parenteral, topical and ophthalmic preparations containing CDs and their derivatives are marketed worldwide.

Therefore the new KLEPTOSE® HPB-LB, parenteral grade is expected to improve active substance stabilisation against light and oxidation in parenteral preparations, and can also be used as a solubility enhancer.

UNIQUE MOLECULAR STRUCTURE

CDs are cyclic oligosaccharides (Figure 1) obtained from starch by enzymatic cyclisation using cycloglycosyltransferases. They are composed of α-(1.4) linked glucopyranose subunits. The beta-cyclodextrin, composed of 7 α-(1.4) glucopyranose units, is the most accessible and useful one with significant industrial usage. Roquette has branded its beta-cyclodextrin as KLEPTOSE®.

The HPβCD is a CD chemically modified by hydroxypropylation. HPβCDs are purified polydisperse products resulting from the controlled reaction of propylene oxide and native beta-cyclodextrins under base catalysis.

HPβCD has the highest aqueous solubility (65% at 25°C) and, combined with its safety profile, it represents an ideal profile for pharmaceutical applications. Thanks to its safety profile, the HPβCD is a suitable excipient for parenteral applications as well as for oral, topical and ophthalmic applications.

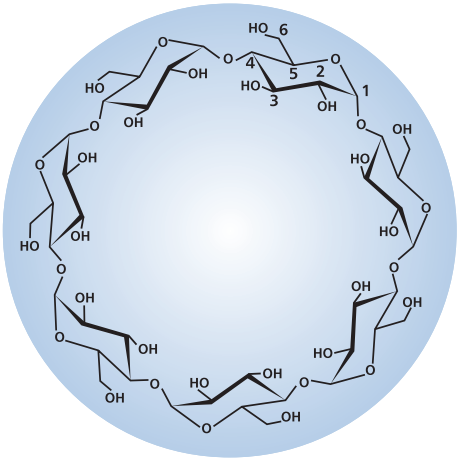
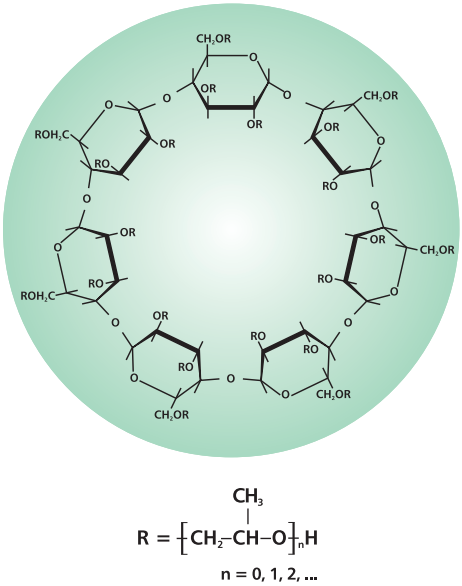


Figure 1: Chemical structure of beta-cyclodextrin.

The HPβCD molecule is a torus-shaped ring with a polar hydrophilic exterior and an apolar hydrophobic cavity. This structural feature is due to the spatial distribution of its external hydrophilic properties. As a result of this structure (Figure 2), HPβCD encapsulates or entraps guest molecules to form so-called inclusion compounds when in an aqueous solution.



$$R = \left[CH_2{-}CH{-}O\right]_n H \quad \begin{matrix} CH_3 \\ | \end{matrix}$$

n = 0, 1, 2, ...

Figure 2: Chemical structure of hydroxypropyl-beta-cyclodextrin.

The secondary OH groups on C-2 and C-3 are on the opposite edge, which gives HPβCD its external hydrophilic properties. The inside of the HPβCD ring is composed of a surface of hydrophobic C-3 and C-5 hydrogens as well as glycosidic ether-like oxygen.

The molar substitution (MS) is the average number of hydroxypropyl groups per anhydroglucose unit.

The degree of substitution (DS) is the number of hydroxypropyl groups per molecule of HPβCD and is obtained by multiplying the MS by 7. KLEPTOSE® HPB-LB is a composite product with a specific substitution pattern. The consistency of this substitution pattern is guaranteed by the manufacturing conditions applied by Roquette. The MS range of KLEPTOSE® HPB-LB complies with the EP/USP requirement (0.40-1.50) and ChP requirement (0.50-0.71.)

HPßCD INCLUSION COMPLEXES

With HPβCD, the preparation of inclusion compounds or complexes in aqueous media is very simple. The general principle involves the solubilisation of the predetermined amount of HPβCD. An instant aqueous solution is obtained. The active ingredient is added to this solution and mixed until a clear solution is formed. Ultimately, the complex can be freeze dried or spray dried (Figure 3).

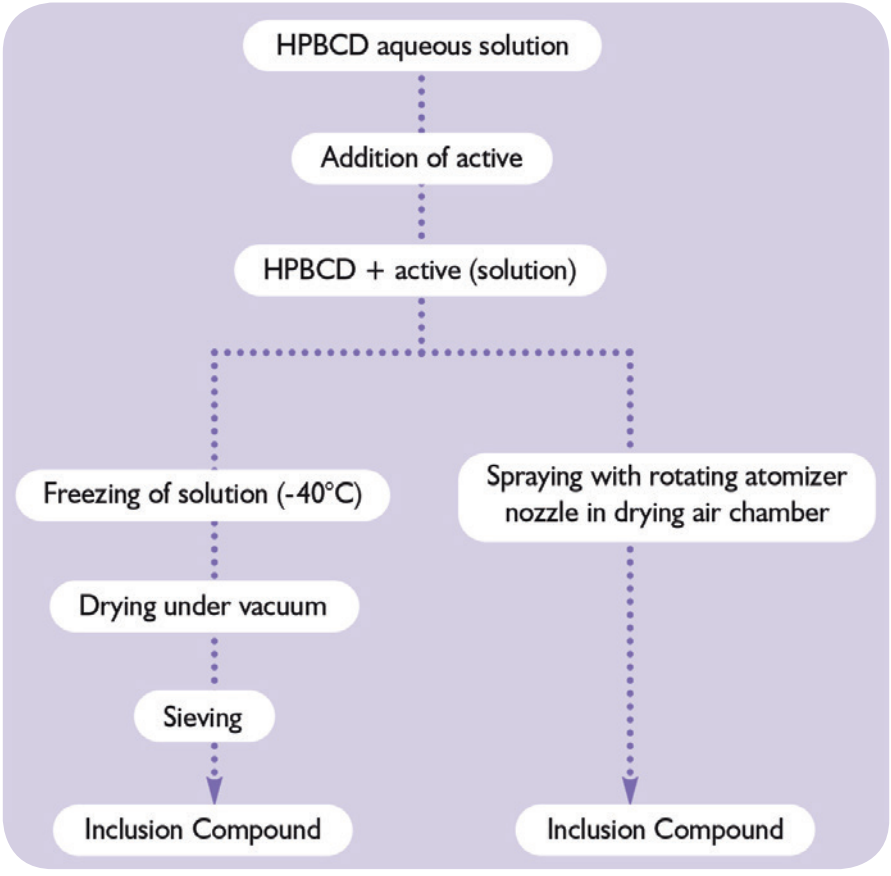


Figure 3: Preparation of inclusion complex in aqueous solution.

"HPßCD is an attractive excipient in injectable dosage forms as it is highly water soluble and with high biological tolerance."

Other more sophisticated techniques such as supercritical CO_2 exist. For initial trial purposes, and to determine the right amount of HPβCD to be used, the following protocol can be applied: add the active ingredient to a 50% HPβCD solution until a precipitate is formed.

It is the ability to form inclusion compounds through molecular encapsulation that gives HPβCD its interest as a formulation aid. Molecular encapsulation between HPβCD and a guest molecule is an equilibrium reaction (no covalent bonds) characterised by a binding constant (Kc) which is specific to each guest – HPβCD complex (Figure 4). In practical terms, the higher the binding constant, the higher the affinity of the guest molecule for the HPβCD.

The ability of a guest molecule to form a complex with an HPβCD molecule is a function of two main factors:

- Steric factor (size and shape of the guest molecule), which explains that a molecule can be partially or totally encapsulated
- Thermodynamic interactions between the different components.

Molecular encapsulation, like any other chemical reaction, is ruled by thermodynamic laws. Consequently, the addition of formulation additives may influence the inclusion either positively through the formation of ternary complexes (e.g. with aqueous soluble polymers, organic hydroxy acids or certain organic bases) or negatively because of competition with the guest molecule (e.g. with bile salts). Moreover, an energy input through temperature increase or operations (shear, pressure) can increase the complexation efficiency (Figure 5).

The release of the guest molecule from the HPβCD complex is driven by two main factors:

- The dilution effect
- Competition with other molecules which have a higher affinity for HPβCD complexation.

Figure 4: Inclusion complex equilibrium reaction.

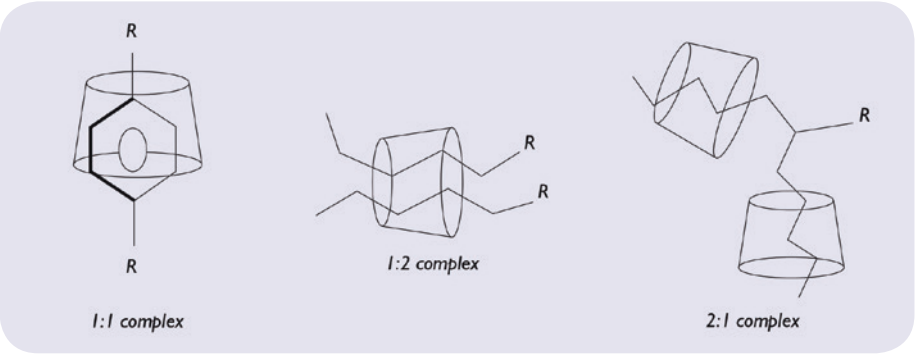


Figure 5: Representation of molecular encapsulation possibilities.

"One of the reasons for using the injection route of administration is for a systemic fast-acting result, which is why the drug must not only be more soluble but also dissolve more quickly."

Other factors can influence complex formation. Interaction between formulation ingredients is of particular importance and must be evaluated. For instance, thiomersal and benzylic alcohol can be recommended as preservatives because they do not compete with the guest.

PARENTERAL APPLICATIONS

HPβCD is an attractive excipient in injectable dosage forms as it is highly water soluble and with high biological tolerance.

The main functionality of HPβCDs are:

- Enhancing solubility of poorly soluble active substances to improve their bioavailability
- Stabilising active substances against oxidation, hydrolysis, heat degradation and light degradation
- Reducing irritation at the injection site while having low toxicity.

One of the reasons for using the injection route of administration is for a systemic fast-acting result, which is why the drug must not only be more soluble but also dissolve more quickly. There are numerous publications on the solubilising power of HPβCD; the examples given here are for illustration only: the effect of HPβCD on the solubility of some drugs of interest in injectable application is shown in Table 1.

VALUE-ADDED BENEFITS

The new KLEPTOSE® HPB-LB, (HPβCD), parenteral grade presents multiple benefits with regards to regulatory compliance, physical and chemical properties, performance, quality systems and enhanced packaging:

- Multi-compendia, enabling access to the global market
- High water solubility (ideal for small volume parenterals)
- Low viscosity: 20 cP at 20°C, and 40% HPβCD: ideal for injection, especially subcutaneous

- Endotoxin controlled, making it suitable for parenteral applications
- Encapsulation process versatility
- Encapsulation efficiency of a wide range of molecules
- Stability at high temperature allowing terminal steam sterilisation
- Stability at hydrolysis over a wide range of pH
- Production and quality systems following GMP principles
- Fibre-free packaging, with tamper-proof evidence
- Enhanced packaging with recyclable materials.

ROQUETTE RANGE OF MODIFIED KLEPTOSE®

Roquette has a full range of modified HPβCD. The key points of each grade of KLEPTOSE® HPβCD are listed in Table 2.

CONCLUSION

For more than 40 years, Roquette has made patient safety, improving health and ensuring formulation safety among its top priorities. As a pioneer in pyrogen-free pharmaceutical ingredients, Roquette has set the standard for highly purified excipients and APIs – enabling formulation with confidence. With multiple manufacturing sites across the world, supported by a vertically integrated supply chain, Roquette provides the confidence needed to develop safe and efficacious pharmaceutical products.

As an innovator in the industrial development of cyclodextrins with its KLEPTOSE® range of beta-cyclodextrins, Roquette proudly introduces its new KLEPTOSE® HPB-LB parenteral grade product to the portfolio. As a trusted partner and leading integrated supplier offering full traceability and supply chain security, your pharmaceutical applications will meet the highest quality and regulatory requirements because Roquette is committed to securing the purest ingredients for use in reliable oral and parenteral preparations to customers and future customers globally.

	Carbamazepine		Danazol		Albendazole	
HPβCD (mM)	Solubility mg/mL	S/SO mg/mL	Solubility mg/mL	S/SO mg/mL	Solubility µg/mL	S/SO µg/mL
0	0.097	1	1.42×10^{-4}	1	1.254	1
10	0.788	8	0.193	1362	20.181	16
20	1.45	14	0.34	2396	37.178	29
30	2.197	22	0.523	3684	46.806	37
40	3.107	31	0.774	5451	70.376	56
50	3.927	40	0.94	6623	74.153	59
100	6.723	69	1.983	13965	146.353	116
200	11.805	121	4.239	29854	352.701	281

SO is the drug solubility in DI water

Table 1: Solubility increase as a function of HPßCD molarity.[1]

REFERENCES

1. *Popescu C et al, "Determination of the Thermodynamic Solubility and the Affinity (Binding) Constants of Carbamazepine, Danazol and Albendazole in Hydroxypropyl Beta Cyclodextrin (KLEPTOSE®HPB) Solutions". AAPS Annual Meeting, 2011.*

	KLEPTOSE® HPB, parenteral grade	KLEPTOSE® HP, parenteral grade	KLEPTOSE® HPB , oral grade	KLEPTOSE® HP, oral grade	KLEPTOSE® HPB, Biopharma	KLEPTOSE®, HP Biopharma	KLEPTOSE® HPB-LB, parenteral grade
Grade	Parenteral	Parenteral	Oral	Oral	Biopharma (low endotoxins)	Biopharma (low endotoxins)	Parenteral
Molar Substitution (MS)	0.58 – 0.68	0.81 – 0.99	0.58 – 0.68	0.81 – 0.99	0.58 – 0.68	0.81 – 0.99	0.50 – 0.71
Applications	Small molecule	Small molecule	Small molecule	Small molecule	Large molecule	Large molecule	Small molecule
Route of administration	Parenteral, ophthalmic and topical	Parenteral, ophthalmic and topical	Oral and topical	Oral and topical	Parenteral	Parenteral	Parenteral, ophthalmic and topical
Regulatory compliance	EP / USP NF	EP / USP NF	EP / USP NF	EP / USP NF	EP / USP NF	EP / USP NF	EP/ USP NF / ChP
CEP	Yes	Yes	No	No	No	No	No
DMF	US DMF (type II & IV)	US DMF (type II & IV)	US DMF (type IV)	US DMF (type IV)	US DMF (type IV)	US DMF (type IV)	Chinese DMF

Table 2: Key points of the KLEPTOSE® range of hydroxypropyl beta-cyclodextrins (HPßCDs).

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ON drugDELIVERY

2019/2020 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Jun 2019	Connecting Drug Delivery	DEADLINE PASSED
Jul 2019	Novel Oral Delivery Systems	Jun 6, 2019
Aug 2019	Industrialising Drug Delivery Systems	Jul 4, 2019
Sep 2019	Wearable Injectors	Aug 1, 2019
Oct 2019	Prefilled Syringes & Injection Devices	Sep 5, 2019
Nov 2019	Pulmonary & Nasal Drug Delivery	Oct 3, 2019
Dec 2019	Connecting Drug Delivery	Nov 7, 2019
Jan 2020	Ophthalmic Drug Delivery	Dec 5, 2019
Feb 2020	Prefilled Syringes & Injection Devices	Jan 9, 2020
Mar 2020	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 6, 2020
Apr 2020	Pulmonary & Nasal Delivery	Mar 7, 2020
May 2020	Injectable Drug Delivery	Apr 2, 2020

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For further details, or to learn more about **KLEPTOSE® HPB-LB**, please get in touch with our experts.

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10TH GLOBAL DRUG DELIVERY & FORMULATION SUMMIT

Berlin, Germany, March 11–13, 2019

By Josh Lowth, Marketing Director, MA Exhibitions

The second week of March is a key date in the delivery and formulation event calendar. This is when the good and the great of Europe's pharmaceutical development community gather in Berlin, Germany, for the DDF Summit – a high-level scientific event for industry and academia.

This year, the 10th edition of the summit, was attended by 400 scientists and technologists representing, big pharma, SMEs, solution providers and academia. The summit is positioned at the intersection of high science and commercial thinking, bringing an exciting future focused angle to the content and discussions.

The three-day agenda is split into four dedicated streams of sessions: Small Molecules; Biologics; Technology & Innovation; and Device Development. This allows attendees to pick and choose the specific topics most interesting to them. The Device Development stream was added last year to reflect the growing trend in combination products and regulatory challenges around delivery devices. The sessions in the device room were packed out from start to finish.

> "The Device Development stream was added last year to reflect the growing trend in combination products and regulatory challenges around delivery devices. The session in the device room were packed out from start to finish."

Each day opened and closed with keynote sessions, bringing everyone together in the main room to discuss bigger picture issues and wider themes. Day One started with Kerstin Walke, Head of Pharmaceutical Development, Biologicals at Boehringer Ingelheim, discussing how next-generation biopharmaceuticals will influence formulation and device development. As formats become more complex there is a growing need for more powerful predictive tools and high throughput screening systems in early stages. She also explained how patient self-administration is playing an increasingly important role across various indication areas, as well as pointing out that high-volume devices are going to be important due to the challenges of high concentration formulations.

The day ended with another biologics-focused keynote, this time given by Alan Harris, Senior Vice-President, Global R&D Lifecycle Management at Ferring. Dr Harris's talk looked at the challenges and opportunities specifically for oral delivery of peptides. This has been a recurring and popular theme at recent DDF Summits and 2019 was no different. He outlined the importance of taking a patient-centric approach, which was a strong recurring theme throughout the three days in Berlin.

Day Two opened with an excellent talk by Stefan Bracht, Vice-President, Head of Disruptive Technologies at Bayer. Dr Bracht talked through the recent trends and solutions making waves in the field of drug delivery. We heard about the latest

ideas around patient centricity, specifically for children and the elderly. As well as the unmet need in parenteral drug targeting, with a focus on brain and solid tumours.

Day Two closed with the first panel session of the summit, which looked at the impact of the EU Medical Device Regulation (MDR) as it applies to combination products. The panel featured Bjorg Hunter, Regulatory Manager, Devices at GSK; April Kent, Regulatory Affairs Manager, Combination Products and IVDs at Amgen; Louise Place, Head of Regulatory at Cambridge Design Partnership; James Mellman, Device Manager at Novartis, and Torsten Kneuss, Quality Assurance Manager, Combination Products at Bayer. The main topic of conversation was Article 117 of the MDR. This has introduced the need for single integral medical products with a device component of class IIa and above to have a Notified Body opinion.

The final day kicked off with Beate Bittner, Senior Portfolio Strategy Director at Roche, on formulation and device lifecycle management. This session looked at the factors driving the development of devices that allow self-administration. With rising healthcare costs and more complicated combination therapies coming to market, companies are looking to simplify drug delivery. The talk covered how connected devices with features such as dosing reminders, adherence trackers and patient diaries allow an ongoing dialogue with healthcare professionals.

The summit closed with a panel discussion looking at the regulatory issues surrounding patient-centric drug development. With new guidelines being released by the both the US FDA and the EMA on patient-focused drug development (PFDD), this is becoming mandatory for the pharmaceutical industry. Sven Stegemann, Director of Business Development at Lonza; Leonie Wagner-Hatller, Formulation Scientist at Roche; and Louise Place from Cambridge Design Partnerships, suggested we should take an opportunistic view, explaining how PFDD can help create a competitive advantage by adding real value to patients and payers.

As well as the content, the DDF Summit is very much a networking event. With four hours of dedicated networking time built into each day, roundtable discussions, drinks receptions, a poster competition and pre-arranged one-to-one meetings, there are plenty of ways for attendees to interact. After 10 years, there's a real sense of community at the summit, which gives the networking a relaxed and informal feel.

The poster competition was expanded this year with 14 posters displayed around the exhibition hall. The competition is open to all attendees and gives everyone an opportunity to contribute and display their work. Attendees can then vote for their favourite through the official summit app. This year's winner was "Protein-Protein Interaction and its Influence for High Concentrated Liquid Formulations", which was submitted by Josef Hartl of Boehringer Ingelheim.

The summit's resounding success was reflecting in the attendee survey feedback: 99% of attendees said the summit met, exceeded or greatly exceeded their expectations; 96% learned something new and useful; 96% would attend again; 98% would recommend the summit to a colleague and 84% met somebody who could help with their current challenges.

The DDF Summit returns to Berlin, Germany, on March 9-11, 2020. www.ddfevent.com

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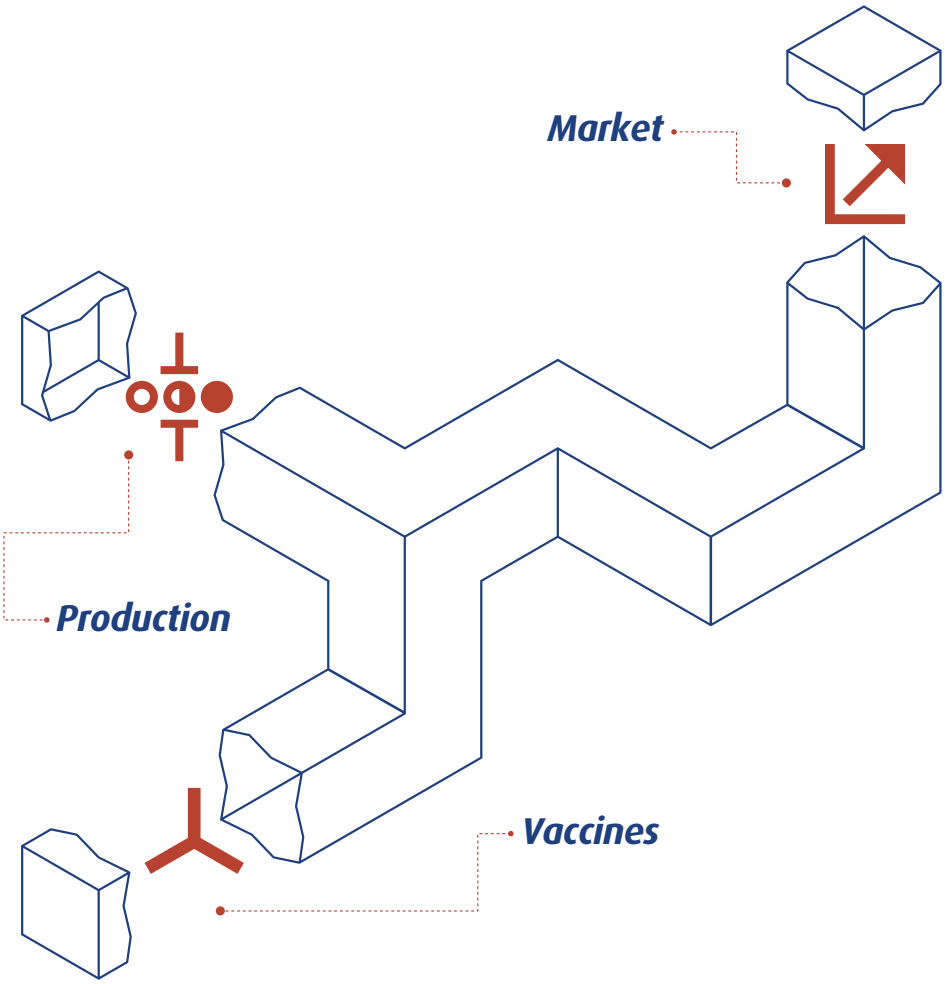
THE COMPLEX MADE SIMPLE



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Plunger cannot detach when removing the RNS.

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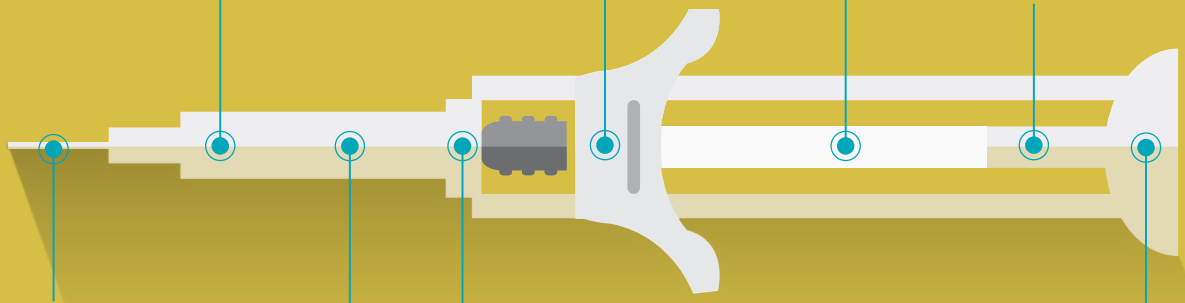

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Owen Mumford

SKIN-MOUNTABLE FLEXIBLE NEEDLE PATCH FOR MINIMALLY INVASIVE CONTROLLED DRUG DELIVERY

In this article, Chi Hwan Lee, PhD, Assistant Professor, and Eun Kwang Lee, PhD, Postdoctoral Fellow, both of Purdue University's Weldon School of Biomecical Engineering, introduce a skin-mountable flexible needle patch and discuss its applications in non-invasive drug delivery applications.

INTRODUCTION: MICRO- AND NANO-SCALE NEEDLES

Minimally invasive injection of therapeutics, including biomolecules, into living cells or tissues is a crucial element of various controlled drug delivery systems.[1] Research on effective injection methodologies for biomolecules should consider:

1) Ensuring minimal risk to cellular survival and function
2) Delivery of broad range of biomolecule types with controlled dosage.[2]

Conventional needle injection penetrates the *stratum corneum*, the outermost layer of the skin which acts as a barrier for the dermis and epidermis, allowing direct delivery of drug molecules into the vascular circulation.[3] This method yields a prompt therapeutic response. However, a challenge remains with the size of commercially available hypodermic needles, typically ranging from millimetre to centimetre, which can be difficult for patients to use themselves, due to pain caused by improper handling or reluctance caused by needle-phobia. Especially in developing countries, spread of bloodborne pathogens by needle re-use is also a major issue.[4] Hypodermic needles are therefore primarily utilised by healthcare professionals in a clinical setting or at home by well-trained patients who have learned the correct injection method and safe needle disposal.[5] Thus, there is an unmet need for the development of an effective and safe drug delivery system comparable in terms of efficiency with conventional needle-injection methodologies but without its disadvantages.

For the minimally invasive injection of biomolecules, recent approaches involve the use of micro- or nano-scale needles capable of penetrating the skin or into cells at their required length scale.[6] The incorporation of nanoscale textures on the surface of needles, where drug molecules are bonded, can increase the drug loading capacity, providing high-throughput delivery.[7] Examples of different types of micro/nanoneedles are summarised in Figure 1.[8]

- **Solid needles** without active pharmaceutical ingredient (API) are used for skin pre-treatment. The solid nanoneedles are applied to the desired skin site and removed, leaving micron-scale holes in the skin. Then ointments or medical creams are applied and cross slowly through the pores.
- **Dissolvable needles** made of water-soluble or biodegradable polymers that contain drug molecules are used for direct drug delivery. The key benefit of this needle form is that there remain no sharp scars after the needles are completely degraded in the skin.
- **Coated needles** are solid needles coated with dissolvable polymers that contain drug molecules. The stronger physical properties of this type of needle enable deeper penetration into the skin.
- **Hollow needles** are manufactured with empty spaces inside them into which liquid drug molecules are filled, ready for delivery into the skin after injection. Hollow nanoneedles can contain high molecular weight compounds such as proteins, vaccines and oligonucleotides.

More recently, vertical silicon nanoneedles (Si NNs) have been used for intracellular and intratissue delivery of biomolecules, providing further advantages from their intrinsic bio-dissolvability.[7] The resultant platform allows the nanoneedles to interact with adjacent cells and tissues during/after the injection, without inducing toxicity, degradation of cell metabolism

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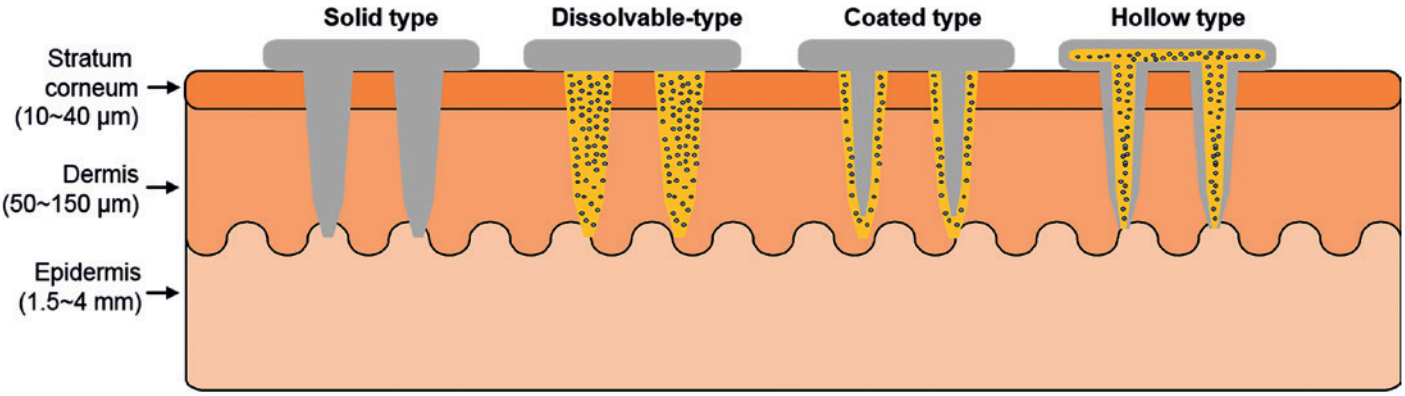

Figure 1: Schematic illustration of various needle forms.

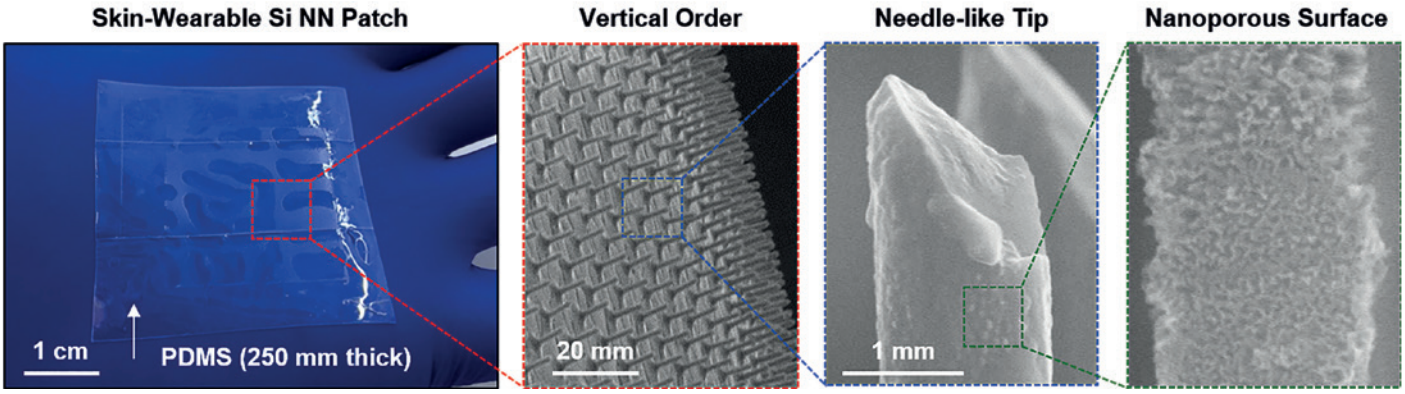

Figure 2: Photograph of a representative Si NN-patch (left) and magnified images of the tips and the nanoporous surface.

or substantial physical damage or cell rupture, followed by complete dissolution in a harmless manner.[7] Due their nano-scale size, Si NNs can penetrate the skin without causing pain or damage.

Si NNs are constructed on Si wafers, which provides compatibility with existing Si processing methods and facilities. The sizes, shapes and configurations of Si NNs can be precisely controlled in order to tailor them to specific delivery applications.[3,5] Nevertheless, a challenge is posed by the flat, rigid surface of Si wafers, which yield a large mechanical mismatch to the soft, curvilinear and dynamic surface of biological systems, thereby inevitably resulting in suboptimal surface contact. There is therefore a need for a mechanically soft, flexible form of vertical Si NNs, enabling their conformal contact with the surface of cells and tissues and thus efficient intracellular and intratissue drug delivery.

Our research group recently developed a novel flexible form of vertical Si NN array on a thin elastomer patch (referred to hereafter as an Si NN-patch), which provides mechanical elasticity, optical transparency and cell and tissue compatibility.[7] The flexible platform provides unique capabilities to yield a mechanically elastic interaction between the vertical Si NNs and biological cells and tissues, simultaneously enabling direct, real-time imaging of their interactions due to the patch's transparency.

Figure 2 shows a series of optical images of the Si NN-patch that incorporates a large array (3x3 cm) of vertically ordered Si NNs on a silicone elastomer, such as polydimethylsiloxane (PDMS). These images demonstrate the mechanical flexibility and optical transparency of the Si NN-patch. The magnified images highlight the needle-like sharp tip of Si NNs with nanoscale pores (8–20 nm diameter) on the surface, formed by using the metal-assisted chemical etching (MACE) method,[9] leading to a substantial increase of drug-loading capacity.

FABRICATION OF THE SI NN-PATCH

The fabrication of the Si NN-patch began with a Si wafer to form vertically ordered microscale Si pillars (3 μm diameter) by exploiting standard photolithographic patterning and a deep reactive ion etching (DRIE) processes. A partial passivation of the surface of Si pillars, followed by an isotropic dry etching step, allowed the formation of an undercut in the bottom area. A subsequent anisotropic wet etching step was used to reduce the size of the Si pillars down to nano-scale (<1 μm diameter). A thin layer of PDMS was then deposited on the top area of the Si NNs, where an airgap exists between the PDMS and Si wafer. The entire structure was immersed in an organic solvent solution, such as hexane and dichloromethane, allowing the PDMS to absorb the solvent and swell its volume. The swelling of the PDMS enabled the formation of uniform cracks at the bottom undercut areas where the most significant mechanical strains are concentrated. Subsequent annealing in a convection oven at 70°C for approximately one hour returned the swelled PDMS (now incorporating Si NNs on the surface) to its original volume. A wide range of needle diameters (80 nm to 3 μm) and heights (8–70 μm) were demonstrated in our studies.

INTRACELLULAR NANO-INJECTION UNDER SIMULTANEOUS REAL-TIME OBSERVATION

The mechanically soft and flexible form of the Si NN-patch provides the ability to form a highly elastic interface between Si NNs and biological cells or tissues. Figure 3A shows an example of the Si NN-patch interfaced with MCF7 (breast cancer cell line) cells. The elasticity of the PDMS substrate allows it to

efficiently adapt to the deformation of Si NNs induced by the cell movements, yielding no mechanical distortions or fractures, as are often observed using control Si NNs on a standard rigid Si wafer.

In addition, the Si NN-patch is transparent (the optical transparency is 90%), enabling direct, real-time observation of the interaction between Si NNs and cells or tissues. Figure 3B is a series of differential interference contrast (DIC) microscopy images of MCF7 cells interacting with the Si NNs, all captured from 36 hours of continuous monitoring. The experimental demonstrations of minimally invasive injection and delivery of biomolecules (siRNA) into various kinds of biological cells and tissues provide the feasibility and validity evidence.[7]

Figure 3C is a schematic illustration of the possible injection scheme of the Si NNs into cells from either top or bottom, for tailored applications. Due to the transparency of the Si NN-patch, this platform enables systematic studies of the biological interactions between cells and Si NNs observed through the substrate in detail *in vivo* as well as *in vitro*.

INTRATISSUE NANO-INJECTION IN AN ANIMAL MODEL

In vivo nano-injection of biomolecules into tissues is also possible using either a skin-wearable or implantable variant of the Si NN-patch. Figure 4 shows sets of photographs and the corresponding *in vivo* imaging system (IVIS) images in which the Si NN-patch is applied on the skin (4A) and subcutaneous muscle (4B) of mice, respectively. The Si NN-patch provides excellent biocompatibility for integration with the skin and subcutaneous muscle without provoking any inflammation responses. The contact quality at the interface between the patch and the skin or muscle undergoes negligible changes even with motion of the awake mice due to the substantial resilience of the Si NN-patch, which is able to tolerate the mechanical deformation. These aspects enable minimally invasive, uniform injection of small molecules throughout the curved spinal regions.

CLOSING REMARKS

Drug injection using micro- or nano-scale needles in a minimally invasive fashion provides many advantages, such as avoiding significant tissue damage and associated side effects, justifying the recent considerable interest in the field. As detailed in this article, an advanced engineering technique has emerged, enabling the heterogeneous integration of vertically ordered Si NNs containing biomolecules of interest with a flexible, transparent layer of silicone elastomer. The resultant platform provides not only mechanical flexibility to provide conformal contact with the curved surface of cells and tissues, but also optical transparency that enables simultaneous real-time observation during drug delivery. The flexible Si NN-patch would enable many fundamental studies on cellular interactions with Si NNs, including on cellular detection, drug discovery and therapeutic effects of drug/gene delivery.

In order for the Si NN-patch to be commercially available, fundamental studies and technological elaboration should proceed together. Research on the synergistic effects of various biomolecules using nanoporous Si NNs has yet to mature, and progress towards fabrication of the Si NN-patch in an industrially manufacturable and cost-effective manner is still in its infancy.

ABOUT THE SCHOOL

Purdue University's Weldon School of Biomedical Engineering is a leading biomedical conducting recognised education and translational research programmes. The school fosters academic, industrial, and clinical ties that create a dynamic, productive environment for experiential learning, scientific discoveries, and technology development. Through commercial partners, licenses of clinical technologies have generated over US$20 million (£15 million) in royalties from products that have helped millions of patients worldwide. The entrepreneurial spirit of faculty members has resulted in the launch of more than 24 spin-out companies with over $75 million in venture capital raised. Concurrently, hundreds of students at the BS, MS and PhD levels have graduated from the school.

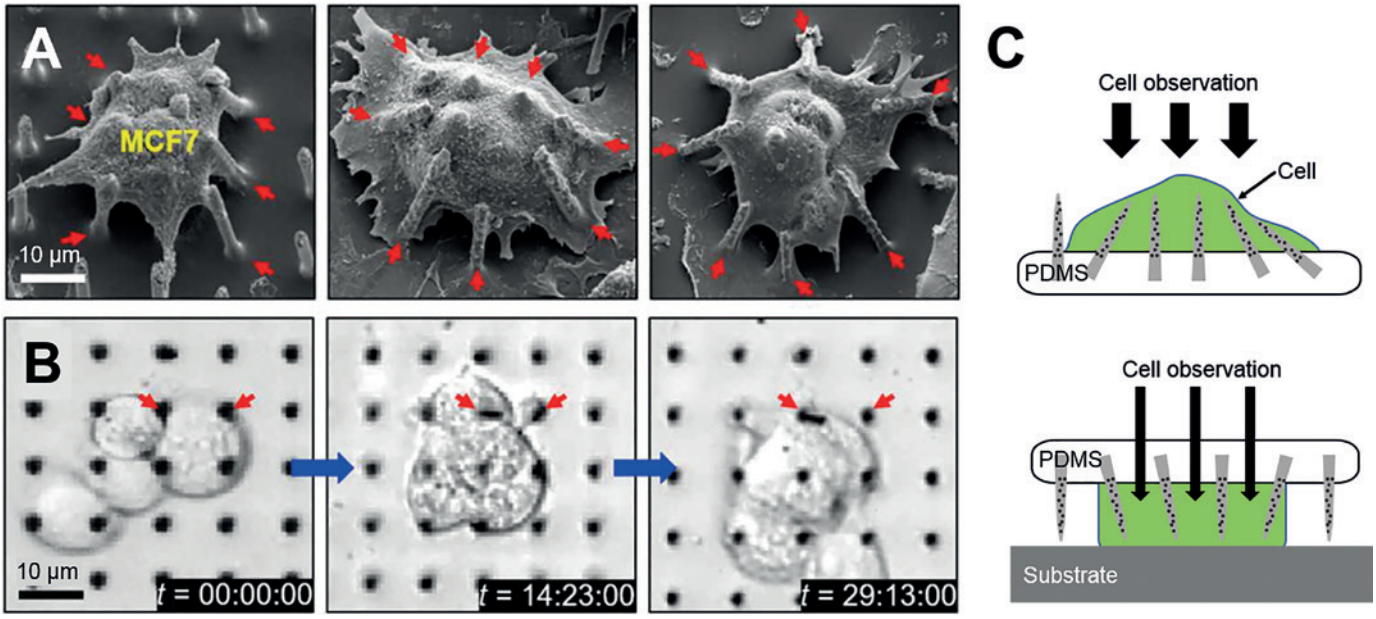

Figure 3: SEM images of tilted Si NNs on a PDMS substrate interacting with a MCF7 cell (A), real-time observation of the MCF7 cells through the transparent PDMS substrate (B) and schematic illustrations of the possible injection schemes from either top or bottom of cells (C).

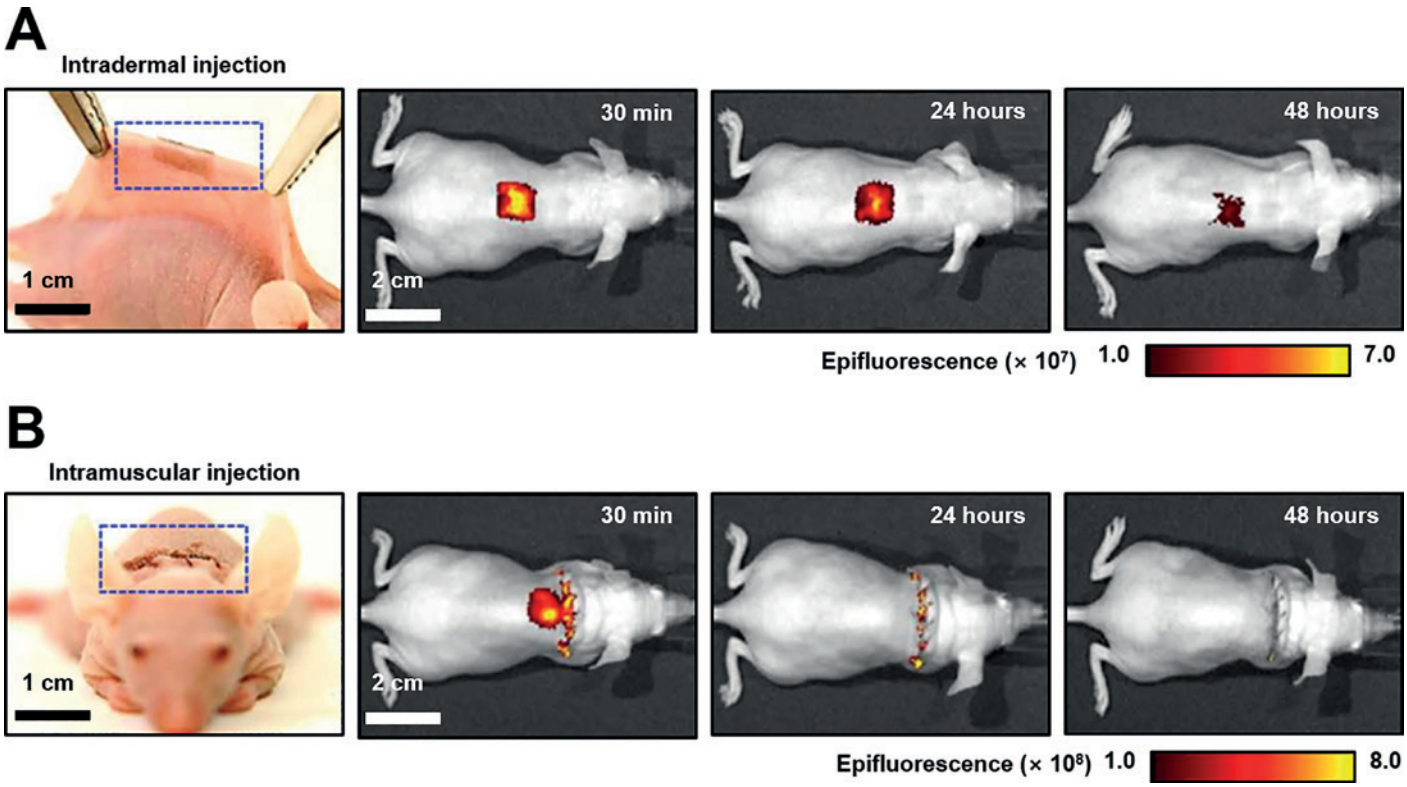

Figure 4: Demonstrations of intradermal (A) and intramuscular (B) injection of the Si NN-patch in mice. The *in vivo* imaging system (IVIS) images display the diffusion of small-molecule dyes through the skin and muscles after injection.

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TECHNOLOGY SHOWCASE: Credence MedSystems Multi-Site™ Injection System

Figure 1: The Credence Multi-Site™ Injection System.

While Credence MedSystems has become known for its Companion® Safety Syringe System and Dual Chamber Reconstitution products (see this issue, Page 62), another focus area for the company is the development of products to support specific therapeutic applications. As a result of this approach, Credence is now introducing the Multi-Site™ Injection System – a product that addresses specific needs in the high-growth dermal filler market, which is expected to exceed US$8.5 billion (£6.5 billion) by 2024.[1]

Administration of cosmetic injections such as dermal fillers and cosmetic botulinum toxin is performed by healthcare professionals (HCPs) in an office/clinic setting. During this procedure, the HCP administers several small-volume injections, often of a highly viscous substance through a fine-gauge needle, into multiple sites on the recipient's face or other areas of the body. Some of these cosmetic injectable products are delivered to the market in a vial and must be drawn up into a commodity syringe at the time of injection, while others are already in a prefilled syringe (PFS).

This latter PFS presentation has benefits such as simplified user steps, diminished risk for error or contamination, reduced waste from overfill and improved product/procedure traceability. In either presentation, the HCP must endeavour to inject precise doses using only the dose-line markings on the syringe as guidance. The conventional attempt to facilitate this is to use syringes with a reasonable distance/volume between dose lines, such as narrow Tuberculin syringes in the vial presentation or narrow PFS customised for the application.

Neither solution is ideal for the manufacturer or the user. The preferred solution is to use a standard PFS, such as a 1 mL "long" configuration, but the larger diameter makes metering the injection very challenging since the distance between the dose lines is too short. A system is needed that can preserve the benefits and efficiencies of a standard PFS configuration while enabling the procedure to be performed safely, accurately, quickly and effectively.

Credence is addressing this need with the Multi-Site™ Injection System (Figure 1), which enables the user to deliver a precise dose into multiple injection sites without fear of over- or underdosing. Each time the user presses on the plunger rod to perform

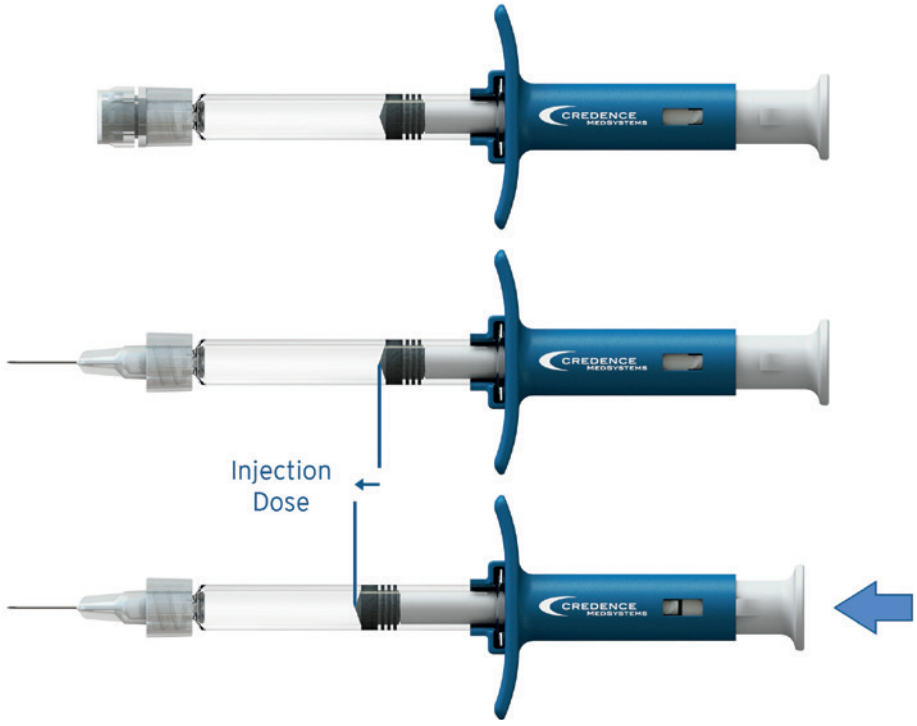

Figure 2: The Multi-Site System enables precise dosing into multiple injection sites.

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"The Multi-Site System has been designed to be simple and intuitive for the user but also practical for implementation by the manufacturer."

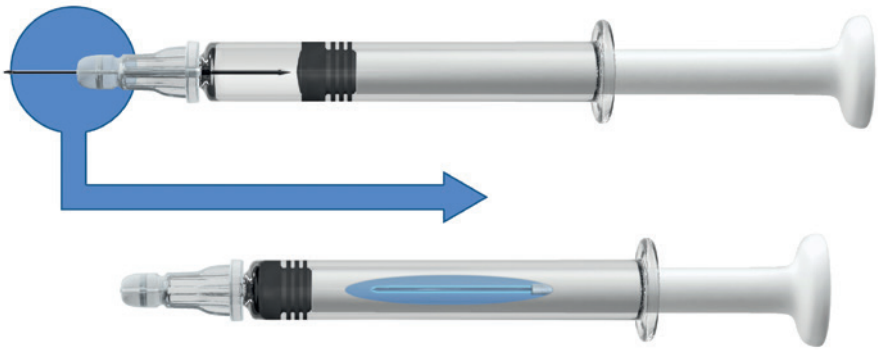

Figure 3: Credence's proprietary Needle-Retraction Technology is an optional feature.

an injection, the plunger rod advances until it reaches a firm stopping point that corresponds to the desired injection dose. The HCP simply presses on the plunger rod until it stops, providing a clear cue that the precise dose has been delivered. This is especially useful on the first injection, where overcoming the break-loose stiction can require an elevated force and a resulting momentum that can cause the HCP to overdose unintentionally.

When the plunger rod is released after each dose is delivered, it resets by retracting to its original position. Each reset is met with a tactile cue that indicates to the user that the syringe is ready for the subsequent injection. To avoid disturbing the patient, that cue occurs when the plunger rod is reset, after the HCP has removed the needle from the site. The process is repeated until the syringe has been fully dosed (Figure 2).

The Multi-Site System has been designed to be simple and intuitive for the user but also practical for implementation by the manufacturer. The Multi-Site components are mounted to the back end of an already-filled syringe, allowing the system to be used with any glass or polymer PFS and any closure components. As a result, the filling process is entirely unaffected. Only two items need to be assembled; the finger flange and plunger rod are mounted in secondary packaging and are compatible with existing processes and machinery. The system therefore enables the use of standard PFS but is also applicable to custom barrels.

Understanding that different applications have unique requirements, and that pharma manufacturers have different preferences and priorities, the Multi-Site System allows for significant flexibility on multiple fronts. The per-injection dose volume and number of doses per syringe can be adjusted. Multiple branding opportunities exist and the grip and shape of the finger flange can be specified by the manufacturer.

The system can be used with standard user-attached needles that exist in the market today – but Credence's proprietary needle-retraction technology can be implemented as an option (Figure 3). In this case, the needle retracts into the plunger rod at the end of the procedure after the final dose has been delivered. This option is available in either a user-attached or pre-attached needle. While the inclusion of needlestick prevention features is not prevalent in this market today, incorporating Credence's needle-retraction technology provides an opportunity as this would render these procedures compliant with needlestick prevention laws.

Finally, pharma manufacturers can choose to include an additional feature called Force-Assist™ (Figure 4), which provides a mechanical advantage to the user. This feature reduces the force required to inject the filler to only one-third of that which would otherwise be required. Because these fillers are generally very viscous – and because fine-gauge needles are used to avoid pain when injecting into the face – the force required to inject can be high. Force-Assist directly addresses this challenge.

Credence is focused on listening to customers, interpreting their needs and inventing solutions that address them. In this case, the result is the Multi-Site Injection System, specifically designed to address unmet needs in the cosmetic dermal filler market, with the potential to simplify and de-risk administration, increase procedure speed and provide enhanced safety and usability.

Figure 4: Force-Assist makes administration of viscous substances through fine-gauge needles easier.

ABOUT THE COMPANY

Credence MedSystems is an innovator of drug delivery devices that solve unmet market needs. Credence's philosophy of Innovation Without Change® allows customers to impress and protect their end users while preserving their existing processes, sourcing strategies and preferred primary package components. By offering the innovation of the final device without the change that customarily accompanies combination product development, Credence delivers implementable solutions to market needs.

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MICROLITRE DOSING WITH PREFILLABLE SYRINGES – WHEN DOES A DEVICE MAKE SENSE?

In this article, Gautam Shetty, PhD, Chief Executive Officer, Congruence Medical Solutions, and Bernd Zeiss, Head of Technical Support Medical Systems, Gerresheimer, outline factors that need to be weighed when considering a device-based approach to microlitre injections.

Prefilled syringes (PFS) have widely reported benefits in parenteral drug delivery applications from safety, convenience and cost perspectives. It was recently published that in intraocular (intravitreal) injections, the Lucentis® (ranibizumab) prefilled syringe, compared with Lucentis® from a vial, reduced the incidence of infectious endophthalmitis (eye infections) from 0.026% to 0.013% – a halving of cases of an adverse event that can lead to blindness and even death.[1]

> "The drug's therapeutic window dictates the criticality of accuracy and precision of microlitre drug delivery."

With the availability of the PFS for Lucentis® and the publicly disclosed impending launch of PFS for Eylea® (aflibercept), PFS are set to become the benchmark for treatments introduced in the ophthalmic space for biosimilars as well as novel therapeutic agents. Lucentis® PFS has also been reported to have a 27-39% reduction in syringe preparation time in one report and 57–63%[2] time savings in another; this saving is significant because of the large projected increase in the number of intraocular injections for the treatment of conditions such as age-related macular degeneration (AMD), diabetic macular oedema (DME), vein occlusions and uveitis.

The drug's therapeutic window dictates criticality of accuracy and precision needed in microlitre delivery. It may seem like the clinical experience of anti-VEGF drugs is evidence proving sufficiency of accuracy with current syringes. A systematic study to check known, related adverse events (for e.g., stroke, cardiovascular events, intraocular pressure, geographic atrophy, etc) relative to accuracy of delivery of anti-VEGF agents is not available. It is yet to be established whether there is a compensatory benefit when presented with increased risk from either underdosing or overdosing of anti-VEGF agents. Besides ophthalmology, there are several other applications that may require microlitre doses – these include dermatology, cell and gene therapy, and vaccines. Many of these applications have a narrower or unknown therapeutic window, requiring better accuracy and precision of the delivered microlitre dose.

It is also important to delineate the dose volume at which the inherent capability/limitations of a standard plunger stopper prefilled syringe system dictate the need for a device-based approach for microlitre delivery. In this article, we will baseline the capability of the current PFS-only approach to delivering a microlitre dose. For the PFS-plus-device approach to delivering microlitre injections, we will also present important considerations in selecting PFS when combining with a device. The PFS-plus-device approach may be an important consideration for potent drugs for applications in dermatology, oncology and also vaccines, in addition to ophthalmology.

PFS-ONLY APPROACH WITH EXTERNAL DOSE MARK FOR MICROLITRE DOSING

Prefilled Lucentis® makes for an interesting case study as it is indicated at different strengths for AMD (0.5 mg) and DME (0.3 mg). The 0.5mg Lucentis® is a 50 µL dose volume. Rather than deliver a 30 µL dose volume for the 0.3 mg, Lucentis® was reformulated to deliver 0.3 mg in a 50 µL dose. Data has been published showing overlap between a 30 µL and a 50 µL dose using a 1 mL tuberculin syringe (equivalent internal diameter to a 0.5 mL PFS). This

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overlap encapsulates the challenge where the syringe is operating at the limits of human capability to administer discriminating a sub-50 µL dose from a 50 µL dose. There is data that shows a marked decrease in the confidence of opthalmologists to accurately and precisely deliver a 30 µL or lower dose. Even with 50 µL, ophthalmologists' confidence is little more than 50%. Yet, the lowest dose volume for a US FDA-cleared ophthalmic drug is 5 µL.

The conventional approach would be to reformulate the drug to get the required drug strength to a volume that has precedence of being delivered with a syringe currently in use. Inherent in this approach is the duplication of CMC and related quality assurance efforts to produce, control, maintain and distribute different strengths of the same drug, and hence multiplication of costs. This problem finds particular resonance during clinical trials of drugs dosed in microlitres to study its dose response (evaluation of different strengths of the drug). The additional reformulation effort(s) and other downstream costs constitute a significant portion of clinical trial costs, and add potential risks from having to handle the same drug at different strengths.

Following are some of the factors (unweighted) that have to go right for an accurate, precise microlitre dose to be delivered using a standard PFS-only approach:

1. Accurate printing of the dose reference marking (Figure 1)
2. No/low variation of syringe internal diameter
3. Low break-loose force
4. Drug fill amount
5. Proper positioning of plunger stopper by user with start of dose reference
6. Control by the user of plunger position at the end of injection stroke.

Figure 1: Dose reference marking on PFS.

	0.5 mL PFS	1 mL "long" PFS
Internal diameter variation	±2.2 µL	±1.5 µL
Dose marking variation	±4.3 µL	±8.2 µL

Table 1: Impact of variations of PFS different factors (non-user) on delivered volume for a 50 µL dose.

Factors #1 and #2 are controlled and limited by manufacturing capabilities. Marking on the external syringe surface is typically achieved using a pad printing process; the best automated printing process with a custom visual inspection module can yield a dose mark position tolerance of ±0.25 mm . The variation in internal diameter of a PFS is typically ±0.1 mm. However, at additional cost, an internal diameter tolerance of ±0.05 mm can be made available.

Table 1 illustrates the expected impact of these variations on the potential inaccuracy of the delivered dose; this is before user-related inaccuracy and imprecision are factored in. Given low fill volumes for applications with microlitre delivery, consideration for factor #3 is necessary to ensure that the user does not accidentally overshoot the target dose mark position when setting the dose. Break-loose force, dead space in the syringe and dead space in the injection needle all need to be factored in to determine an adequate drug fill volume; this is necessary to deliver an accurate, precise microlitre dose.

Another source of variation is from the user bottoming out the plunger stopper at the end of the dose (Figure 2). There is clear, visible variation either if the plunger stopper is just bottomed out (a) or if the user forces the plunger stopper into the shoulder region of the syringe (b), hence compressing it. There is variability in this shoulder region as this part is formed in a free-forming process. The variation in dose volume per 0.1 mm of axial travel of the plunger stopper in a 0.5 mL syringe is 1.7 µL and, in the case of a 1 mL "long" syringe, is 3.3 µL. In hypodermic syringes, this overdosing was shown to be as much as 55.2 µL; a >100% dosing error for a 50 µL dose.[3] Additionally, should the user remove applied pressure after forcing the plunger stopper into the shoulder region, decompression of the plunger stopper causes the plunger stopper to move back (c). This contributes to additional dose inaccuracy, imprecision and general uncertainty.

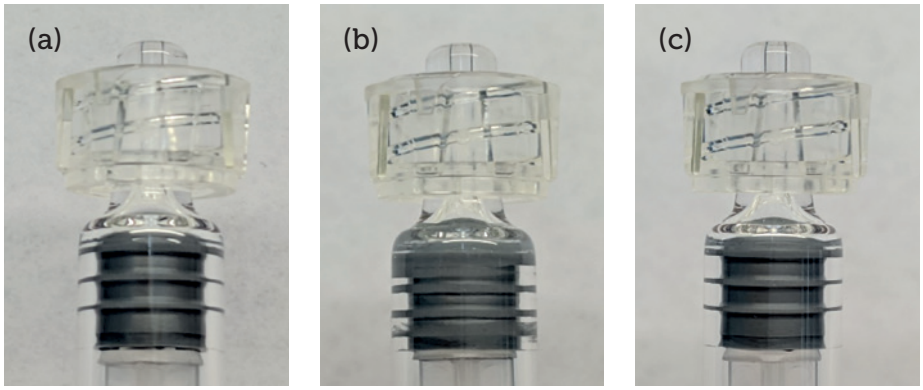

Figure 2: User variation in end-of-injection position of plunger stopper: just bottomed out (a), forced into the shoulder region (b), and retracted having been forced into the shoulder region (c).

PFS-PLUS-DEVICE APPROACH FOR MICROLITRE DOSING

A PFS-plus-device approach to microlitre dosing should certainly be considered when the therapeutic window of the drug is narrow (e.g. potent drugs), irrespective of microlitre dose volume. PFS-plus-device should also be generally considered when the volume to be delivered is less than 50 µL. During clinical development, this consideration extends to the use of hypodermic syringes as well. Devices can either be mechanical or electromechanical. However, electromechanical systems may have limitations in terms of cost, and single-use and secondary sterilisation requirements.

"Published studies have shown that there is a tendency towards overdosing when it comes to delivering microlitre injections."

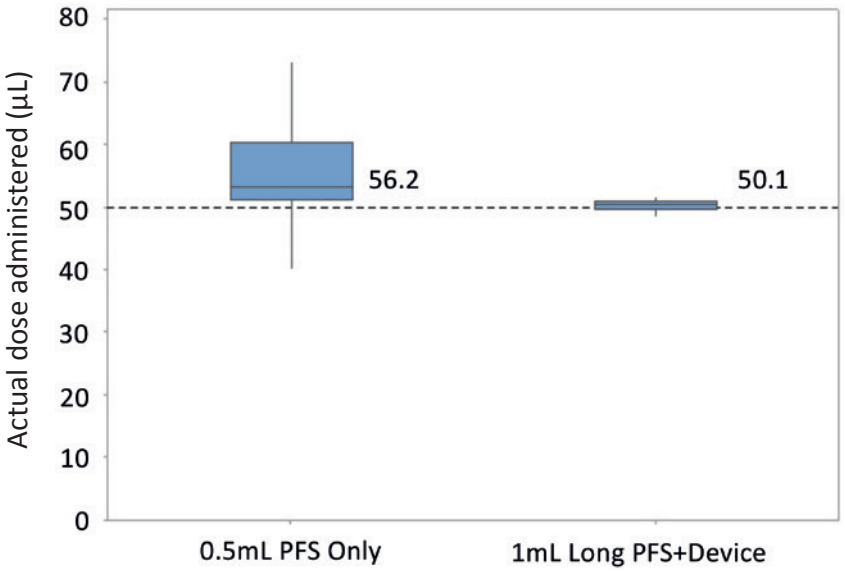

Figure 3: Boxplot with 95% CI of ophthalmologists (n=21) attempting to inject 50 µL with a 0.5mL PFS only and device + 1 mL "long" PFS (n=100) in a lab setting.

In a human factors study, 21 ophthalmologists attempted to inject a 50 µL dose using a 0.5 mL PFS with an external dose mark (Figure 3). The average dose was 56.2 µL (12% error) with 13.2% co-efficient of variation. The lowest injected dose volume recorded was 40 µL and the maximum was 73 µL. This inaccuracy and imprecision could be accommodated for a drug with a large therapeutic window. However, for a drug with a narrow or unknown therapeutic window, allowance of such inaccuracy and imprecision would need to be justified.

A device-based approach for the 50 µL dose volume but with a larger syringe internal diameter (1 mL "long" PFS) showed an average dose of 50.1 µL (Figure 3) with a 1.6% co-efficient of variation (min volume 48.2 µL, max volume 51.5 µL). The study demonstrated that a PFS-plus-device approach can deliver a more accurate, precise microlitre dose despite a larger internal diameter. The PFS-plus-device approach can be used to attenuate user-related factors causing inaccuracy and provide better control over fill volumes and break-loose force.

"The correct choice of PFS is essential relative to the intended application."

This capability can extend to volumes lower than 50 µL, which can provide significant efficiencies and cost benefits when preparing different strength drug solutions during clinical trials. Rather than reformulating and then manufacturing, controlling and distributing different strengths of the same drug, a device can be used to deliver different strengths of the same drug by simply modifying the deliverable dose volume. This approach eliminates several redundancies and helps reduce cost and/or risk.

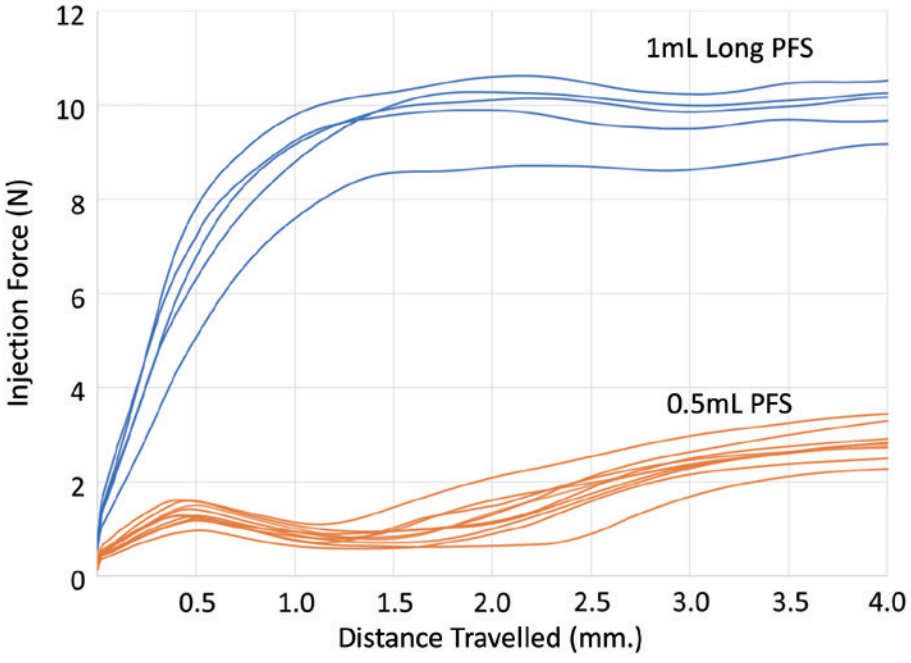

Figure 4: Force with 0.5 mL PFS (orange) and 1 mL "long" PFS (blue), both with baked-on silicone when injecting water with 30-gauge ½" needle.

SINGLE OR MULTIPLE MICROLITRE DOSES

Published studies have shown that there is a tendency towards overdosing when it comes to delivering microlitre injections. However, if more than one microlitre dose is to be administered using a single syringe, it is expected that overdosing would be followed by eventual underdosing. Such dose-fractioning applications require a PFS-plus-device approach to simplify the injection procedure, and avoid bifurcation of the clinician's cognitive bandwidth between dose measurement and anatomical considerations of the injection site.

PFS CONSIDERATIONS IRRESPECTIVE OF PFS-PLUS-DEVICE OR PFS-ONLY APPROACHES

Injection force: Ophthalmic and dermatological applications require injection using a fine needle (30 gauge or finer). This has an impact on the injection force. As shown in Figure 4, injection force with a 0.5 mL PFS is lower than a 1 mL "long" PFS. This difference may be

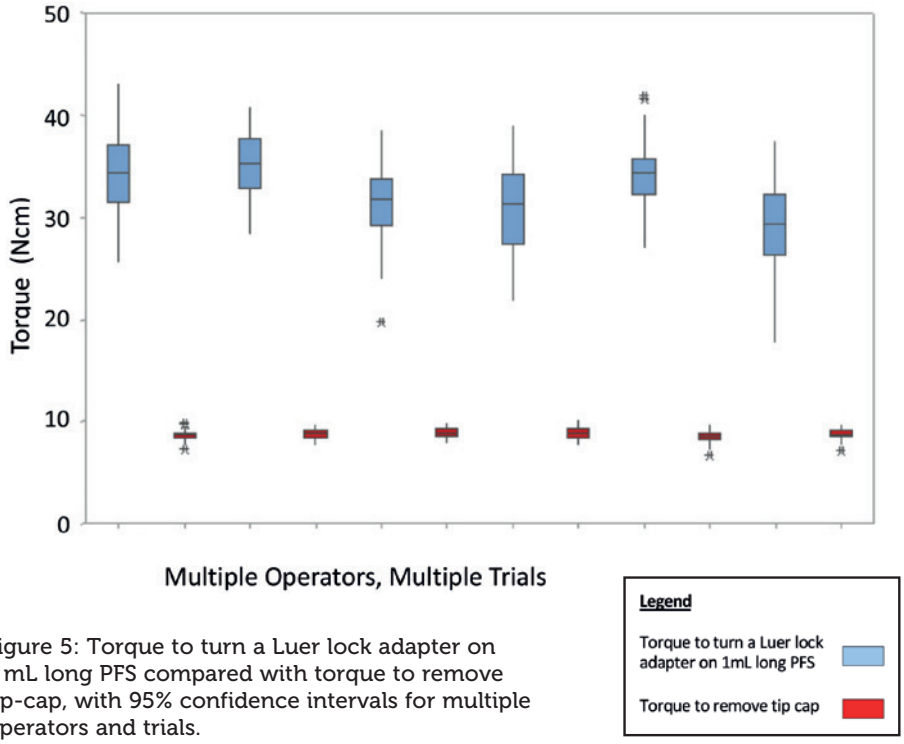

Figure 5: Torque to turn a Luer lock adapter on 1 mL long PFS compared with torque to remove tip-cap, with 95% confidence intervals for multiple operators and trials.

more acute for viscous formulations. The device could provide mechanical advantage to help reduce the injection force even when accuracy of dose is not an issue. Lower injection force for stability is useful when delivering an injection in applications such as ophthalmology and dermatology.

Luer lock adapter removal torque: Luer lock is the most appropriate PFS configuration to be used for most microlitre applications. The Luer lock adapter on a glass PFS is typically a plastic component press-fit onto the glass Luer cone, having a tiny undercut. In human factors studies, it was observed that none of the clinicians held the Luer lock collar when attaching the needle. It is hence important to ensure that torque to dislodge/rotate the Luer lock adapter (Figure 5) is always greater than either torque for the user to attach the syringe or torque for the user to remove the tip cap.

Subvisible particulates: Applications such as ophthalmology require conformance with USP<789> for subvisible particulates. Baked-on silicone or silicone-free PFS can help confirm to this requirement.

Other requirements: Other PFS requirements for microlitre applications may include low endotoxin levels, silicone free, tungsten free, low oxygen and moisture permeability, and allowance of drug storage as low as -80°C.

CONCLUSION

When does a PFS-plus-device approach make sense? A PFS-plus-device approach is essential when accuracy and precision is necessary in the delivery of a microlitre dose. A PFS-plus-device approach is also required for doses of 50 µL or less for drugs with a narrow or unknown therapeutic window. Irrespective of whether a PFS-plus-device or PFS-only approach is employed for microlitre dosing, the correct choice of PFS is essential relative to the intended application.

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Gautam Shetty is the founder of Congruence Medical Solutions. Prior to Congruence, he was General Manager of a Novel Drug Delivery Systems business unit. He pioneered development of ophthalmic drug delivery devices and targeted organ delivery systems. Prior to that, he held a number of positions at BD, involving R&D, strategic marketing, commercialisation planning and M&A. Dr Shetty holds a PhD in Biomedical Engineering from Case Western Reserve University (Cleveland, OH, US). He has authored more than 12 patents in the injectable drug delivery device space covering ocular drug delivery systems, pen injectors and patch pumps.

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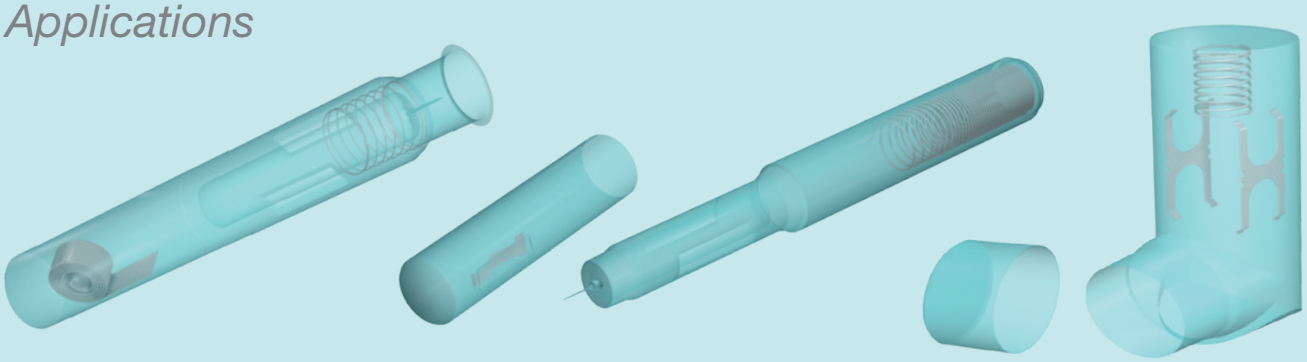
SAFETY SYRINGES

Applications



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ALTERING PATIENT TREATMENT: HOW SC DELIVERY CAN HELP PATIENTS MANAGE CHRONIC CONDITIONS

Here, Victoria Morgan, Director of Segment Marketing, Biologics, at West Pharmaceutical Services, looks at the benefits of combining an active pharmaceutical product with a novel subcutaneous delivery device, and highlights some of the partnerships West has with biopharmaceutical and other companies, which have led to market launches of products incorporating its on-body delivery system.

In recent years, the pharmaceutical industry has become steadily more patient centric. The impact can be seen in nearly every aspect of the industry – from regulatory guidance, trial design and drug delivery to new drugs proliferating the pipeline, such as biologics. Biologics are helping to revolutionise the treatment of chronic diseases such as multiple sclerosis and other autoimmune diseases – by helping patients take less frequent injections.

> "There is a paradigm shift underway in terms of what is possible in a pain-tolerant larger-volume injection."

Additionally, by targeting specific components of a disease in ways never thought possible before, these therapies may also help some acute conditions, including certain types of cancer, become manageable chronic conditions.

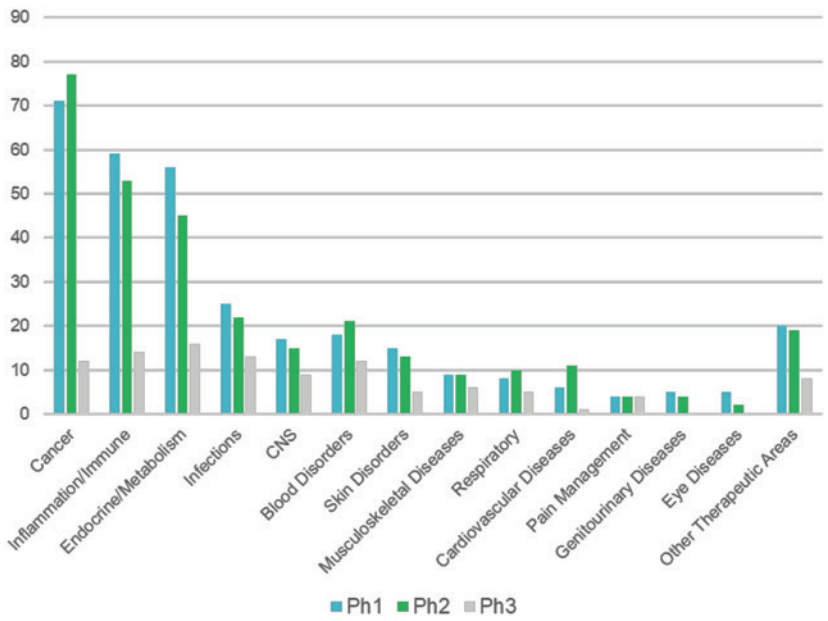

Figure 1: Number of NME SC biologics programmes in the clinic.[1]

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A real focus of biologics research and development lies in new molecular entities which can be administered into the subcutaneous (SC) tissue. Therapeutic areas such as growth hormones and diabetes have long shown efficacy through SC delivery and an established patient acceptance of self-injection and pain tolerance. These therapeutic areas are rapidly being joined by oncology, and autoimmune and blood disorders, which traditionally had IV and infusion as the main routes of administration but which are now seeing novel drug launches with SC delivery routes (Figure 1).

THE SC SPACE IS NO LONGER THE NEW FRONTIER

Administration of large-volume medicines has always been a challenge – one that has traditionally forced many drugs to be formulated into the <1 mL space. This was the approximate volume which would be tolerated by the patient while still being an efficacious dose. Yet there is a paradigm shift underway in terms of what is possible in a pain-tolerant larger-volume injection – all because of new ways of accessing the SC space.

Whereas intravenous (IV) infusions usually have to be administered in a hospital or a doctor's office, SC administration may be performed by a healthcare professional at the patient's home or even by patient self-administration.[2] In addition, subcutaneous administration helps to treat patients with poor venous access or to spare patients' venous capital.[3] SC administration is of particular benefit for long-term or chronic drug treatments. In addition, SC administration may be better tolerated, compared with IV administration, as the slow absorption may abrogate side effects related to high serum concentrations.

> "Amgen's on-body infuser incorporates West's wearable - the first generation of which was the first of its kind to be FDA approved in combination with an approved drug."

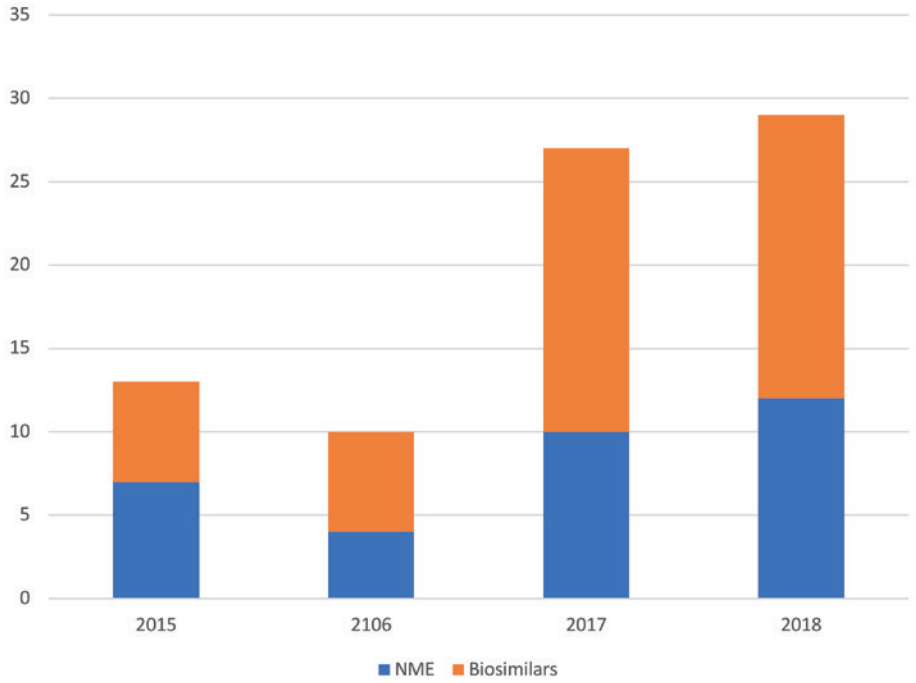

Figure 2: Global SC biologic approvals by year.

LET'S TALK SUBCUTANEOUS

For patients diagnosed with haemophilia A, a typical treatment regime would be octolog alfa every 48 hours, with numerous injections to treat on-demand bleeds. The total number of injections each week could easily be more than 10. Patients diagnosed with multiple sclerosis may relapse when adherence to therapeutic regimens wanes, forcing a 3–5 day hospital stay for IV steroids.

While some diseases have moved the needle forward in terms of patient compliance – such as the regular use of insulin pens in diabetes – many people worldwide still suffer from the daily reminder and pain of their injections. The SC space allows us to think differently about how a patient perceives his or her illness by allowing larger volumes to be administered less frequently. When patients are not frequently reminded of their condition, adherence can be improved. Pharmaceutical companies recognise this, as do regulators, as evidenced by the increasing number of SC product approvals per year (Figue 2).[4]

The benefits of SC delivery flow through to the clinic, thanks to pharmacy efficiencies with faster drug prep time, less set-up which reduces nursing time and fixed dosing which reduces waste and medication error.[5-6] SC administration is a win for the patient, the clinic and the pharmaceutical company, while offering a way of differentiating the product to gain (or, in the case of biosimilar threat, slowing the loss of) market share.

DELIVERY DEVICES AS PART OF A COMBINATION PRODUCT

Combining an active pharmaceutical product with a novel SC delivery device makes joining the world of combination devices a well-timed move. Precedents have been set by Amgen with the launch of Onpro®, an on-body injector presentation of Neulasta® (pegfilgrastim) for neutropenia during chemotherapy, as well as Pushtronex® single-use on-body infuser containing Repatha® (evolocumab) for hyperlipidaemia.

Amgen's on-body infuser incorporates West Pharmaceutical Services' wearable drug delivery platform – the first generation of which was the first of its kind to be US FDA approved in combination with an approved drug. These combination products have revolutionised the way a patient visualises their illness as they enable the patient to home administer their treatment, thereby avoiding a repeat trip to the hospital or clinic.

FROM DEVICE TO PLATFORM

In the drive to formulate biologics for patient adherence, higher volumes and higher viscosities are typical product profiles of many SC drugs. However, higher viscosities may not allow for conventional delivery due to the need for longer injection times to reduce patient discomfort. West recognised this trend and

Figure 3: West's on-body injector platform, SmartDose®.

responded by developing its SmartDose® drug delivery platform, which includes a first-generation device that allows up to 3.5 mL of liquid drug to be administered over a longer period.

First, human trials were conducted between 2011 and 2014, and development on wider-platform offerings – including large volume and preloaded options – started soon after. With Amgen's FDA approval in 2016, EMA approval in 2017 and Japan/rest of the world approval in 2018, global acceptance of combination products has begun.

The SmartDose® platform has expanded with a user-loaded second-generation up to 10 mL device which leverages the success of the first-generation device with proven engineering and industrialisation on a larger scale. With options available for dose volumes up to 10 mL, the second-generation SmartDose® device can adapt to a variety of drug delivery needs (Figure 3).

> "Patients have never before been on the receiving end of such a rapid wave of advanced therapies."

REASSURANCE OF KNOWING DEVICE IS PATIENT FRIENDLY

In the words of poet Alexander Pope in 1711, "to err is human"[7] and this is still very apt in 2019 when we think about human factors and user error. The simplest of devices in the hands of device engineers can become a behemoth in the hands of a patient – hence the importance of human factors in Phase III trials.

Extensive human factor studies and user interface development have been done by West using the 10 mL user-loaded second-generation SmartDose® device. This work included body mass index (BMI), age and previous injection experience – with people who were patients (and took injections) and healthy volunteers (who did not take regular injections). The design usability, acceptability and comfort were assessed, along with establishing whether the user needs were addressed and what the monthly dosing preference was.

The results showed that the second-generation SmartDose® 10 mL device had a well-received on-body size and was intuitive, easy to use and desirable. When treating a chronic condition with the need for an 8 mL monthly dose, seven total treatment options were evaluated. The second-generation SmartDose® 10 mL device was voted the most preferable treatment, compared with the other treatment options, which included weekly autoinjectors, monthly dosing via multiple autoinjectors, visiting a clinic or via infusion. Patients don't like taking frequent injections and a second-generation SmartDose® 10 mL device monthly injection helped them with less frequent injections.

CUSTOMERS CHOOSE SMARTDOSE® DRUG DELIVERY SYSTEM

In January 2019, scPharmaceuticals (Burlington, MA, US) announced it had signed a development agreement with West Pharmaceutical Services to incorporate its SmartDose® drug delivery system for delivery of FUROSCIX® (furosemide) – scPharmaceuticals' lead programme for the treatment of oedema in patients with heart failure. scPharmaceuticals selected the SmartDose® drug delivery system for FUROSCIX® based on, in part, the features and functionality it offers for improving the overall patient experience.

During its recent investor day, Alexion Pharmaceuticals (New Haven, CT, US) announced that it had chosen the SmartDose® drug delivery platform for its clinical trial programme for the delivery of ULTOMIRIS® (ravulizumab-cwvz) once-weekly SC injections. West and Alexion have signed a development agreement for the first-generation SmartDose® and potentially for second-generation development for exclusive use to deliver Alexion's ULTOMIRIS® clinical development programme. ULTOMIRIS® is used in the treatment of paroxysmal nocturnal haemoglobinuria (PNH) – a chronic and debilitating, potentially life-threatening ultra-rare blood disorder. Using the SmartDose® drug delivery platform, the drug has the potential to be the first-to-market SC option for PNH and atypical haemolytic uraemic syndrome.

SMARTDOSE® MAKES DEVELOPMENT EASIER

By partnering with West for an Integrated Solutions Program that includes regulatory support and clinical filling of SmartDose® device cartridges, customers can ease their path to market for combination products. In 2019, West announced it had commenced discussions with Swissfillon (Visp, Switzerland) – a provider of aseptic fill-and-finish services to pharmaceutical and biotechnology companies – that are intended to lead to a non-exclusive global collaboration to provide fill-finish capabilities to customers using the SmartDose® platform for complex molecules.

Through the collaboration, it is anticipated that West will be able to deliver an integrated solution with filled Daikyo Crystal Zenith® cartridges for the SmartDose® wearable device, which is expected to accelerate clinical development and enable customers to bring their innovative injectable drugs to market quickly. This new collaboration is expected to offer customers a robust fill-finish capability later this year.

AIMING FOR SUCCESS

Patients have never before been on the receiving end of such a rapid wave of advanced therapies – and biologics are at the heart of this wave. However, the ever-increasing list of demands a biologic drug places on drug developers is a significant challenge. In a price-sensitive, patient-centric world, value has never been more necessary. Working with a partner, such as West, which has proof of performance and a collaborative spirit can help navigate the challenges found along the drug development road. Let us help you to improve your patients' outcomes, avoid costly delays to launch and provide a better return on investment. By choosing the SmartDose® drug delivery system, you choose to improve the treatment experience of your patients as they confront their illness.

ABOUT THE COMPANY

West Pharmaceutical Services, Inc. is a manufacturer of packaging components and delivery systems for injectable drugs and healthcare products. Working by the side of the world's leading pharmaceutical, biotechnology, generic drug and medical device producers from concept to patient, West creates products that promote the efficiency, reliability and safety of the global pharmaceutical drug supply. In addition, West provides a comprehensive Integrated Solutions Program that combines high-quality packaging and delivery systems with analytical testing, device manufacturing and assembly, and regulatory services to support customers throughout the drug development lifecycle.

West is headquartered in Exton, PA, US, and supports its customers from locations in North and South America, Europe, Asia and Australia. West's 2018 net sales of US$1.7 billion reflect the daily use ofapproximately 112 million of its components and devices, which are designed to improve the delivery of healthcare to patients around the world.

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ABOUT THE AUTHOR

Victoria Morgan has been in the pharmaceutical industry for more than 25 years with extensive experience in the area of injection drug delivery products, such as primary packaging and combination products for vial, prefilled syringe systems, cartridges and devices. Throughout her tenure at West, she has served in various functions across sales and marketing. Ms Morgan spent more than 17 years in global sales roles, with her most recent position being Director of Segment Marketing, Biologics, where she has responsibility for global biological strategy development and implementation.

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West seeks partners for its SmartDose platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company.

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PATIENT TOLERABILITY WITH HIGH-VISCOSITY, LARGE-VOLUME SUBCUTANEOUS INFUSIONS

In this article, based on two blog articles, "Advantages of Subcutaneous Drug Delivery" and "Patient Tolerability with High-Viscosity, Large-Volume Subcutaneous Infusions", originally published earlier this year on the Enable Injections web page, Jennifer King, Marketing Manager, and Matthew J Huddleston, Executive Vice-President & Chief Technology Officer, both of Enable Injections, discuss the advantages of subcutaneous drug delivery and how these have yet to be fully harnessed in currently marketed therapeutics.

Prepared by ONdrugDelivery Magazine for and on behalf of Enable Injections.

ADVANTAGES OF SUBCUTANEOUS DELIVERY

Recent innovations have led to the development of numerous novel small-molecule and biologic formulations that require parenteral administration, mainly intravenous (IV), subcutaneous (SC) or intramuscular (IM). Concurrently, innovative drug delivery systems, such as infusion pumps, autoinjectors and wearable infusers, have been developed to facilitate patient access to parenteral therapies.

The number of new product approvals of parenterals has risen in recent years accordingly (see Figure 1), in particular of products for SC delivery. There were 95 biologic therapies for SC administration approved by the US FDA in 2017 alone and approximately 240 SC biologics are either in development or have been submitted for approval by the FDA.[1]

> "What is it like to inject 5, 10, 15 mL and greater volumes of a high-viscosity biotherapeutic into SC tissue at high flowrates? More importantly, can the patient continue to tolerate this approach?"

IV administration requires a medical facility with trained medical professionals, travel to and from which is inconvenient,

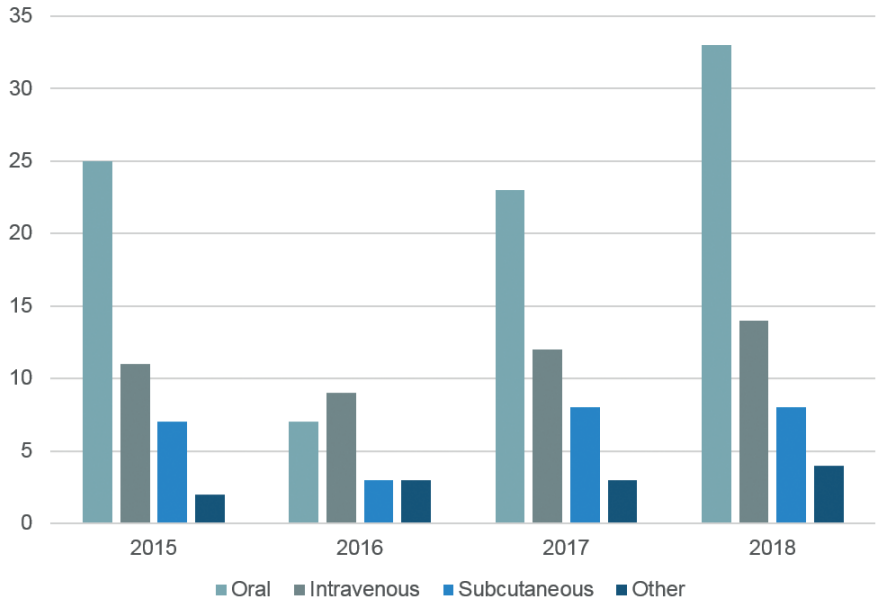

Figure 1: 2015-2018 US FDA novel drug approvals by year and route of administration.

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often prohibitively so, for many patients. IV administration also typically requires a trained medical professional to set-up an IV infusion set and determine appropriate dosing/infusion rate and time. In addition to the risk of infection at the injection site, IV administration is also associated with the risk of systemic infection, potential exposure to IV particulate matter, and exposure to hospital-acquired infections.

For IV administration, additional time is required before, during, and after the actual infusion for the preparation, infusion duration, and observation post-infusion. Because of the extended time, supplies, facility, trained staff, and equipment required for administration, IV therapeutics are generally more expensive compared with other methods of administration.[2]

SC administration allows therapeutics to be self-administered by patients or healthcare providers using a variety of different delivery systems. Because SC administration facilitates patient self-administration in home or outpatient clinical environments, it reduces medical facility fixed costs. In a 2015 Belgian meta-analysis evaluating socio-economic impact of SC versus IV administration of trastuzumab in HER2 positive metastatic breast cancer, it was estimated that SC administration could contribute to a cost saving of €758-2576 (£653-2376) per annual course. SC administration was also reported to enable a threefold reduction in the total preparation and administration compared with IV administration.[3]

SC administration provides flexibility in the anatomical infusion site, and options include the stomach, thighs, and backs of the arms. SC infusion systems can be designed with smaller needle sizes, which may decrease pain during infusion. While the risk of infusion site infection still exists, SC infusion site infections are generally limited to cellulitis and very rarely progress to systemic infections. Further, administration at home reduces the risk of exposure to hospital-acquired infections.

In a 2015 meta-analysis, a literature search was conducted to identify clinical studies published from 1980 to February 2015 that included comparison of IV, IM, and SC administration in order to determine the advantages and disadvantages of each administration route and investigate patient preference. In studies comparing SC to IV administration, more patients reported a preference for SC administration (88.9%) than IV (9.6%).[4] An international, randomised, two-cohort study (PrefHer) reported similar results, in which 92% of patients stated they preferred SC administration of trastuzumab versus 8% for IV.[3]

> "Key device design characteristics that may influence patient experience and tolerability during SC infusion of high-viscosity, large-volume therapeutics include flow rate, skin/needle interface, and needle size."

In addition, a systematic review of randomised, controlled trials and/or crossover studies investigating patient preference reported that patients preferred SC versus IV administration in four of six trials.[5] In addition, a non-interventional time and motion study was conducted in 2016 in eight countries to determine time savings with rituximab SC injection compared with IV infusion. The study determined that patient SC self-administration at home decreased treatment time.[6]

THE NEED FOR SOMETHING DIFFERENT

Traditional methods of SC drug delivery include autoinjectors and infusion pumps. These delivery regimens have traditionally been limited by the volume which can be delivered (<1-2 mL), injection site degradation of the therapeutic (absorption), and dose range. But with recent advances in formulation and delivery technologies, SC is increasingly becoming a viable means of administering a wide variety of therapeutics.

Patient experience is becoming more important, as it relates to overall drug efficacy and safety. The introduction of biotherapeutics, which require higher concentrations of active pharmaceutical ingredient to meet efficacy requirements, has not only challenged the previously established limits of volume, viscosity, and flowrate, but the devices used to deliver them. Thus, while the trend for SC administration is moving to large-volume injections of high-viscosity drugs, there are many questions that are not well understood. For example, what is it like to inject 5, 10, 15 mL and greater volumes of a high-viscosity biotherapeutic into SC tissue at high flowrates? More importantly, can the patient continue to tolerate this approach?

Many peer-reviewed studies[7,8,9,10] have focused on administration volumes of up to 3 mL, flowrates of up to 10 mL per minute, and viscosities of up to 50 cP. These studies have been singularly focused on one or two performance attributes due to limitations with the devices used for delivery. Data is needed on patient tolerability with the combination of large volumes, various flow rates, and higher viscosities associated with SC infusion.

Devices need to adapt to this new class of drugs. The best design will incorporate a unique set of device attributes and requirements, as well as anticipate key drug and patient variables to produce a safe and efficacious delivery, while maximising a positive patient experience.

DEVICE VARIABLES & CONSIDERATIONS

Key device design characteristics that may influence patient experience and tolerability during SC infusion of high-viscosity, large-volume therapeutics include flow rate, skin/needle interface, and needle size. These attributes are discussed further below with respect to patient impact. It is also likely that these variables are interdependent.

Flow Rate

Previous studies[9] have focused on high-speed injection (autoinjectors) or constant flowrate delivery (infusion pumps). The value proposition has been to minimise injection time or allow for a fixed injection time, both of which could be desirable if, for example, the user needs to hold an injection device against their skin or be tethered to an infusion pump.

Infusion time may become less relevant if the user is uninhibited during daily activities while receiving therapy, such as using an on-body delivery device, and a slower flowrate (and the associated longer injection time) might well be preferred by the patient and improve tolerability of large volumes. It is hypothesised that slower flowrates could lead to a lower incidence of site reactions and injection pain.

Skin / Needle Interface (Tissue Tent)

In general, previous studies[10,11,12] have investigated SC injection by needle and syringe, or using infusion sets and butterfly needles. In either case, the user has the ability to control the depth of the needle by either pinching or stretching the tissue at the injection site prior to needle insertion.

This pinching or stretching, known as the tissue tent, may also provide a secondary benefit by applying a small amount of pressure at the injection site, which may have several advantages, including reducing needle insertion pain by disrupting the tissue at the injection site, similar to a nurse pressing on the injection site prior to needle insertion. It is also hypothesised that pressure at the injection site could encourage a deeper deposit of drug into the subcutaneous space, especially in cases of large delivery volume. It could also potentially prevent leakage and backflow, similar to a nurse applying pressure to the injection site at the completion of delivery.

Whilst manually inserted needles require manual pinching / stretching, devices can incorporate a mechanism to stretch the tissue at the injection site automatically, ensuring the needle inserts to the correct depth, that drug is delivered into the appropriate anatomical space and conferring any additional advantages relating to pain and drug deposition.

Needle Size

Previous studies with needles and syringes, or infusion sets, typically involve needles ranging from 31-26 gauge, with the majority being at the larger end of the range. A few publications have theorised that smaller-gauge needles introduce greater discomfort due to increased fluid velocity at a constant flowrate.[13,14] However, this is unlikely with low pressure delivery. It is likely that flowrate in conjunction with needle size could be important, with a smaller needle size being preferred. In general, smaller needle sizes produce less injection site pain[11,12] with less leakage and backflow.

DRUG VARIABLES AND CONSIDERATIONS

Characteristics of the drug that impact patient tolerability of high-viscosity, large-volume SC infusion must be considered.

Volume and Viscosity

Typically, pharmaceutical companies have had the mindset to pursue high-concentration (high-viscosity) and low-volume formulations based on limitations with previously available delivery systems. But studies suggest that injection site pressure is less affected by volume and more dependent on viscosity.[10,12] Pharma and biopharmaceutical companies could instead take advantage of the flexibility in the drug concentration and delivery volume that high-volume injectors allow, to open up new possibilities in formulation development for SC administration.

Other Drug-Specific Attributes

Other drug-specific variables which affect patient tolerability may include pH, osmolality, excipients, and temperature. Much is known about patient tolerability with low-volume SC injections,[15] but what is the pain tolerance and how is it affected by these drug-specific attributes of the therapeutic?

PATIENT VARIABLES AND CONSIDERATIONS

Injection Pressure and Backpressure

Previous studies have investigated tissue backpressure as a function of flowrate, viscosity, and delivered volume.[8,16] However, these studies were executed with constant flowrate pumps. Studies of a system that adjusts the flowrate of the drug based on the backpressure being created within the injection site could explore potential advantages in terms of patient preference and tolerability compared with constant flowrate pumps.

Patient Characteristics

The abdomen is a popular location for SC injections, due to its easy access and amount of available space. Additional SC injection sites, including the inner thigh and back of the arm, could also be considered, although the suitability of these sites for larger infusion volumes is not established. The impact of other patient demographics, such as body mass index (BMI) and skin integrity/type, on infusion and patient tolerability should also be evaluated.

ABOUT THE COMPANY

Enable Injections is an investigational-stage company developing and manufacturing on-body subcutaneous infusion delivery systems designed to help improve patient quality of life. Enable's body-worn enFuse™ platform utilises any standard container closure system to deliver large-volume pharmaceuticals and biopharmaceuticals. Enable's device platform can be developed for use with small-molecule and biologic drug formulations across a range of viscosities.

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Subcuject

A PATIENT CENTRIC *AND* PHARMA COMPANY CENTRIC PREFILLED WEARABLE BOLUS INJECTOR

In this article, Jesper Roested, Chief Executive Officer, Subcuject, explains why the pharma/biotech drug development process often means device selection occurs after Phase II despite the advantages of earlier selection being well understood, and how this then precludes the selection of novel primary packaging and delivery systems. He goes on to describe Subcuject's wearable injector, which meets the requirements of, and does not disrupt, existing pharma development processes and infrastructure.

Over the past few decades, the drug delivery device industry has developed injection solutions to meet the requirements of new biologic treatments coming through pharma pipelines. These devices are patient friendly, with focus on usability, leading to e.g. a number of cost effective and easy-to-use autoinjectors that are prefilled and require no assembly or setting by the patient. Furthermore, disposal of conventional, single-use injection systems presents only a minor challenge as the environmental impact of disposal is minimal.

As the patient experience with an injectable drug is heavily influenced by the delivery device, the advantage of selecting the delivery device for a specific drug early in development is well known in the industry. However, the reality is that the delivery device is often chosen late in the process.

Over the past years, pharma companies have come to focus on biologics as their source of genuine new targets. Whilst the rewards for success are high, there is of course always a high risk with biologics of not meeting ambitious clinical endpoints. Therefore, pharma companies emphasise the advancement of clinical results as early as possible and the choice of the delivery device tends to be pushed until efficacy is indicated in a successful Phase II trial (Figure 1).

As a consequence of this, pharma and biotech companies often conduct their preclinical chemistry, manufacturing and control (CMC) studies using standard materials such as glass and standard rubbers and so when Phase II is successfully completed, and Phase III is about to commence, little time is available to investigate the stability of the drug in other primary packaging materials.

Furthermore, manufacturing must be ramped up during Phase III and primary packaging solutions that do not fit in to existing filling lines would be cumbersome to handle. Therefore, injection devices that are not based on standard materials or which do not fit in to existing filling lines are often ruled out by pharma at the very point in the development process where the decision on delivery system is made.

For autoinjectors, device developers have managed to present solutions that

> "Devices that are prefilled must be relatively inexpensive – taking up only a few percent of the expected drug sales price in order to fit with the conventional pharma business model – and also allow for pricing flexibility at a later stage."

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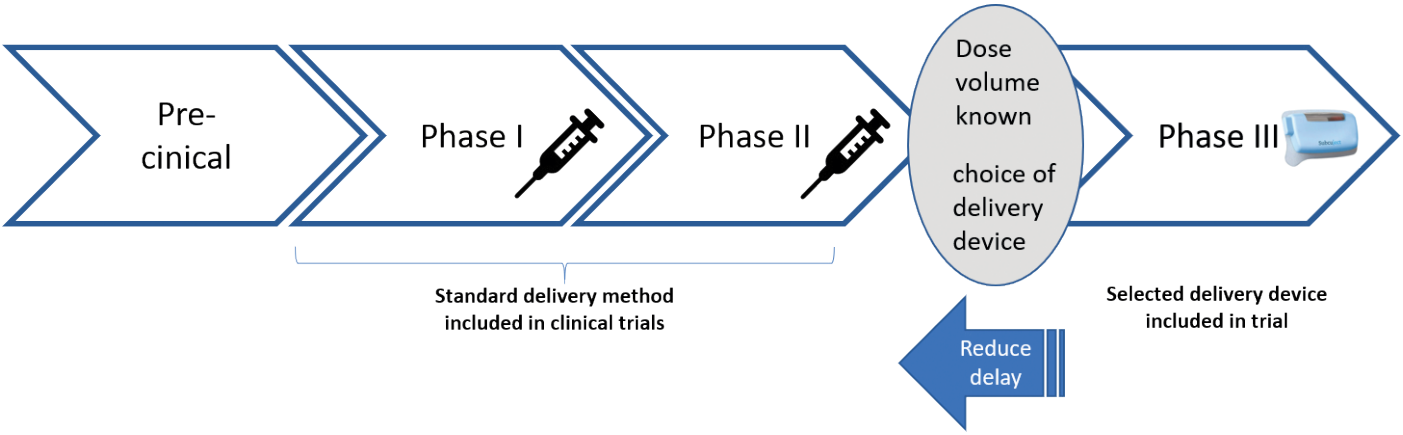

Figure 1: The delivery device is often chosen after Phase II, despite the advantages of earlier selection being well known.

incorporate standard primary packaging materials covered by standard CMC packages and that fit in to existing filling lines. Thereby, the hurdle for a pharma company to select such an autoinjector solution prior to Phase III introduces only small additional risk regarding development and manufacturing.

Furthermore, devices that are prefilled must be relatively inexpensive – taking up only a few percent of the expected drug sales price in order to fit with the conventional pharma business model – and also allow for pricing flexibility at a later stage. Inexpensive manufacturing requires a low number of components, an uncomplicated set-up when it comes to assembly process of the device, and an uncomplicated process at the legal manufacturer (usually the pharma company or filling CMO). Inexpensive manufacturing also requires that sterility barrier solutions do not set requirements for assembly in a sterile environment or require terminal sterilisation.

Eventually, the complete prefilled product must have a shelf life comparable with that of the same drug delivered in a syringe, and the disposal of the single-use device must be acceptable to patients and society in terms of patient/HCP safety and the environment.

The popularity of wearable larger volume injectors is expected to grow considerably over the coming years and many solutions are in development. The challenge faced by developers of larger volume injectors is to inject the drug slowly and in a controlled manner. Many of the wearable injector systems in development rely on electromechanical solutions and these systems seem to function well in this respect. However, many of the systems require either patient assembly of parts (e.g. due to sterility barriers), or they use primary packaging materials that require new drug stability testing because the materials used were not included in the early drug CMC studies.

> "The primary packaging will not pose any drug stability risks due to new materials and its filling may be done on existing filling lines."

Furthermore, the electromechanical and electronic components in such devices result in complex, relatively expensive injection solutions that may be less easily disposed of in an environmentally friendly way after single-use by patients.

Additionally, electromechanical injectors tend to become rather bulky. And finally, they require batteries, which are not the best fit with another requirement of these devices, the ability to remain unaffected by years of cold storage.

SUBCUJECT'S SOLUTION

Aware that it is not possible or reasonable to ask the entire pharmaceutical industry to transform the way it develops its products, Subcuject is developing a prefilled, single-use, wearable bolus injector for injection volumes below 10 mL (Figure 2), which takes into account all of the requirements outlined above and meets the challenges arising, meaning the pharma industry can select it at any stage of development, without introducing undue additional disruption, cost and risk….

Figure 2: Subcuject's prefilled, single-use, wearable bolus injector (first version with a 3 mL standard cartridge).

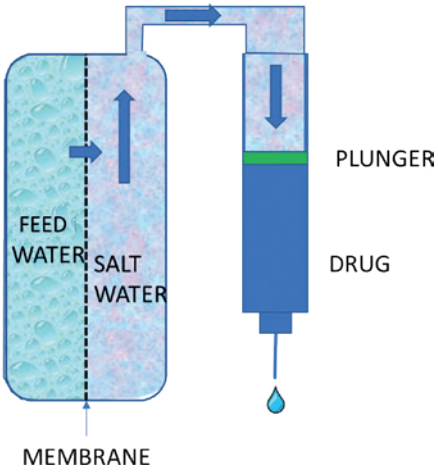

Figure 3: The Subcuject wearable's internal osmotic drive unit uses fluid to push the plunger of a standard drug cartridge.

The Subcuject wearable is based on an internal osmotic drive unit using a fluid to push the plunger of a standard drug cartridge (Figure 3). It represents a very simple mechanical concept, yet with high drive capacity.

Overall the Subcuject device is smaller than most other wearable bolus injectors, it is fully mechanical and it has a low part count. The only operations to be carried out by the user are to peel off a paper backing, place the device on the body and push a button. Needle insertion and retraction is handled automatically. The device can be adapted to inject even highly viscous drugs at around 1 mL per minute. After use, the device is removed from the body and discarded.

"Only the needle unit needs to be sterilised and the drug cartridge is filled and sealed in a standard aseptic production environment. The rest of the device does not require sterilisation and no terminal sterilisation is needed."

The cartridge used in the device is a standard glass cartridge with a plunger of a standard rubber material and the sealing of the cartridge towards the needle unit consists of the same rubber material as used for the plunger. Thereby, the primary packaging will not pose any drug stability risks due to new materials, and its filling can be done on existing filling lines.

The Subcuject device is designed such that the drug in the cartridge and the needle unit both have sterile barriers. Thereby, only the needle unit needs to be sterilised and the drug cartridge is filled and sealed in a standard aseptic production environment. The rest of the device does not require sterilisation and no terminal sterilisation is needed. The drive fluid does not come in contact with the drug or the patient.

The device only consists of relatively few and simple parts and it is designed for automated assembly at a device CMO. The legal manufacturer (pharma or drug filler) will only need to insert the drug cartridge and click on the housing before release. Thereby, the resulting total cost of goods for the device gets close to the cost of a prefilled autoinjector.

The Subcuject device is designed for not compromising the drug shelf life at cold storage and as the device is fully mechanical, battery discharge is not an issue. Additionally, the absence of electronics means that disposal after single use is no bigger issue than it is for e.g. autoinjectors.

Currently the Subcuject device concept for 3 mL drug volume is undergoing performance testing.

"The resulting total cost of goods for the device gets close to the cost of a prefilled autoinjector."

CONCLUSION

Subcuject can confidently claim that its wearable bolus injector is just as pharma company centric as it is patient centric. It achieves this by fitting in with the reality of the device selection process of pharma companies, while presenting a very convenient, easy to use wearable bolus injector for patients.

ABOUT THE COMPANY

Subcuject develops an innovative and proprietary device platform for wearable bolus injection. It is organised as a virtual company, working closely with external experts and specialist organisations. The management team and Board of Directors has decades of experience and proven track record in medical devices, pharma and drug delivery. The company is located north of Copenhagen, Denmark. It is privately held.

ABOUT THE AUTHOR

Jesper Roested holds an MSc in Medical Electronics and Physics and has 25 years of experience most of which has been in business development and management roles in the life science industries. He spent seven years as Partner in a venture capital fund, specialised in medtech. Mr Roested is Chief Executive Officer of Subcuject.

TRAINING DEVICES INCREASE PATIENT ENGAGEMENT AND ADHERENCE – CREATING BETTER OUTCOMES

In this article, Erin Miller, Marketing Co-ordinator at Noble, outlines a study looking at how patients interact with training resources during the first 14 days of a new treatment – and how training devices can help increase confidence, adherence and, ultimately, overall outcomes for the millions of patients who manage their diseases through self-injection.

Across the US, half of all adults live with a chronic disease – and many of them are prescribed a self-injectable therapy to help manage their condition.

As the patient population and demand for self-injection treatments continue to grow, so will the number of patients being introduced to self-injection drug delivery devices. This growing trend increases the importance of effective training and the onboarding process (the first 30-90 days of treatment) as more patients find themselves self-managing their treatments away from clinics.

Unfortunately, even with this growth in prescribed self-injectables, 49% of these patients are not trained in a healthcare provider's (HCP's) office. What's more, 43% of HCPs have not received training devices themselves – limiting their ability to train patients from the very beginning.[1]

> "Lack of training, among other factors, has led to 84% of patients incorrectly administering their medication with an autoinjector."

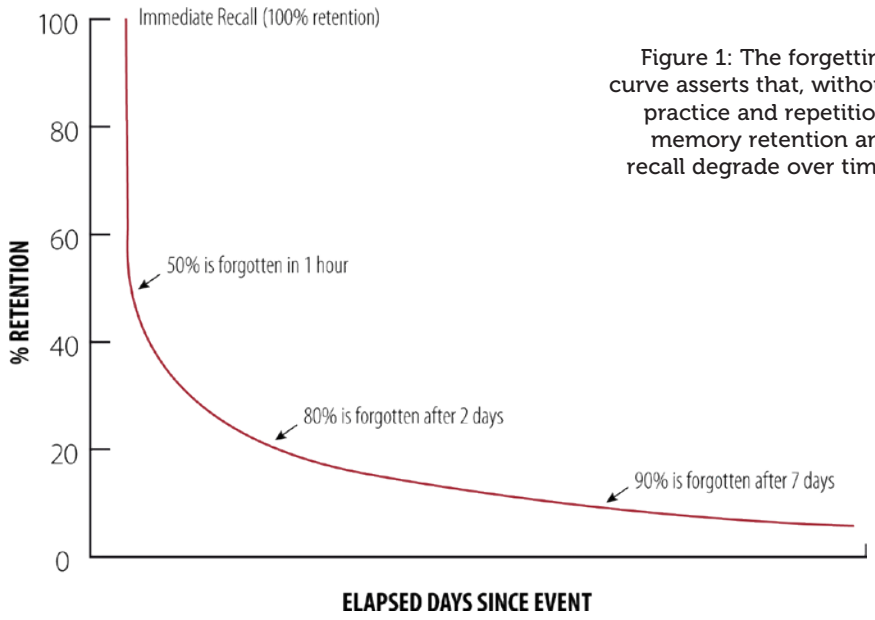

Figure 1: The forgetting curve asserts that, without practice and repetition, memory retention and recall degrade over time.

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> "The forgetting curve suggests that 50% of information is forgotten within one hour – and 90% within one week – after training with an HCP."

This lack of training, among other factors, has led to 84% of patients incorrectly administering their medication with an autoinjector.[2]

Additionally, it has been found that patient nonadherence – whether from a lack of training in an HCP's office, the absence of training devices in the home or patients not reading the instructions for use (IFU) – costs the pharmaceutical industry approximately US$637 billion (£492 billion).[3]

THE FORGETTING CURVE

The forgetting curve – which asserts that, without practice and repetition, memory retention and recall degrade over time – has an important impact on patient adherence. This decline in retention and recall can result in an increase in device usage errors, such as injecting at the wrong angle or removing the device prematurely from the injection site, thereby increasing overall nonadherence to treatment (Figure 1).

The forgetting curve suggests that 50% of information is forgotten within one hour – and 90% within one week – after training with an HCP.[4] Patients can work to reverse these statistics by having training devices on hand at home to practise with throughout the course of their therapy.

Noble conducted a study that set out to confirm and then shed light on these real patient issues and show how training devices can help increase confidence, adherence and, ultimately, overall patient outcomes for the millions of patients who manage their diseases through self-injection.

STUDY METHODOLOGY

Over the years, Noble has conducted multiple cross-sectional studies to understand patient onboarding needs and how training could be used to increase confidence and decrease anxiety. Using these research outputs as a foundation, Noble launched a first-of-its-kind longitudinal training device study to learn more about patient recall, retention, adherence, engagement and more.

The study, which was sponsored by Noble and conducted by Insight Product Development, explored three conditions as they relate to the performance, engagement and preferences of injection-naïve people experiencing a self-administered injection for the first time.

Researchers sought to understand how patients interact with training resources during the first 14 days of treatment. To do so, the study employed a 14-day decay period, which was used to mimic a common fortnightly injection frequency.

Specific objectives of the study included:

- Assessing the effects of different training materials on self-injection performance
- Understanding how patients engage and interact with training materials
- Evaluating the effects of different training materials in relation to patient confidence, anxiety, preparedness, preference and potential compliance.

To create the most realistic onboarding experience for participants, the study employed a deception paradigm to ensure participants would practise at home throughout the study in the same way they would if they were truly onboarding to a new self-injection therapy. Participants were told they would be injecting themselves using a real autoinjector during the second session. Because of this paradigm, the study protocol was reviewed and approved by a third-party institutional review board.

The study comprised 27 healthy adults – with no prior knowledge of self-injections or formal training as an HCP – randomly assigned to one of three cohorts. Each cohort was assigned different training stimuli for use during the decay period.

THE STUDY

To begin the study, participants across the three cohorts attended an introductory session where they received self-injection training, just as they would in a doctor's office if they were prescribed a self-injection course of therapy.

During this first session, researchers replicated an optimal introductory in-office learning experience between an HCP and a patient. This session focused on introducing participants to the drug delivery device and then training them on how to use it with a device that did not include medication or a needle (Figure 2). Afterwards, participants could practise on themselves with a training device, with researchers present. Participants were also given feedback and recommendations for improvement, as would occur during training with an HCP. After the 45-minute training session, they were sent home.

To understand the effects of having access to a training device in-office only, cohort A – the control group – was sent home with only an IFU. This cohort was not intended to represent the minimum amount of training a patient may receive but to set a baseline for evaluating the effects of having additional support, such as training materials, at home.

Figure 2: A participant injects with a training device on an injection pad.

Cohort B was sent home with both an IFU and a training device that mimicked the actual device they would self-inject with later in the study. Cohort C was given both the IFU and the training device, as well as an interactive training video to use at home (Figure 3).

Participants were instructed to practise at home as little or as often as they preferred and were told to keep track of how many times they used their materials.

Participants then did not hear from researchers for 14 days, allowing them to practise with the various materials as frequently or infrequently as they preferred. The purpose of this was to uncover the correlation between successful and unsuccessful self-injections and subjects' access to training materials.

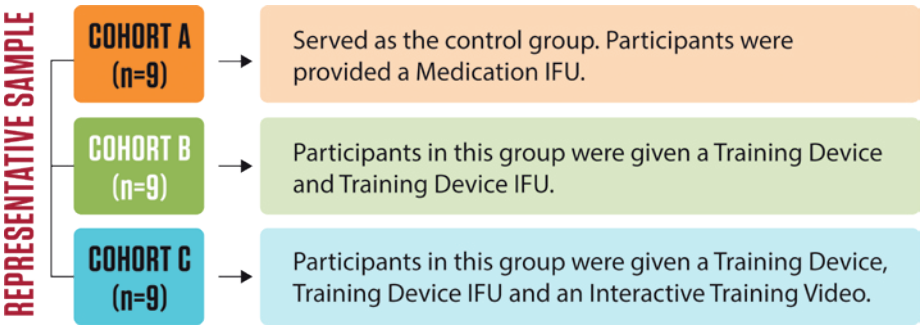

Figure 3: Twenty-seven participants were randomly assigned to one of three cohorts with various training materials.

FINDINGS HIGHLIGHT NEED FOR TRAINING DEVICES

Following a 14-day decay period, researchers conducted a second session to evaluate participants' ability to recall the correct self-injection technique properly with an actual device.

During this follow-up session, participants' performance was evaluated based on their ability to self-inject successfully using an injection pad on their preferred site. Participants were asked to complete this evaluation under the observation of a human factors engineer.

Critical steps evaluated were:

- Removing the cap
- Placing the autoinjector at a 90° angle
- Actuating the device by depressing the needle shield, and pushing and releasing the injection button
- Holding the autoinjector in place on the skin for the full injection duration.

TRAINING DEVICES HELP WITH SUCCESSFUL INJECTIONS

Overall, performance in self-administering the injection differed starkly between the three training groups. Those with training devices performed better – successfully completing all critical steps during their simulated injections.

The research found that 100% of cohorts B and C completed all critical steps for a successful self-injection, while only 44% did so from cohort A.

PATIENTS MORE ENGAGED WITH THEIR TREATMENT

It was also found that engagement in general increased for participants who had training devices to practise with at home. Participants in cohorts B and C prepared for their injection more often at home than those in cohort A, who only had an IFU.

Cohorts B and C both saw 100% of participants practise at least three times – and, in the case of cohort C, 83% practised 5–9 times. This is in contrast with cohort B, where only 33% practised 5–9 times (Figure 4).

> "Engagement in general increased for participants who had training devices to practise with at home."

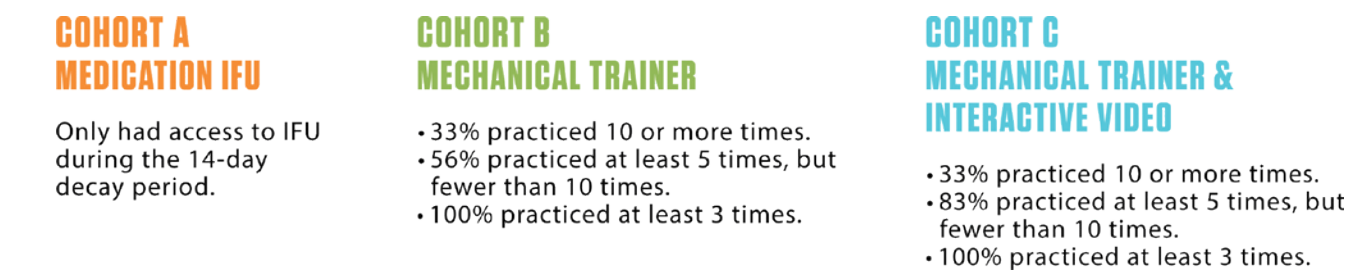

Figure 4: Research found participants with additional training resources were more engaged during the decay period.

RESEARCH SHOWS VALUE OF TRAINING DEVICES

The findings suggest that trainers and other support materials could be extremely valuable to patients who self-inject, as successful injection nearly doubles with training materials that go beyond the standard IFU. The vast majority of participants – 92% – reported that they would prefer to bring home a training device to practise with prior to conducting a self-injection (Figure 5).

A participant from cohort A told researchers: "I would [have liked] the training device. If I had it, I would have remembered [important steps like] taking the cap off." Similarly, a participant from cohort B told researchers: "The trainer device was helpful [because] you can actually practise and get to be hands-on." Another participant from cohort B stated: "Taking the trainer home was so helpful. I was much more comfortable having it."

Participants who did not have a training device at home had to rely on the experience of using the training device in the first session and on rote memory from reading the instructions – resulting in more critical errors relative to the other cohorts.

With the training devices to take home, participants from cohorts B and C were able to practise and, as a result, build motor memory and improve performance. These participants were more confident about how to manipulate the device and the order in which they needed to perform tasks.

SIGNIFICANT FINDINGS

Overall, giving a patient a training device that is close in design and function to the commercial device to practise with at home facilitates the development of a mental framework and motor memory conducive to a successful self-injection.

> "The findings from this study suggest that the implementation of training devices and their use in a home environment helps the user perform successful self-injections."

92%

Of participants would prefer to receive a training device to take home and practice with prior to conducting their self-injection

Figure 5: The vast majority of participants stated how important a training device would be to have in the home for practice.

It is also widely understood that learning the proper self-injection technique involves multiple practise sessions to get acquainted with the various steps involved, beyond that of practising with an HCP during an in-office visit. Having a training device to help with this memory reinforcement is crucial. This, in turn, proposes a critically important conclusion: when anxiety over self-injection is diminished, and patients have mastered the self-injection technique, they may have a higher likelihood of adhering to their treatment, thus obtaining the maximum benefit from it.

In addition to having training devices for practice, research has also found that patients who are more involved in their healthcare experience achieve better outcomes and incur lower costs. These training devices help patients become – and stay – more engaged and involved, thus promoting adherence.

CALLS FOR IMPROVEMENT

To ensure successful self-administration techniques, patients and their HCPs should develop a strategy to improve therapeutic outcomes. An informed patient is essential for developing a framework focused on treating his/her illness and preventing behaviours detrimental to treatment. HCPs must also be informed of the existence of – and the need for – training devices and other materials.

Overall, the findings from this study suggest that the implementation of training devices and their use in a home environment helps the user perform successful self-injections. This highlights the benefit of providing patients with training resources during the onboarding phase and beyond.

ABOUT THE COMPANY

Founded in 1994, Noble is a global leader in medical device training solutions, patient onboarding strategies and multisensory product development for the world's top pharmaceutical brands and biotechnology companies. Focused on driving innovation, Noble works closely with brand, device and commercialisation teams to develop turnkey solutions that improve onboarding and adherence, bringing value to clients and patients alike.

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ABOUT THE AUTHOR

Erin Miller, Marketing Co-ordinator, Noble, is responsible for supporting marketing and advertising efforts at Noble through copywriting and editing as well as content creation for Noble's print and digital communications platforms. Erin holds both a bachelor's and master's degree in public relations.

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SIMULATING STRESSFUL, EMERGENCY-USE SCENARIOS DURING USABILITY TESTS OF INJECTION DEVICES

In this article, Allison Y Strochlic, Research Director – Human Factors Research & Design, Emergo by UL, highlights the importance of simulating environments that are as realistic as possible when conducting usability tests of emergency-use injection devices, and provides case studies with examples of how to create more realistic tests.

INTRODUCTION

Imagine you are walking in the park on a nice spring day. The sun is shining, the birds are chirping, and kids are running around and playing. Then, next to the playground up ahead, you hear someone yell "HELP! HELP!" and see a young girl lying on the grass, gasping intensely for air and holding her throat. A few people have gathered around the child, and you run over to join them. A frenzied babysitter begs you and the other bystanders to help, almost sobbing while she stammers: "It's the first time I'm babysitting for her… I know she's allergic to bee stings, but I have NO idea how to use this thing… She just got stung, and she's already having trouble breathing!" She is frantically waving a tube-shaped object in the air: "Can one of you please help me give her this allergy shot? I called 911 but nobody's here yet, and I'm SO scared!"

> "Human factors researchers need to find creative ways to simulate stressful scenarios when conducting usability tests of emergency-use devices."

Sounds stressful, doesn't it? This is just one example of the emergency situations that injection devices are used in every day. Human factors (HF) researchers need to find creative ways to simulate stressful scenarios such as the one above when conducting usability tests of emergency-use devices, when basic usability testing approaches might not suffice.

USABILITY TESTING PRIMER

Now, to back up for a moment, usability testing is a common method employed by HF researchers to evaluate the interactive qualities of a given design. The method is most frequently applied to devices with hardware and/or software components, and it involves asking people – specifically, representative end-users – to try using a product or service, observing how it works for them, and seeking feedback regarding various attributes. Such attributes often include usability (whether something is easy or difficult to use), clarity, learnability, and perceived use-safety, depending on the test objectives.

Some consider usability testing to be a "test drive" of sorts, albeit one performed while the "car" is still in development and before it hits dealership sales floors.

There are several types of usability tests, but the most common ones conducted during injection device development are formative and HF validation, the latter of which was previously called summative testing.

> "When conducting usability tests of these devices, researchers will be well-served by "amping up" the level of environmental and scenario realism, especially when conducting late-stage formative and HF validation tests."

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Aspect	General description	Autoinjector formative test – one potential configuration
Users	Test participants who represent the device's expected end-users	People with a particular medical condition and lay caregivers who support people with this condition
Use scenarios	Activities researchers ask participants to perform that represent how people might interact with the final device	Preparing for and administering a simulated injection, selecting from among two different dose strengths
Use environment	The setting in which participants interact with the device and perform the use scenarios	A room that that is relatively spacious, quiet, and clean with tables and chairs, representing a home use environment

Table 1: Three key usability testing aspects and potential configurations during a formative usability test of an autoinjector.

A formative test is one conducted iteratively and often as the design is being *formed*, while an HF validation test is one conducted to *validate* that the device can be used safely and effectively.

THE NEED FOR REALISM

Table 1 outlines three key usability testing aspects and how each might be represented in a formative usability test evaluating an autoinjector. The basic approach (described in the right-hand column of Table 1) can be applied to usability tests for a wide variety of injection devices, modified as needed for different drugs and indications, not just emergency use (e.g. including people with diabetes to test an insulin pen-injector).

There are a wide range of devices that have to be used urgently – truly as quickly as possible – to be maximally effective. When it comes to injection devices, those that administer the following medications come to mind:

- epinephrine (for severe allergic reaction)
- glucagon (for severe hypoglycaemia)
- naloxone (for opioid overdose)
- atropine (for nerve agent exposure).

When conducting usability tests of these and other emergency-use devices, researchers will be well-served by "amping up" the level of environmental and scenario realism, especially when conducting late-stage formative and HF validation tests.

SIMULATION FACTORS

During a typical usability test session, a HF researcher invites test participants into a room, usually one at a time, and engages them in various use scenarios after a brief introduction and informed consent process. It is all very orderly and calm, with the researcher observing a participant's interactions with a given device and asking questions about the device's use (Figure 1). However, there are times when more excitement and creative thinking are needed to ensure the usability test – and, the use environment in particular – is as realistic as possible, especially when it comes to testing emergency-use devices.

This need arises not only from researchers' desire to collect complete, representative data, but also from US FDA and other regulators' expectations that devices be evaluated and validated within realistic use scenarios and environments.

Figure 2 lists some of the factors one can consider when it comes to simulating realism and emergency-use scenarios during an injection device usability test.

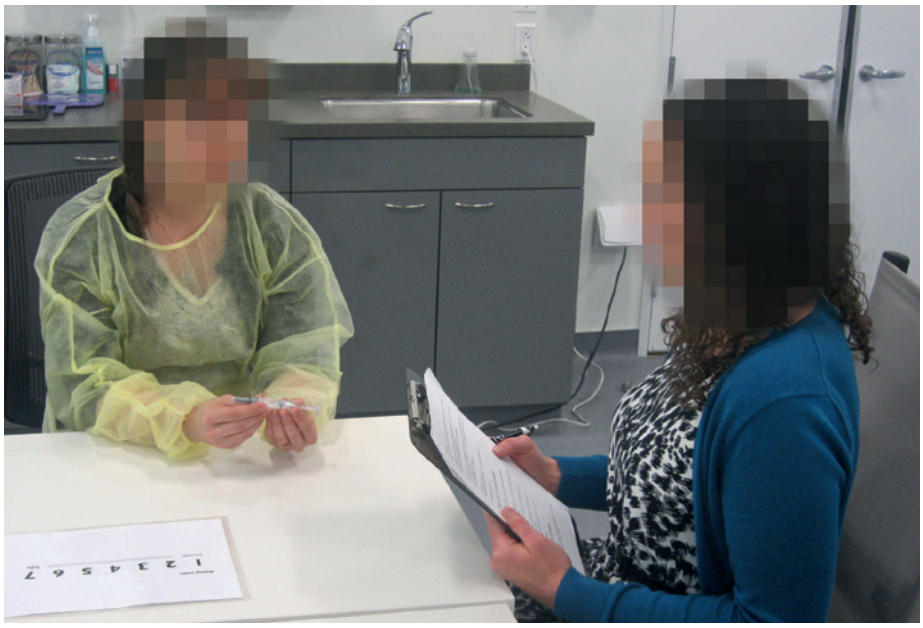

Figure 1: A typical usability test session of a prefilled syringe, with a human factors researcher and test participant sitting in a room.

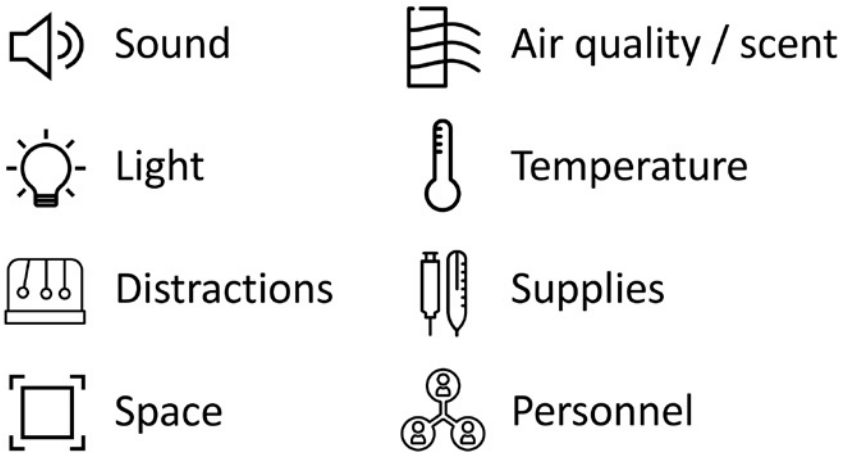

Figure 2: Sample simulation factors.

For example, it's quite common to have a medley of ambient hospital sounds, such as a beeping monitor, hissing ventilator, conversing visitors, and opening/closing doors, playing in the background as test participants interact with a device intended for clinician use in hospitals. When it comes to lighting, some use scenarios might be presented in normal lighting while others might be presented in dim lighting to represent when a device is used in the middle of the night and/or in an otherwise darkened space. Other factors are simulated less frequently but can still be impactful and relevant. Take air quality, for example. Some injection devices – such as those used to administer atropine and other drugs used to treat a nerve agent attack – are sometimes used in spaces filled with thick fog, which naturally limits someone's ability to see.

The balance of this article presents two case studies describing how one can implement a subset of the factors listed in Figure 2 during usability tests to simulate stressful, emergency-use scenarios.

CASE STUDY 1: EPINEPHRINE AUTOINJECTOR

As mentioned earlier, a typical injection device usability test session is relatively orderly and calm. A researcher and participant sit at a table and the participant simulates using the device after signing the informed consent form, answering some background questions, and learning more about the test's focus. When it is time for the "use scenarios," the researcher might ask the participant to "prepare for and simulate administering an injection with this injection device."

Figure 3: Participants rush to inject epinephrine into the manikin, which is being used to represent an allergy sufferer.

Contrast that with the following, this time putting yourself in the participant's shoes: a researcher greets you and asks if you have any final questions about the informed consent form before you sign and walk together to the usability lab's closed door. Then, the researcher briefly describes the research goals, and asks again if you have any questions (you don't). With a serious look on her face, and in a hurried tone, she then reads the following: "You are dining in a restaurant. Suddenly, at the next table, a child about 10 years old calls for help. He says his six-year-old brother has a food allergy and is having a bad reaction. The child says that his brother keeps an emergency shot in his backpack. Find the device and give the child's brother an emergency shot as quickly as possible."

The researcher opens the door to the usability lab and you see a manikin splayed out on the floor with a backpack next to him. You hear someone wheezing and gasping for air, and there is a young woman standing next to the manikin. She is visibly anxious, and is pleading with you: "Can you help him? Is he going to be OK? Is he going to die?" You start to the dig through the backpack. There's a water bottle, a notebook, a sweatshirt, a granola bar… and finally, you find plastic tube labelled "AllergyRSQ injector". You remove the device from the tube, glance at the graphical instructions, and quickly inject the patient's thigh with the device, injecting the life-saving medication. Figure 3 depicts this test scenario.

Which of the two approaches seems like a more effective way to set the scene for and present an epinephrine autoinjector use scenario – the basic usability test setup or the stressful lab scene? While researchers might implement different simulation factors in a different manner, it would be tough to argue that the second approach does not prevail in terms of realism (see Box 1).

BOX 1: ASPECTS OF EPINEPHRINE AUTOINJECTOR USABILITY LAB SCENARIO THAT INCREASE REALISM

- Manikin on floor
- Device in backpack
- Anaphylaxis sound
- Concerned bystander asking urgent questions
- Descriptive task prompt

CASE STUDY 2: MILITARY-USE AUTOINJECTOR

For a project focused on a military-use autoinjector, different approaches were used to simulate stressful, emergency-use scenarios during earlier- versus later-stage formative usability tests (see Box 2). During the early stages of development, a formative test focused on ensuring that users could differentiate between, and comfortably handle, two autoinjector prototypes. The objectives later evolved to a rigorous evaluation of the full injection experience, from autoinjector selection and preparation through simulated drug delivery.

BOX 2: ASPECTS OF MILITARY USE AUTOINJECTOR TEST SCENARIOS THAT INCREASE REALISM

EARLY FORMATIVE	LATER FORMATIVE
Fog	High-fidelity use environment
Flashing lights	Substantial props (buildings, vehicles)
Combat sounds	Reduced visibility (fog)
Large-scale imagery	Actor as victim
Protective gear	

As depicted in Figure 4, the level of environmental simulation factors increased in step with the increase in device prototype fidelity and functionality.

For the early-stage formative test, a traditional usability lab was "dressed up" to represent a combat environment. Specifically, a room with neutral décor was transformed by way of a fog machine, flashing lights, looping soundtrack, and a large-scale image of a combat zone projected on one of the large, plain walls. The researcher shared a detailed scenario prompt outside of the lab, as described for the first case study, and standard Mission Oriented Protective Posture (MOPP) gear was provided and donned by the participants at the start of the scenario (see Figure 4, left).

For a later formative test, the level of realism was increased to evaluate device use in a considerably more dynamic (and, arguably, dramatic) use environment. It started with renting a paintball field called Apocalypse City, complete with an ambulance, pick-up truck, police cruiser, and downed plane, as well as several basic structures with "blown-out" windows

(see Figure 4, right). For the sounds, overlapping and looping combat sounds playing through high-powered speakers created a realistic cacophony.

Someone with prior military experience served as the victim and, at a predetermined time, she screamed "Help!" and began to cough loudly, running into a small brick structure. The participant quickly grabbed the autoinjectors from the supply kit and headed in after the victim, who was lying on the floor gasping for air in a dim and fog-filled space. The participant quickly administered the injection, often counting the "hold time" aloud and reassuring the victim with a gentle tap on their helmet or shoulder. Carefully positioned cameras, including one worn by the actor, captured the action. (Note: The autoinjector prototypes prepared for testing were needleless, so there was no risk of the actor encountering a needlestick injury.)

BEST PRACTICES

In both of the case studies described here, it was evident through observations and participant interviews that the measures implemented to simulate stressful, emergency-use scenarios enabled a more realistic assessment of device use as compared with a typical usability testing approach.

Naturally, there's not a "one-size-fits-all" approach to selecting and implementing simulation factors. Rather, the best approach for a given usability test will vary depending on the test objectives, as well as a given device's expected users, use environment, and use scenarios.

Regardless of the type of injection device, the following best practices are recommended:

- **Increase simulation fidelity as design matures.** It makes sense to implement fewer simulation factors when evaluating initial prototypes in early-stage formative usability tests, and to increase the level of simulation and realism as the design – and usability testing phases – mature, culminating in a relatively high level of realism for HF validation testing.
- **Consider all environmental characteristics.** Don't limit yourself to considering only a testing space's lighting and noise levels, which might be the most obvious factors to modify. Consider all of the factors listed in Figure 2, as well as others that might be warranted based on a given device's expected use environments.

Figure 4: Earlier and later stage usability tests depicting increasing levels of simulation, depicted at left and right, respectively.

- **Implement several simulation factors.** It's common to implement multiple factors, considering the right mix for a given device. But, don't go overboard. The goal is to represent the device's intended use environment – not to win an Oscar for set design.
- **Seek feedback on simulation realism.** Conducting a pilot test is particularly valuable when it comes to simulating stressful, emergency-use scenarios. Related to the points above and below, you want to hit the "sweet spot" in terms of realism, but not go too far such that you create an unrealistic scenario, or cause participants undue anxiety.
- **Seek Institutional Review Board (IRB) review of simulation approach.** When conducting usability tests, human factors researchers need to protect human subjects, or test participants. This task becomes even more important when you are simulating stressful use scenarios. On one hand you, are intentionally inducing stress but, on the other hand, you should ensure that no-one becomes upset or overly-emotional due to the testing scenarios.

CONCLUSION

If a device is tested in an unrepresentative use environment, human factors researchers might miss the opportunity to identify use errors and other interaction problems that, without being identified and mitigated, could hinder immediate, correct use of an injection device needed to administer life-saving medication to someone in dire need. Our goal, therefore, is to test emergency-use devices under conditions that reflect their actual, intended use environments and, as a result, induce the potential stress that would likely accompany device use.

ABOUT THE COMPANY

Emergo by UL's experienced, global Human Factors Research & Design (HFR&D) team specialises in early-stage user research, product design, usability testing, and user interface design. With a primary focus on medical devices and combination products, the team helps clients bring safe and effective products to market and ensures best-in-class user experiences. The team includes more than 65 specialists and has offices in the US, the UK, the Netherlands, and Japan.

ABOUT THE AUTHOR

Allison Strochlic, MS, CHFP, is a Research Director in Emergo by UL's Human Factors Research & Design team, and was one of the team's co-founders. She contributes to a range of research activities that serve to identify user needs and evaluate and validate combination products and other medical technology, and she routinely advises clients on how to meet US FDA and other regulators' expectations. Ms Strochlic is co-author of *Usability Testing of Medical Devices* and several technical articles on applying human factors to medical technology development. She is a Certified Human Factors Professional, and has undergraduate and graduate degrees in human factors.

MITSUBISHI GAS CHEMICAL

MULTILAYER PLASTIC VIALS & SYRINGES FOR BIOLOGICS

Here, Takuya Minezaki, MD, Research Manager, and Tomohiro Suzuki, Associate General Manager, both of Mitsubishi Gas Chemical, provide an overview of the company's OXYCAPT™ Vials and Syringes, explaining how their multi-layered polymer material delivers the advantages of both COP and glass, and is especially suitable for biotherapeutics.

Based on its technologies and experiences, Mitsubishi Gas Chemical (MGC) has successfully developed multilayer plastic vials and syringes called OXYCAPT™ (see Figure 1).

OXYCAPT™ consists of three layers (Figure 2): the drug contact layer and outer layer, both made from cyclo-olefin polymer (COP); and the oxygen barrier layer, which is made from a proprietary, novel polyester. This enables OXYCAPT™ to offer:

- excellent oxygen barrier properties
- high water vapour barrier properties
- excellent UV barrier properties
- very low extractables
- high pH stability
- low protein adsorption and aggregation
- a silicone-oil free barrel
- high transparency
- high break resistance
- easier disposability
- lighter weight.

As regulatory authorities have reported, there are problems with some existing glass and plastic vials and syringes. For example, glass suffers from breakage, delamination, etc, and traditional plastic does not represent a sufficient oxygen and UV barrier. Especially in glass, the US FDA has pointed out such problems and reported more than 50 recalls. To address these problems from glass, many suppliers have launched plastic vials and syringes as alternatives, but their oxygen barrier properties have not always met customer demands.

OXYCAPT™ represents a plastic material with oxygen barrier properties almost the same as glass, and more than 100

Figure 1: OXYCAPT™ Vials and Syringes.

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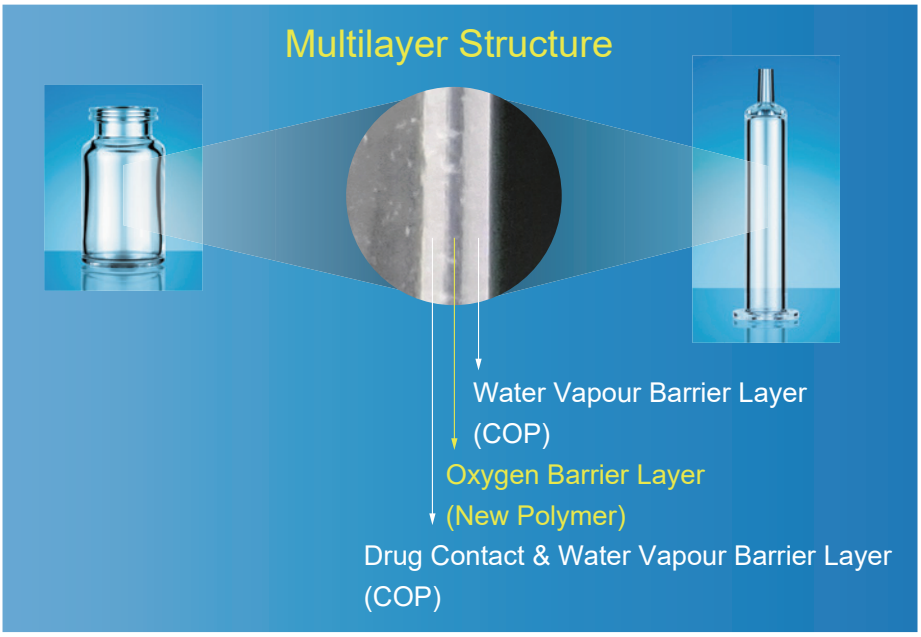


Figure 2: The multilayer structure of OXYCAPT™ Vials and Syringes.

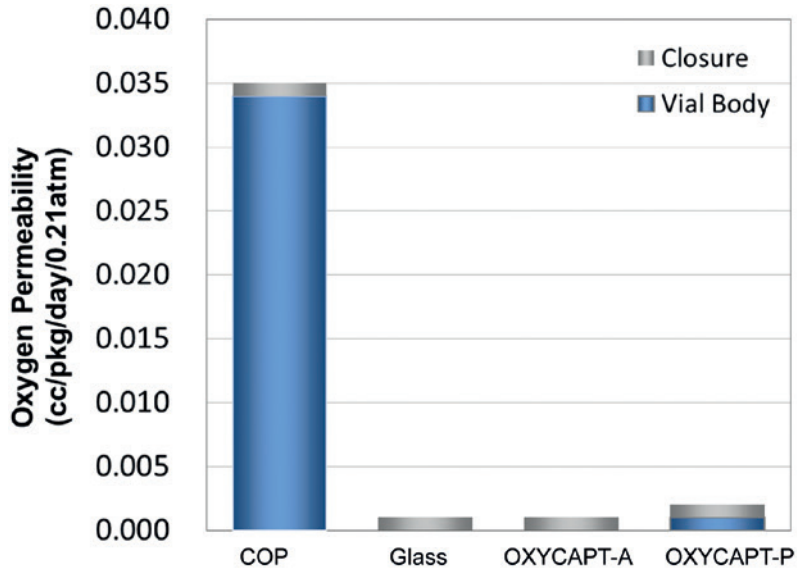


Figure 3: Graph comparing oxygen permeation properties of OXYCAPT™ with COP and glass.

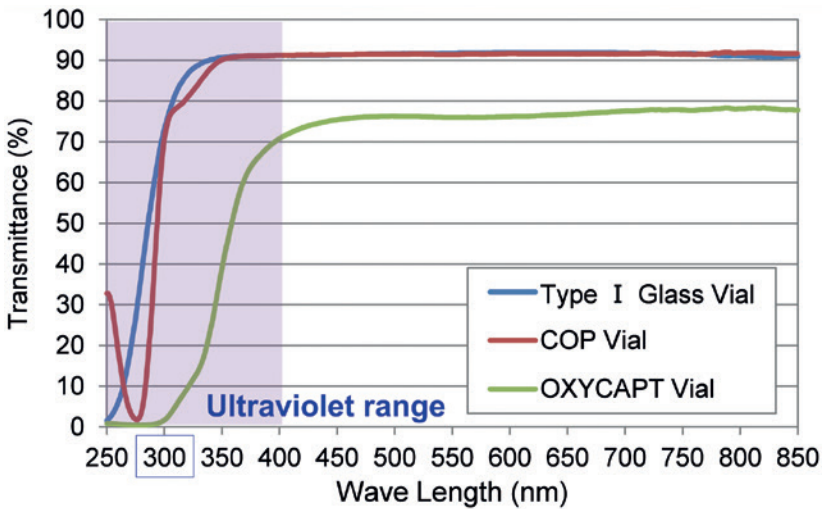


Figure 4: Graph comparing UV transmission properties of OXYCAPT™ with COP and glass.

"OXYCAPT™ vials and syringes are produced by co-injection moulding technology. This technology has been applied to beverage bottles for many years, but we are the first company that has succeeded in developing multilayer plastic syringes."

times better than COP (Figure 3). According to our internal studies using antibodies, OXYCAPT™ also outperformed both glass and COP in terms of preventing oxidation. Biologics are often vulnerable to oxidation, and OXYCAPT™ can contribute to the stability of such oxygen sensitive drugs.

OXYCAPT™ UV barrier properties also compare very favourably indeed to other materials. For example, about 70% of UV (300 nm) light transmits through glass and COP, whereas only 1.7% transmits through OXYCAPT™ (Figure 4). We have confirmed that this feature of OXYCAPT™ also contributes to stability of biologics.

As a barrier to water vapour, OXYCAPT™ cannot outperform glass. Nonetheless, it is comparable with COP and, like COP, OXYCAPT™ comfortably meets with the ICH guideline for water vapour barrier properties.

Studies have shown extremely low extractables with OXYCAPT™. One study was conducted to confirm volatile, semi-volatile and non-volatile impurities from OXYCAPT™. Water and four solutions (50% ethanol, NaCl, NaOH and H_3PO_4) were used and impurities were measured by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control, no impurities were detected in any of the OXYCAPT™ containers. A second study was conducted to measure inorganic extractables from OXYCAPT™. The level of extractables was similar to those from COP, which is well-known as an extremely pure polymer, and less than that of Type I glass (Figure 5).

The OXYCAPT™ Syringe consists of tip-cap, barrel, polytetrafluoroethylene (PTFE)-laminated stopper, and plunger rod. Although a very small amount of silicone-oil

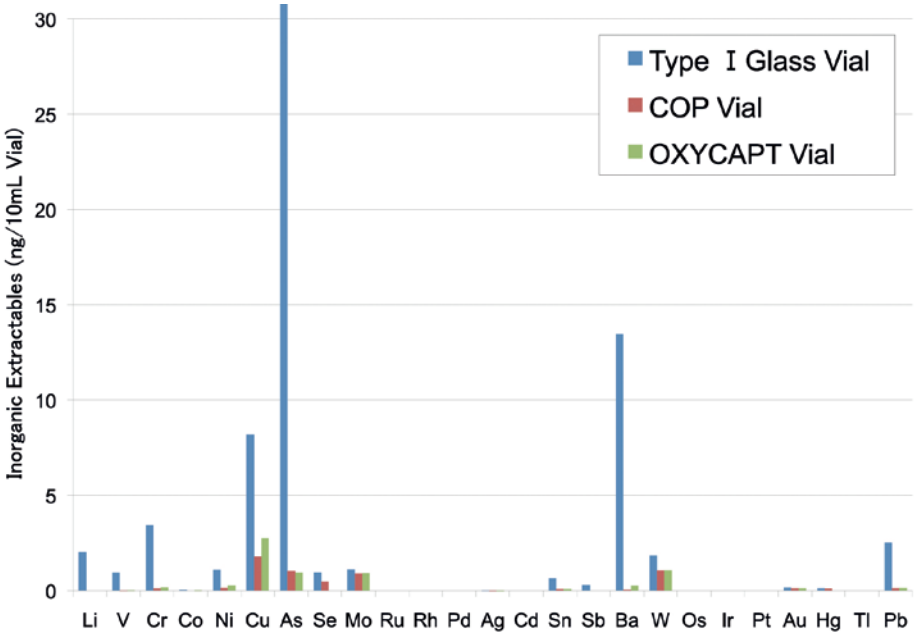


Figure 5: Graph comparing inorganic extractables levels from OXYCAPT™ with those from COP and glass.

"Vials were dropped from 150 cm height to confirm break resistance. All of the glass vials were broken, but zero breakage was observed with OXYCAPT™ vials."

is sprayed on stoppers of the OXYCAPT™ Syringe, no silicone oil is baked-on to the barrel. According to MGC internal studies using antibodies, this feature leads to much less protein aggregation compared with Type 1 glass syringes.

OXYCAPT™ vials and syringes are produced by co-injection moulding technology. This technology has been applied to beverage bottles for many years, but we are the first company that has succeeded in developing multilayer plastic syringes. We have also successfully developed inspection methods for the oxygen barrier layer such that all containers are 100% inspected by state-of-the art inspection machinery.

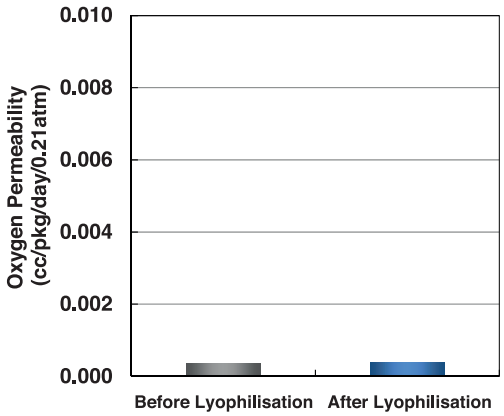
MGC can offer bulk vials, ready-to-use (RTU) vials and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO based nest & tub formats. The nests & tubs are mainly sterilised by gamma irradiation. MGC offers 2, 6 and 10 mL vials, and 1 mL "Long" and 2.25 mL syringes, and the company is able to provide samples for initial testing free of charge.

Each polymer meets the requirements of USP661, USP87, USP88, EP and has been filed in the FDA's drug master file (DMF). The vials and syringes are also compliant with each pharmacopoeia and have been filed in the DMF. The syringes are produced and controlled in accordance with ISO 13485.

In recent studies of lyophlisation and cold storage resistance, after being filled with albumin solution, vials were primarily frozen at -50°C for six hours, secondary dried at 4°C for 48 hours, and finally dried at 25°C for nine hours. We measured oxygen barrier, appearance and dimensions, and found OXYCPT™ maintained its properties and dimensions before and after lyophilisation (Figure 6).

In addition, vials were dropped from 150 cm height to confirm break resistance. All of the glass vials were broken, but zero breakage was observed with OXYCAPT™ vials (Figure 7). Vials were also stored at -80°C to confirm cold storage resistance. When

Oxygen Barrier



Appearance & Dimensions

10 mL vial	After Lyophilisation
Appearance	No Change
Dimensions	No Change

Figure 6: Resistance to lyophlisation – oxygen barrier properties (top) and dimensions and appearance (bottom) maintained.

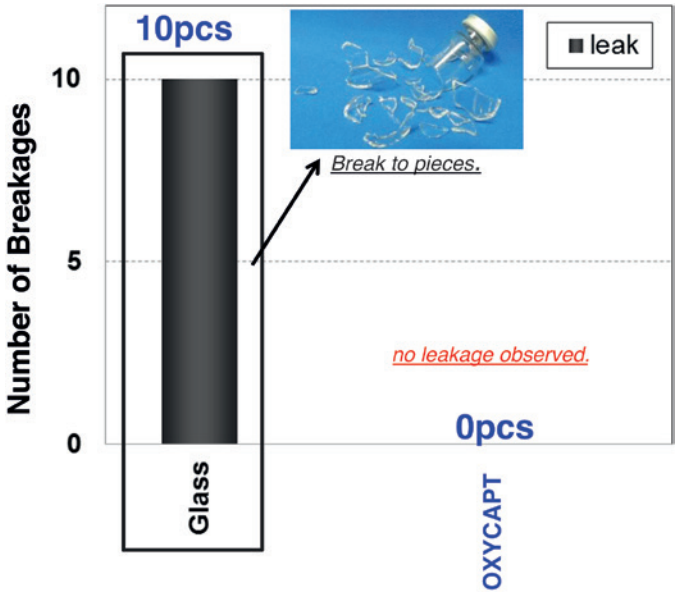


Figure 7: Zero OXYCAPT™ breakages during drop test, compared with 100% breakage with glass.

frozen OXYCAPT™ vials were dropped from 150 cm height, no breakage was observed. To understand any influences on long-term cold storage, the same studies will be conducted over six-month and two-year periods.

Our targeted application for OXYCAPT™ is biologic therapeutics. As the ICH Guideline "Stability of Biotechnological/Biological Products Q5C" mentions, oxidation is one of the causes of protein instability. The excellent profile of OXYCAPT™ with regard to oxygen and UV barrier properties promises to contribute to stability of biologic products.

In addition, we believe OXYCAPT™ can be applied to epinephrine, because it is well known to be an oxygen sensitive drug. Glass syringes, having problems with breakage, are not ideal for emergency drugs, so some suppliers have tried to develop new pen injectors made of plastic.

Customisability is another feature of plastic, and MGC can customise OXYCAPT™ containers to meet specific requirements.

CONCLUSION

OXYCAPT™ has been developed to overcome the current problems the pharmaceutical industry is experiencing with syringes and vials made from traditional materials. OXYCAPT™ combines the benefits and features of COP, such as high water vapour barrier properties, high break resistance, very low extractables and low protein adsorption, with the high oxygen & UV barrier properties associated with glass. In the rapidly growing biologics sector, OXYCAPT™ vials and syringes deliver substantial benefits.

ABOUT THE COMPANY

Mitsubishi Gas Chemical (MGC) develops and manufactures chemical products ranging from basic to fine chemicals and performance materials. It comprises the Natural Gas Chemicals Company, the Speciality Chemicals Company, the Aromatic Chemicals Company and, of particular relevance to those interested in drug delivery, the Information & Advanced Materials Company and the Advanced Business Development Division.

MGC established its Advanced Business Development Division in 2012 as a centre for continually creating new businesses across the fields of medical/food, information and communications, mobility, energy and infrastructure. The group has developed OXYCAPT™ Vial & Syringe as an alternative to glass containers for parenteral primary packaging.

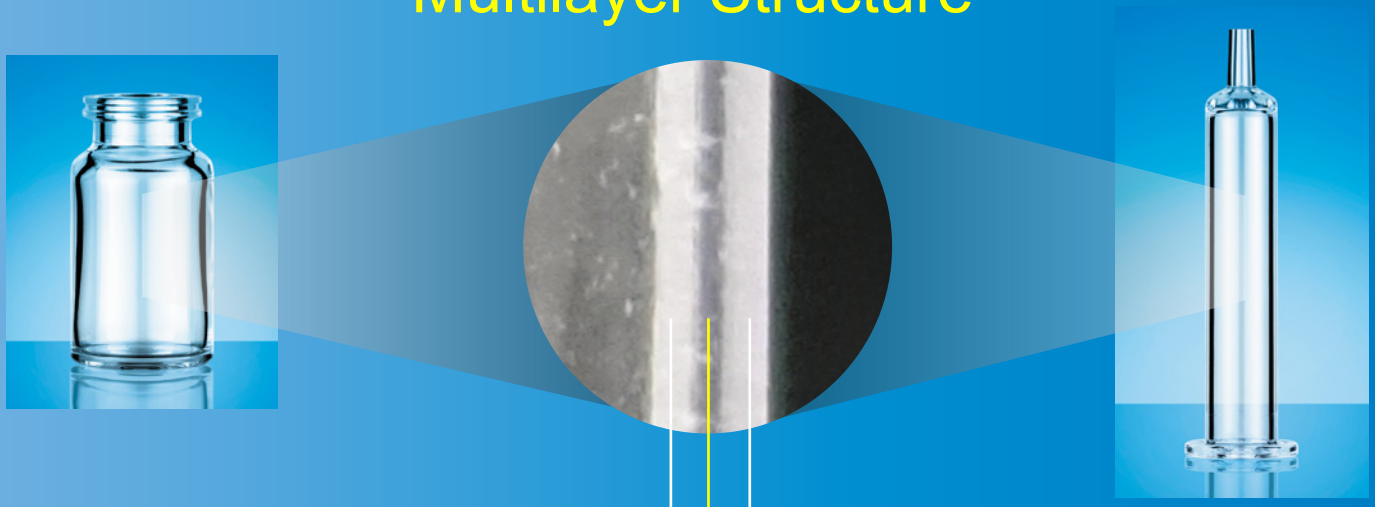
ABOUT THE AUTHORS

Takuya Minezaki joined Mitsubishi Gas Chemical in 2005. He specialises in the synthesis and injection moulding of polymers, and has worked in the development of oxygen absorbing polymers. Since 2017, he has worked on the development of new pharmaceutical containers by utilising oxygen absorbing resins. He is also in charge of the development of secondary materials, such as plunger stoppers and tip-caps. Mr Minezaki holds a Master of Engineering in Applied Chemistry from the University of Tokyo, Japan.

Tomohiro Suzuki joined Mitsubishi Gas Chemical in 1998. He belonged to the Oxygen Absorbers division until 2011, after which he was transferred to Advanced Business Development division in 2012, to be a member of the OXYCAPT™ development team. Since then, he has been in charge of marketing for OXYCAPT™ Vial & Syringe. His current position is Associate General Manager.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer
(COP)

Oxygen Barrier Layer
(New Polymer)

Drug Contact & Water Vapor Barrier Layer
(COP)

- ✓Excellent Oxygen Barrier
- ✓High Water Vapor Barrier
- ✓Low Extractables & High pH Stability
- ✓High Break Resistance & Lightweight
- ✓Excellent UV Barrier
- ✓High Transparency
- ✓Silicone Oil Free Barrel
- ✓Low Protein Adsorption & Aggregation
- ✓Suitable for Biologics
- ✓Customizable

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A RE-USABLE CONNECTED AUTOINJECTOR CUSTOMISED FOR THE CREDENCE COMPANION® SAFETY SYRINGE SYSTEM

In this article, Bjarne Sørensen, Director of Front-End Innovation at Phillips-Medisize, and John A. Merhige, Chief Commercial Officer at Credence MedSystems, explore the latest developments in modular autoinjector platforms and the benefits for end users and pharmaceutical customers. They also discuss the two companies' recent partnership for the development of a combined system that capitalises on important synergies between two compatible technologies.

Phillips-Medisize has significant experience developing re-usable electronic injectors. The company has successfully brought several to market and currently has additional devices in various stages of development.

Re-usable electronic injectors offer numerous features which make them especially suited to innovative applications. These advantages include:

- A lower cost per injection – ideal for frequent injections
- The ability to significantly enhance the user-friendliness of the complete drug administration process
- A higher driving force on the plunger than can be reasonably expected from a patient
- A seamless opportunity for advanced control options, connectivity options and user interfaces
- Low production volume compared with disposable devices, supporting a lean manufacturing set-up.

THE MODULAR ADVANTAGE

Phillips-Medisize combined its extensive experience and knowledge of electronic injectors with its successful technology accelerator strategy, which is designed to streamline the development and continuous improvement of innovative concepts. The result is a modular autoinjector platform optimised for functionality, cost, efficiency and flexibility.

Multiple modules are embedded in the modular autoinjector platform architecture, such as a combined spring-motor drive system, the key components of which include:

- Spring for insertion of needle by sledge movement
- Motor drive for depressing plunger rod and retracting sledge mechanism
- DC motor with infrared rotational sensor and attached gearbox connected directly to lead screw
- Plunger rod pushed by a nut on the lead screw, so plunger depression accuracy is directly linked to the motor rotational sensor.

"Using the modular platform, the development process can be completed quickly and efficiently, resulting in a very cost-effective solution."

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There is also a miniature electronic module with:

- Microcontroller
- Switch interfaces
- Wireless connectivity – BLE or other
- Orientation sensors and accelerometers
- Rechargeable battery pack
- USB or wireless charging, lasting up to 30 days.

Additionally, a flexible, configurable platform supports a variety of primary packaging containers, such as:

- Safety syringes with full needle safety
- Cassette solution for syringe with full needle safety
- Customised proprietary syringes
- Standard syringes.

The modular autoinjector platform also offers numerous other benefits, including:

- Injection volumes up to 3 mL
- Automated rigid needle shield (RNS) removal option for improved usability
- Flexible operation for user feedback options (e.g. sound, lights and/or graphical displays)
- Direct interface to the Phillips-Medisize third-generation connected health platform, enabling swiftly customised functionality with mobile apps and device systems.

In addition, the development documentation is also executed as a platform, allowing efficient execution of device variations built on the same technical platform. This supports a rapid, low-cost development process, enabling Phillips-Medisize to deliver devices ready for clinical trials within a year and for commercial launch within two years.

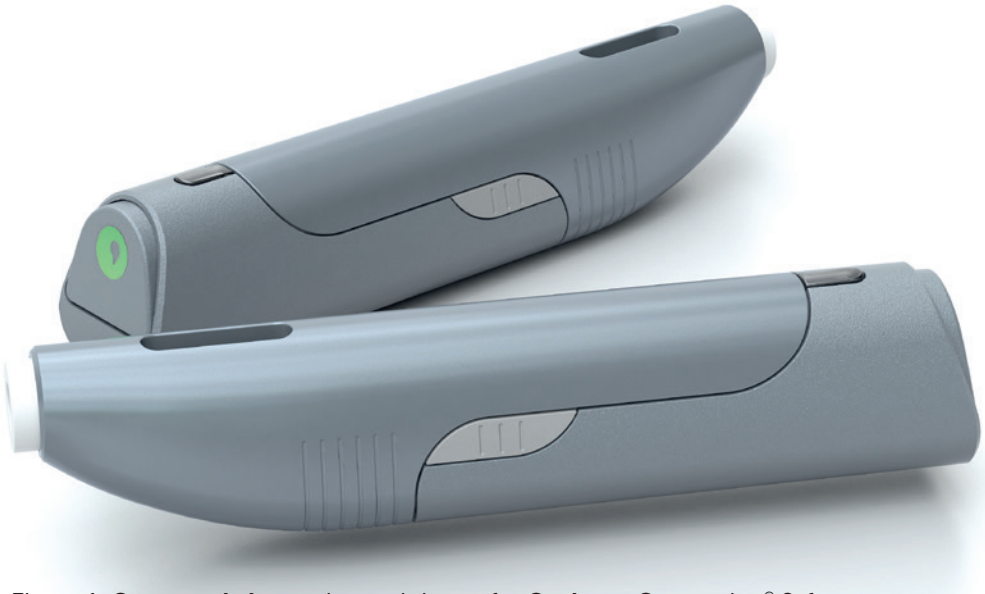

Figure 1: Connected electronic autoinjector for Credence Companion® Safety Syringe suitable for 1 mL "long" and 2.25 mL syringes.

"The re-usable connected autoinjector is straightforward and easy to use."

Modular platforms are widely used in other industries as well. A prime example is automotive manufacturer Volkswagen (VW) Group's strategy that supports a significant level of platform and component sharing across all brands and models across VW Group – boosting efficiency and generating significant savings.

Phillips-Medisize's modular platform approach offers numerous advantages. For example, the company can develop autoinjectors for the exact primary packaging used for certain drugs and also provide customer-brand-aligned industrial designs of the device suited for the specific therapy. Using the modular platform, the development process can be completed quickly and efficiently, resulting in a very cost-effective solution. As an added benefit, the in-house capabilities of Phillips-Medisize and its parent company, Molex, ensure state-of-the-art capability for manufacturing the device.

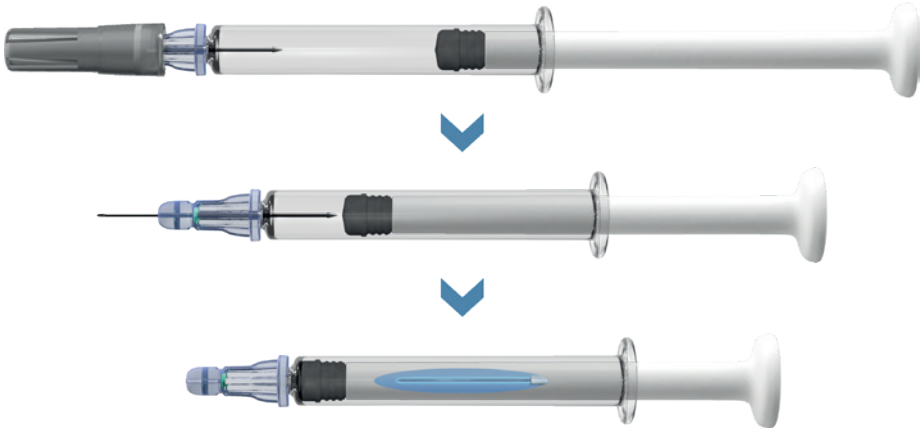

Figure 2: With the Credence Companion®, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, preventing re-use.

INNOVATION IN ACTION

Phillips-Medisize's recent partnership with Credence MedSystems illustrates the efficiency of this strategy, enabling the development of a combined system (Figure 1) that capitalises on important synergies between two compatible technologies: the Re-usable Connected Autoinjector Platform and the Companion® Safety Syringe System.

Credence's innovative Companion Safety Syringe System (Figure 2) features improved usability and enhanced safety due to integrated passive needle-safety technology. It includes a "staked" needle version, which comes to the user with the needle already mounted, and a Luer lock needle version, where the user can attach the needle of choice at the time of use.

In either option, the user benefits from a familiar-looking system that allows full visibility of the barrel and the drug product. After completing the injection, the user receives an end-of-dose "click" cue as the needle simultaneously and automatically retracts into the barrel of the syringe and plunger rod. This renders the syringe needle free and unusable, thereby preventing re-use and achieving compliance with the various needlestick and re-use prevention mandates.

The Companion Safety Syringe System uses existing standard primary package components as its foundation, so it is readily compatible with commercially available syringe barrels, plunger stoppers and needle shields from the spectrum of industry-leading manufacturers. Multiple sizes are available, including 1 mL (shown in Figure 3) and 2.25 mL. In addition, the system is compatible with standard nest/tub configurations and filling lines, while also simplifying secondary assembly.

The Companion Safety Syringe System offers a third option as well: the dual chamber reconstitution syringe (DCS). A viable alternative to "ready-to-inject" solutions, it maintains separation of diluent and drug product during storage but allows simplified mixing and injection at the time of use. In addition to single step reconstitution, the DCS incorporates the passive needle retraction and user cues featured in the Companion Safety Syringe System. Because the system uses commercially available, uniform-diameter syringe barrels, with the fluid transfer performed via an internal bypass created at the time of use, the DCS is also available in multiple syringe sizes.

COLLABORATION ON TWO COMPLEMENTARY TECHNOLOGIES

After seeing the re-usable connected autoinjector concept at the PDA's Universe of Prefilled Syringes & Injection Devices Conference (Orlando, FL, US, October 8-9, 2018) ("PDA"), Credence management saw the potential of combining the two innovative technologies and engaged Phillips-Medisize to customise the autoinjector for the Companion Safety Syringe System.

Phillips-Medisize delivered – quickly. The company had the first device up and running only four weeks after receiving the CAD data on the syringes, and delivered three fully functioning models of the device seven weeks after initiation. Credence has used the new autoinjectors in demonstrations with the Companion Safety Syringe System's staked syringe with its pharma customers, adding a complementary element to the overall value of the Companion Safety Syringe System.

The re-usable connected autoinjector is straightforward and easy to use, by following these simple steps:

1. Remove the autoinjector cover, load the syringe, replace the cover and push the "on" button
2. Discard the RNS after the device indicates that it has been removed
3. Push the device against skin, push the injection button and wait for the indication that the dose is complete
4. Remove the autoinjector cover, and remove and discard the safe, protected syringe
5. The device automatically sends data to the customer app or the app connected to the Phillips-Medisize platform via Bluetooth and then shuts down.

A recent study on the initial device (first shown at PDA) demonstrated its intuitive usability for patients. Relevant feedback regarding cover release, visibility of syringe, colours and other factors was also provided and then implemented in the Credence version.

Figure 3: Autoinjector loaded with 1 ml "long" Companion Safety Syringe.

> "Incorporating the Companion Safety Syringe System with the smart autoinjector addresses some fundamental market challenges in a highly effective manner."

MEETING MARKET CHALLENGES

In discussions with pharma customers, there has been consistent recognition that incorporating the Companion Safety Syringe System needle safety technology with the "smart" autoinjector addresses some fundamental market challenges in a highly effective manner.

Challenge #1: pharma companies need to provide the market with innovative, user-friendly, safe and compliant delivery systems. In the self-injection market, which is growing at more than 22% per year and expected to reach US$119 billion (£92 billion) by 2024,[1] most pharma companies prefer to provide both a syringe and a device presentation to meet varying user preferences.

Solution: these two technologies provide enhanced usability and safety, whether a syringe or device administration is employed. The staked Companion Safety Syringe provides end-of-dose cues and passive needle-stick safety when used as a naked syringe. Incorporating the autoinjector introduces the additional benefits of automated RNS removal, hiding of the needle before injection, device-assisted injection and more user cues. The combined concept is also suitable for high-viscosity drugs, due to the motor-driven plunger.

Added flexibility is introduced by the re-usable nature of the autoinjector in combination with the fact that fully assembled Companion syringes are used with it. Users may choose to inject with the naked syringe or with the autoinjector on an injection-by-injection basis, depending on daily preference and the environment where the injection will take place.

Challenge #2: pharma must provide these innovative solutions in the most efficient and least disruptive manner possible.

Solution: the Companion Safety Syringe System uses existing primary package components from preferred industry-leading suppliers and will be available through traditional procurement channels in ready for filling, pre-sterilised nest and tub configurations. Using the same primary container syringe, with the plunger rod mounted in both the "naked" syringe and in the compatible autoinjector presentation, allows for development, regulatory and manufacturing efficiencies.

"An electromechanical drivetrain allows for reliable repeated use and dose volume accuracy when compared with spring-driven mechanisms."

The autoinjector has been designed to allow significant platform flexibility. While the models discussed use the 1 mL "long" Companion syringe version, Phillip-Medisize's engineering design enables the 2.25 mL Companion version to be delivered with minimal adaptation to the syringe cradle and the embedded firmware. Further, a version for the Credence DCS can be efficiently executed on the same platform and can include orientation sensing and motion sensing for verification of appropriate mixing agitation. It can also feature an enhanced sequential user interface for the reconstitution process.

Challenge #3: in addition to requiring cost-efficient approaches, the industry must consider the environmental impact and related pressures associated with disposable drug delivery devices. Re-usable autoinjectors can address these factors, especially for more frequent dosing. However, the market has been largely dominated by disposable single-use devices due to a variety of factors, including: the conventional requirement to dispose of a dirty, exposed needle after injection; scepticism regarding the reliability of spring powered devices for repeated use over the long term; a desire to reduce the number of user steps to perform an injection; and lack of other compelling factors supporting the change.

Solution: the Companion Safety Syringe System's ability to retract the needle and protect it in the syringe barrel and plunger rod eliminate concern about disposing of a dirty exposed needle. Building on a re-usable injector platform, the combined concept offers a sustainable solution since the naked syringe/primary package is the only item being thrown away after each injection. This minimises overall waste generated by the therapy and sets a new benchmark, especially when compared with disposable autoinjectors that carry their own packaging and shipping burden.

In terms of dependability, an electromechanical drivetrain allows for reliable repeated use and dose volume accuracy when compared with spring-driven mechanisms. And simple, intuitive syringe loading, while adding a user step compared with disposable devices, can be performed reliably.

Finally, incorporating connectivity strengthens the business case for frequent dosing and offers benefits for medications injected less frequently.

Challenge #4: the industry is clearly and appropriately focused on the patient health and economic benefits of improving adherence to prescribed dosing regimens.

Solution: injection systems and supporting technology platforms help address this need. The connected re-usable autoinjector features embedded connectivity with the award-winning Phillips-Medisize connected platform. Once captured, the injection data can be monitored through data analytics and visualisation portals, linking with patient support programmes to improve medication regimes.

The safety and familiarity of the Companion as a conventional-looking syringe promotes user comfort, and the end-of-dose cues help promote successful injection. Further, the autoinjector offers full flexibility on the use sequence and interface by simply reprogramming the onboard firmware.

Credence and Phillips-Medisize have a history of successful collaboration. This latest effort combines two innovative and synergistic technologies to create a total solution that addresses important needs for end users and pharmaceutical customers.

ABOUT THE COMPANIES

Phillips-Medisize is a provider of outsource design, development and technology-driven manufacturing, with a primary focus in the medical device and diagnostics, drug delivery, primary pharmaceutical packaging and commercial markets. Phillips Medisize operates on a partnering business model, and works with pharmaceutical, biopharmaceutical, consumable diagnostic and medical device companies with the purpose of increasing speed to market. It was the first company to deliver a US FDA-approved connected health system to the market.

Credence MedSystems is focused on the development of its Companion Safety Syringe System, which includes proprietary needle-retraction technology, syringe re-use prevention and other critical safety and usability features in staked-needle and Luer formats. Its dual chamber reconstitution syringe (DCS) platform offers single-step mixing and injection for drugs that require reconstitution at the time of delivery. Additional products such as metered-dose devices, multi-length staked needles and other novel devices address the needs of specific therapeutic markets.

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ABOUT THE AUTHORS

Bjarne Sørensen, BSc, ME, is a Director of Front-End Innovation at Phillips-Medisize. He was previously at Medicom Innovation Partner, which was acquired by Phillips-Medisize in 2016. With more than 35 years of experience within product, strategy and business development, Mr Sørensen has a very visible track record within more business areas, and at Phillips-Medisize he is involved in customer programmes typically involving electronic injectors and connected health systems.

John A. Merhige, BA, BE, MEM, is Chief Commercial Officer at Credence MedSystems. Previously, he was Vice-President, Market Development at Sanofi BioSurgery. He came to Sanofi upon its acquisition of Pluromed in 2012, which Mr Merhige joined in its early stages and where he was a member of the executive management team. He led the commercial activities at Pluromed, which developed and commercialised rapid transition polymers for cardiovascular and other surgical procedures. Prior to Pluromed, Mr Merhige founded Prelude Devices to target early-stage medical device technologies for development and commercialisation.

SELECTING THE RIGHT PRIMARY CONTAINER FOR INJECTABLES IN ACUTE CARE

Alfred Harvey, Associate Director of Health Economics and Outcomes Research for BD Medical - Pharmaceutical Systems, explains why it's important to select the right primary container presentation – and what can happen if you get it wrong.

Understanding the unmet needs of hospitals and care centres is crucial for providing them with impactful solutions. In the healthcare setting, patient safety concerns exist across the entire drug delivery spectrum. Specifically, in an acute care setting, where decisions are often made quickly or under stress, error rates can be at their highest.[1] These errors result from normal human faults, cutting corners due to resource constraints and/or an inherent medical product failure. Collectively, drug delivery mistakes create challenges when it comes to maintaining optimal safety for patients and healthcare workers – and can increase clinical operating costs. Differences in primary container options for injectable drugs can add value by offering hospitals and care centres configurations that address universal pain points.

> "Reducing medical errors, such as adverse drug events, is a goal for the entire healthcare ecosystem."

INJECTION-RELATED ADVERSE DRUG EVENTS ARE DANGEROUS AND COSTLY

Reducing medical errors, such as adverse drug events (ADEs), is a goal for the entire healthcare ecosystem. Currently, nearly 5% of hospitalised patients experience a drug-related ADE.[2] Of these, injection-related ADEs alone account for US$2.7-5.1 billion (£2.1-3.9 billion) of preventable annual costs to US healthcare payers. On average, this leads to $600,000 per year in extra costs for each hospital, with an additional $72,000 in medical professional liability per hospital.[3] The highest error rates (approximately 50%) have been reported in the administration of intravenous medications due to their greater complexity.[1]

ADEs are dangerous and costly, but those related to administration errors could be limited in the case of injectable drugs by more widespread adoption of primary drug containers that improve workflow, decrease contamination risk and reduce sharps exposure.

VIAL RE-USE IS A RISKY BUT COMMON PRACTICE

Syringe, vial or ampoule re-use is an existing, risky injection practice that can lead to contamination. For example, a class action lawsuit was settled in 2012 against several endoscopy clinics in Nevada in the US because they were cross-contaminating patients with hepatitis C. The cause was found to be linked to the re-use of vials between patients. The two drug manufacturers supplying the drug involved had also been considered liable as it was argued that the large size of the vials induced a re-use, while the

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warnings on the vials and on packaging inserts were deemed inadequate.[4] Data from the Netherlands suggests that 9-22% of its acute infusions contain some level of microbial contamination, 1-3% of these resulting in infections and increased hospital stays.[5] The study showed that using prefilled syringes (PFS) instead of vials reduced the contamination risk to 4%.[5] Despite the risks associated with re-use, a 2017 report revealed that more than half of surveyed nurses admitted re-using multidose vials between patients, and almost 25% admitted using the same needle to re-enter the bottle for the same patient. Also reported was that, in an oncology setting, about 20% of oncologists accepted the practice of re-using vials, bottles and bags between patients.[6] Similarly, a study focused on vial re-use in an anaesthesia setting showed that about 80% of vials for an imaging agent were re-used between patients.[7] In contrast, the same study showed that the re-use went down to less than 1% when the drug was supplied to the anaesthesiologist in a PFS format (Figure 1). These are clear examples where providing medicines in the most "ready to administer" form can help reduce vial/syringe use between patients, decrease cross-contamination and improve safety.

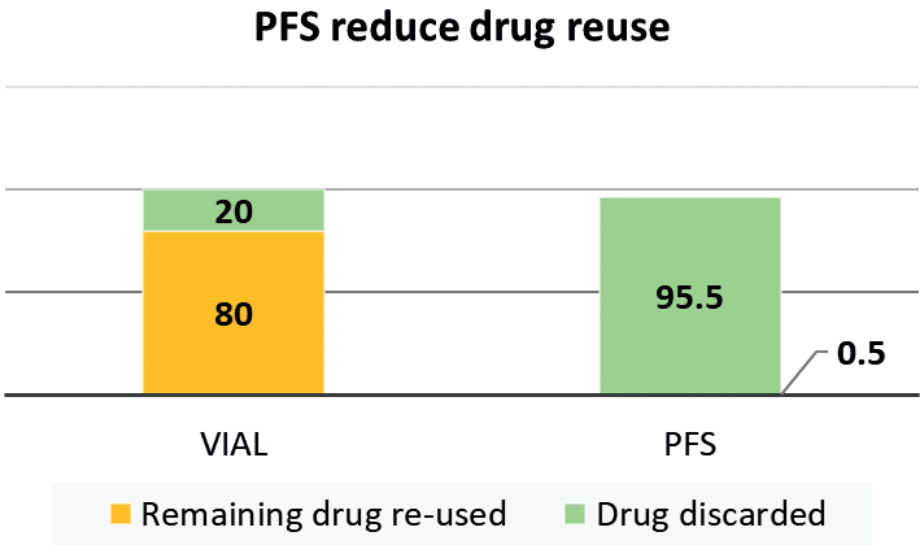

Figure 1: Imaging centre study[7] shows 80% imaging agent re-use in vials compared with less than 1% in PFS.

SAFER FOR PATIENTS AND HEALTHCARE WORKERS

Drug dosage preparation mistakes with a syringe and vial/ampoule are all too common. These can occur from preparing the wrong medicine or the wrong dose.[5] While some have minimal effects, critical dosing errors can cause severe problems and even death. A 2015 study looked at total dosing error rates in vials compared with PFS[8] (Figure 2). They found that 22% of vial-prepared doses resulted in at least one dosing error, with two-thirds of the errors critical – severely over- or underdosing the patient. In contrast, only 4% of PFS-based syringes resulted in a dosing error event, and none of those were considered critical errors. Through the use of PFS instead of vials, the hospital was able to show a complete elimination of critical errors and a significant reduction in non-critical errors. Also, a 2016 meta-analysis of 46 studies concluded that healthcare worker needle-stick injuries were significantly reduced when PFS were used instead of vials and ampoules.

> "Drug dosage preparation mistakes with a syringe and vial/ampoule are all too common."

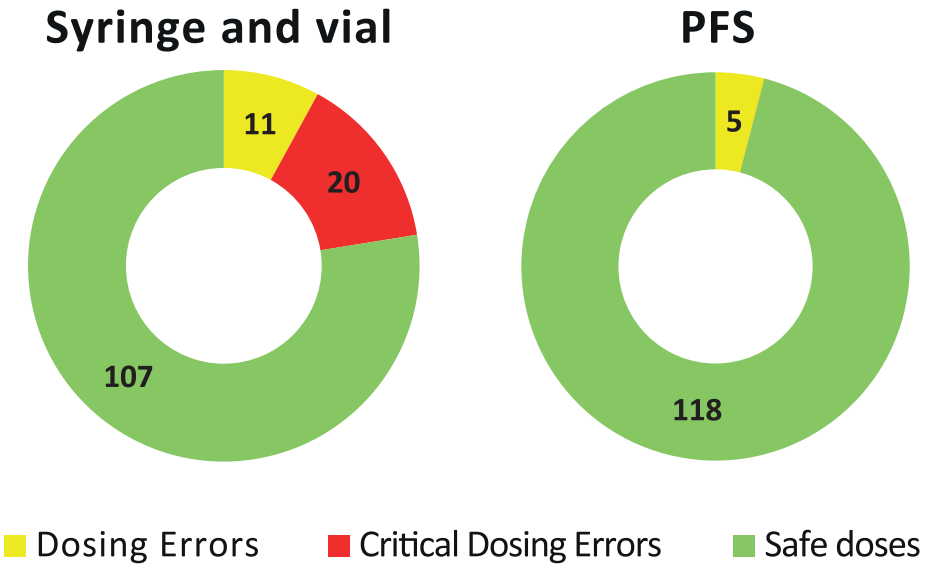

Figure 2: Dosing errors decrease from 31 total errors with vials to five with PFS in pediatric study.[8] Critical errors drop from 20 to zero.

SAVE LABOUR AND DRUG WASTE COSTS

Like all businesses, hospitals try to reduce costs as much as possible. Labour costs and product waste are two areas where the right drug delivery product can impact their bottom line. For example, patients in medical and surgical units receive an average of 10 injections daily.[9] PFS products have been shown to reduce preparation and administration time significantly[10] (Figure 3). In an average 150-bed hospital, if 10 injections daily are given to each patient using PFS instead of vials/ampoules, the hospital could save 14,600 hours annually – or $420,000 in labour costs. Similarly, a 2016 study of drug use in an anaesthesia setting showed that drug waste from discarded vial-based drugs cost institutions around $200,000 per year.[11] This cost was eliminated through the use of pre-packaged, PFS. Similarly, a study by a French university's obstetrics unit compared drug waste between ampoules and PFS. It discovered that switching to PFS for one of its common drugs resulted in a 17% decrease in drug waste – or savings of €0.50 (43p) per patient.[12] Lastly, a budget impact analysis was conducted of French hospitals comparing PFS with standard delivery methods, considering medication

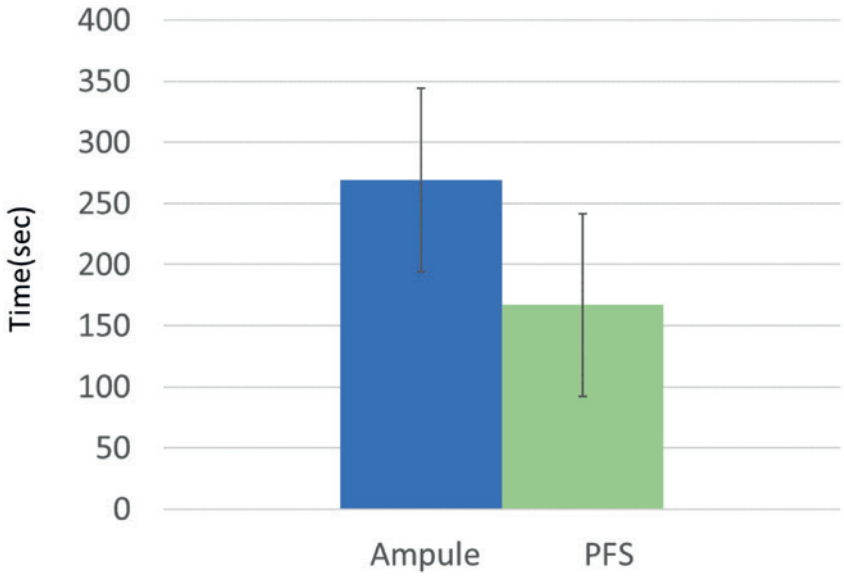

Figure 3: Ampoule preparation took approximately 100 seconds more than when PFS were used (260 seconds versus 157 seconds).[10]

> "As hospitals start to calculate the potential savings PFS can bring, they are likely to look to drug companies that offer these convenient primary containers."

error and drug waste. Looking only at one drug, atropine, PFS use was modelled to yield a net one-year budget saving of €5.3 million (£4.6 million). It concluded that even though PFS were more expensive upfront, their use would result in significant budget savings in both medical errors and drugs waste.[13] As hospitals start to calculate the potential savings PFS can bring, they are likely to look to drug companies that offer these convenient primary containers when they are ready to make a purchase.

PFS OUTPERFORM VIALS FOR DURABILITY AND FILL VOLUME

Several product recalls have been linked to vials in the past, caused by flaws inherent in the vial manufacturing process.[14] Vial glass can delaminate and cause glass particles to appear, reducing glass durability and contaminating the drug.[15] These recalls are costly and inconvenient for both drug manufacturers and their customers. The PFS manufacturing process is different from the process for vials, and results in improved glass durability. In fact, PFS outperform glass vials in most test conditions and perform equivalently in others.[15] For example, chemicals leaching into or out of a primary container can change the make-up of the drug inside. The inner surfaces of PFS were found to have lower chemical leaching than glass vials.[16] Another shared cost for customers and suppliers is the need to over-fill vials with drug. This is done because it is impossible to withdraw 100% of a dose from a vial. The cost of overfilling is either absorbed by the drug company or passed on to its customers. Switching to a PFS as a primary container not only offers a more robust package but also eliminates the need to overfill the container.

SINGLE SOLUTION FOR SEVERAL CHALLENGES

Selecting the right primary container presentation for a drug is an important decision that can directly affect customers. As the healthcare industry focuses more on safety, it will be looking for ways to reduce ADEs and needle-stick injuries. When hospitals look to reduce spending, they will target workstream inefficiencies and product waste. In order to continue providing optimal care, they will seek out robust devices with a low likelihood of recall. PFS have shown the ability to address all these needs (Figure 4) and – now that they are available in a variety of formats up to 50 mL in highly resistant glass or advanced plastic – drug companies have many options to meet the needs of acute care hospitals and care centres.

ABOUT THE COMPANY

BD is one of the largest global medical technology companies in the world and is advancing the world of health by improving medical discovery, diagnostics and the delivery of care. The company develops innovative technology, services and solutions that help advance both

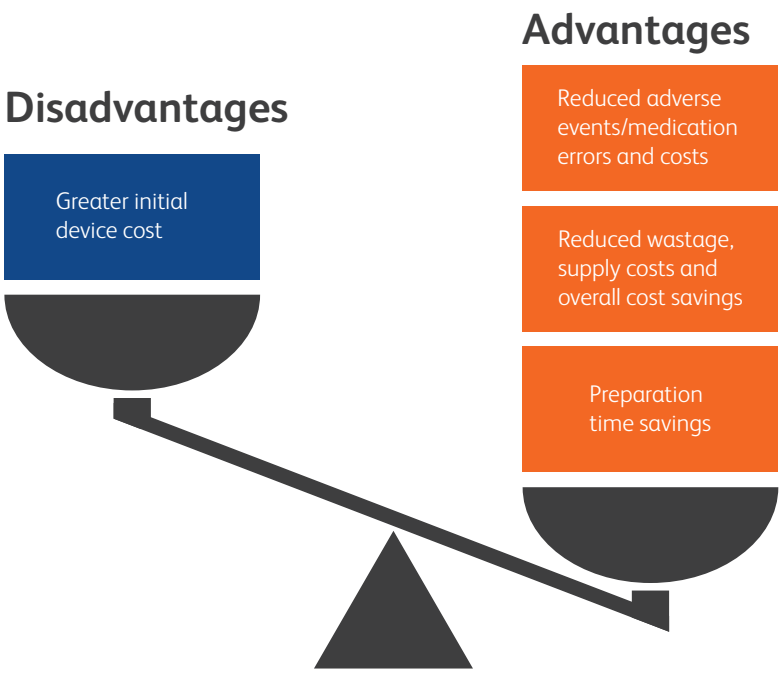

Figure 4: PFS advantages and disadvantages compared with vials. Whilst PFS may cost more upfront, vials are more costly overall.

clinical therapy for patients and clinical process for health care providers. BD has 65,000 employees and a presence in virtually every country around the world to address some of the most challenging global health issues. BD helps customers enhance outcomes, lower costs, increase efficiencies, improve safety and expand access to healthcare.

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ABOUT THE AUTHOR

Alfred Harvey started his career with BD in 2001 as a Research Assistant working in early-stage R&D. With an initial focus on improving parenteral delivery systems, he took on greater roles, eventually managing device teams in a variety of areas such as oncology, diabetes, rheumatoid arthritis and intravenous therapies. In 2017, he took on his current role as Associate Director of Health Economics and Outcomes Research for BD's Medical – Pharmaceutical Systems division, where he is helping lead the strategic focus in prefilled, self-administration and safety systems. Mr Harvey received his MBA from Stetson University (FL, US) and his Masters in Pharmacy – Pharmaceutical Outcomes and Policy from the University of Florida (US).

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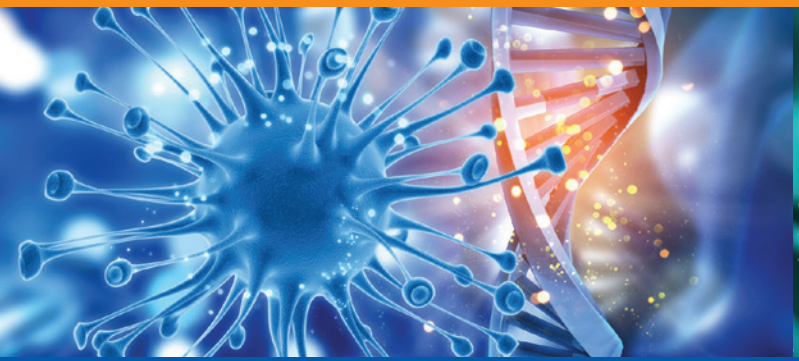

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PRODUCT SHOWCASE: ZwickRoell Autoinjector Testing Platform

ZwickRoell

The autoinjector market is one of the fastest growing across almost all pharma applications. Global market volume of approximately US$2.5 billion (£1.9 billion) is expected by 2020, with autoinjectors representing the largest segment.

Strict US FDA regulation of these Class II devices means that testing to ISO11608-5 is a critical step for manufacturers to ensure product quality and safety. Whether testing is managed in-house or by a contract testing laboratory, for one or for many different product designs, these organisations are turning to testing platforms that are both versatile and comprehensive. Testing must support manufacturing protocols and industry regulations, while maintaining absolute accuracy and reducing time-to-market.

"Manufacturers need solutions that help them test complete device functionality on a single platform in an all-in-one test," explains Erik Berndt, Medical Industry Manager at ZwickRoell. "Market demand and growing expectations when it comes to time-to-market mean our customers are operating in high-throughput environments where there is no margin for error. After all, patients everywhere are depending on reliable test results."

Figure 1: The roboTest R system.

That is why pharma manufacturers strive to achieve a high level of automation in autoinjector technology. The patient simply removes the safety cap, positions the injector, and injects the drug by pressing a button – the injection process is completely automated. However, this also means that all of the injector's relevant functions must be checked before the production batch is released on the market. "During our discussions with pharma, we identified a need for one testing system that can perform all standard tests," says Berndt. Those tests are:

1. Removal force of the safety cap
2. Activation force and displacement
3. Injection time
4. Determination of the administered drug volume, including the last drops
5. Effective needle length
6. Safety function of the needle guard
7. Other optional testing steps.

The answer for these six testing steps is a two-column materials testing machine with safety device, with non-contact sensors that measures the injection time and the effective needle length by means of light barriers. An integrated scale measures the quantity of the administered drug. This ZwickRoell solution is able to perform all of these test steps on just one specimen, reducing the number of specimens required, and increasing throughput.

A typical market solution is a semi-automated testing machine that requires an operator to load the specimen, close the safety door, and start the test. From that point forward, all steps in the test sequence are carried out automatically by the machine within just a few minutes per injector. ZwickRoell also offers a robot-driven fully automated testing system. "The roboTest specimen handling system (see Figure 1) removes the autoinjector from the magazine and inserts it into the testing machine. This solution removes the risk of operator error," explains Berndt.

ZwickRoell's fully automated solution is an efficient system that measures up to 10 different parameters in one continuous process. roboTest is controlled by ZwickRoell's automation software, AutoEdition 3, which directs the robot to remove the injectors one-by-one from the magazine, feed them into the machine, and start the test. Results are accurate because operator influence is minimised and the process is significantly more efficient because of increased specimen throughput. The testXpert III testing software, together with the Expanded Traceability option to FDA 21 CFR Part 11, make it possible to create documentation for the testing process that is complete and tamperproof.

Growth in market demand for autoinjectors is placing greater emphasis on throughput. Yet accurate test results are critical when it comes to patient health. This challenge has motivated manufacturers to seek solutions that streamline and automate the testing process without sacrificing accuracy, repeatability, reproducibility and traceability. Implementation of mistake-proofing mechanisms ensures consistency in testing programs, further elevating accuracy in measurement and supporting excellence in manufacturing in alignment with GMP standards and FDA CFR Part 11 regulations.

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ZAHORANSKY
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NEXT-LEVEL FUTURE MANUFACTURING – ZAHORANSKY'S ONE-STOP SOLUTION FOR MEDICAL TECHNOLOGY

In this article, Berthold Schopferer, Business Development Manager – System Technology at ZAHORANSKY, explains the lengths the production equipment company goes to in its efforts to ensure the customer is always king.

ZAHORANSKY's vision of future manufacturing in medical technology involves reducing the number of separate processes to a minimum, optimising the level of integration – and all without any human touch if possible. The company invests great effort in pursuing this vision, all the while ensuring that customers' products meet the strictest quality standards.

ZAHORANSKY offers an automation line with injection moulding – the Z.BLIZZARD (Figure 1) – which not only ensures customers have an efficient and safe manufacturing process for pharmaceutical products but also gives them the peace of mind that comes with making sustainable solution investments. If the Z.MISTRAL downstream line and the palletising system Z.LODOS (Figure 2) are connected as well, the entire process chain from the granulate to the completely packaged, ready-to-fill staked needle prefillable syringes (PFS) made from cyclo-olefin copolymers (COCs) or cyclo-olefin polymers (COPs), is covered. A real one-stop solution with outstanding autonomy time.

> "A real one-stop solution with outstanding autonomy time."

Figure 1: The Z.BLIZZARD produces ready-to-fill PFS from COC/COP polymer with a very long autonomy time.

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Figure 2: If the Z.MISTRAL downstream line and the palletising system Z.LODOS are connected to the Z.BLIZZARD as well, the entire process chain from the granulate to the completely packaged PFS can be covered.

Figure 3: A detailed view: The Z.NFS needle separating system can separate 4– 32 needles or cannulas with up to 12 cycles per minute. Currently, diameters from 0.2 mm and lengths up to 45 mm can be processed.

Figure 4: Integration of the Z.NFS into the Z.BLIZZARD results in an integrated line that guarantees utmost hygiene during the production process, without any human touches and with clean room compliant processes.

FIRST IN, FIRST OUT AND NO HUMAN TOUCH

The Z.NFS needle feeding system (Figure 3) with separated needle feeding additionally ensures the Z.BLIZZARD's compliance with the "first in, first out" principle: in other words, the system is filled with the required number of cannulas to then process them in order. This way, no needles can remain in the system for a longer period. The Z.NFS can separate 4–32 needles or cannulas with up to 12 cycles per minute – which equals up to 400 pieces per minute. Currently, diameters from 0.2 mm and lengths up to 45 mm can be processed. Integration of the Z.NFS into the Z.BLIZZARD (Figure 4) results in an integrated line that guarantees utmost hygiene during the production process, without any human touches and with clean room compliant processes. The optionally integrable X-ray testing equipment offers a new potential quality benefit, ensuring absolutely safe product control after assembly – a key component of any optimised future manufacturing solution.

A RARE SIGHT: PLASTIC BEATS GLASS

Another element is the use of plastic for the PFS (Figure 5). It offers an advantage over the alternatives made of glass: the needle is moulded over, instead of molten over or glued on. During a melting process – generally performed with materials with great temperature resistance such as tungsten – heavy metals are created at temperatures of over 1,000°C. These can enter the glass container and subsequently settle in the product as well – even if the container is washed, dried and sterilised afterwards. The plastic variants also impress with their greater freedom of design and minimised risk of cracking or breaking.

> "Design freedom extends beyond the finished products."

CONSULTING OR COLLABORATION – THE CUSTOMER IS REALLY ALWAYS KING

Design freedom extends beyond the finished products. There's no such thing as the Z.BLIZZARD – it consists of many functional components that can be tailored to the producer's demands. The final line is assembled based on their wishes. The customer thus has the freedom to decide. Is the angle of the needle straight or angled? Which section is covered by the camera? Do we need integrated X-ray inspections? Do we fit the Z.BLIZZARD with access doors or is this unnecessary? These and further questions are dealt with

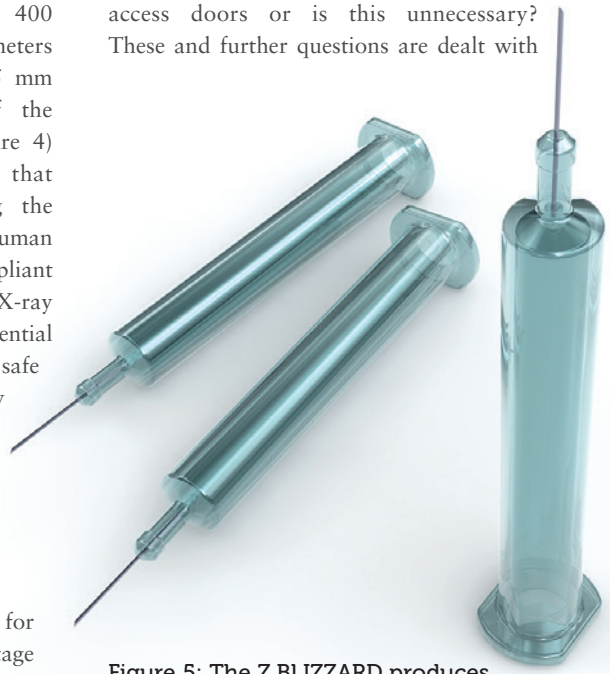

Figure 5: The Z.BLIZZARD produces PFS from plastics. They offer an advantage over the alternatives made of glass – the needle can be moulded over instead of molten or glued in.

in collaboration with the customer and then precisely implemented. Customers are included at an early stage, accompanying the entire construction and production process, which generally takes around 12 months. If desired, the customer can also rely completely on the expertise of ZAHORANSKY. The company will proactively make suggestions and recommendations if customers cannot get intensively involved in designing their machines – but, as a one stop-solution provider, ZAHORANSKY always tries to tie up as little customer resources as possible anyway.

A MATTER OF COURSE: RISK EVALUATION FOLLOWING GMP GUIDELINES

ZAHORANSKY's involvement goes beyond merely making suggestions – the causes and effects of the recommendations are analysed in the form of a medical-technological report, which includes a risk evaluation in accordance with GMP guidelines. Proof is provided that the suggested solution can be implemented without negatively affecting any customer audits. The company demands of itself that it can show why something works or why it doesn't. ZAHORANSKY takes it very seriously, with a constant look to the future of its customers' operations. In other words, even after delivering and setting up the Z.BLIZZARD, it maintains an interest in ensuring that its customers have an innovative and future-proof machine.

> "ZAHORANSKY makes sure that the line is engineered to the exact design and development specifications."

THE COMPANY MOTTO: THINK BEFORE YOU ACT

ZAHORANSKY also makes sure that the manufacturing line is engineered to the exact design and development specifications. If an assembly professional notices that a drill hole is missing, for example, he has to understand or inform himself why this is the case – he can't simply bore a hole himself.

ABOUT THE COMPANY

ZAHORANSKY is a full-range supplier of machinery and production lines, injection moulds, and automation equipment. The company operates with more than 700 associates at production sites in Germany, Spain, China, India and the US. System Technology offers across-system solutions for the injection-related automation. These systems are based on injection moulds by ZAHORANSKY Automation & Molds and on established systems from different modules of automation. ZAHORANSKY Automation & Molds serves the industrial automation and medical devices sectors, with preconfigured solutions provided for medical engineering. Z.BLIZZARD, for example, is an integral solution for making ready-to-fill prefillable syringes as primary medical packaging.

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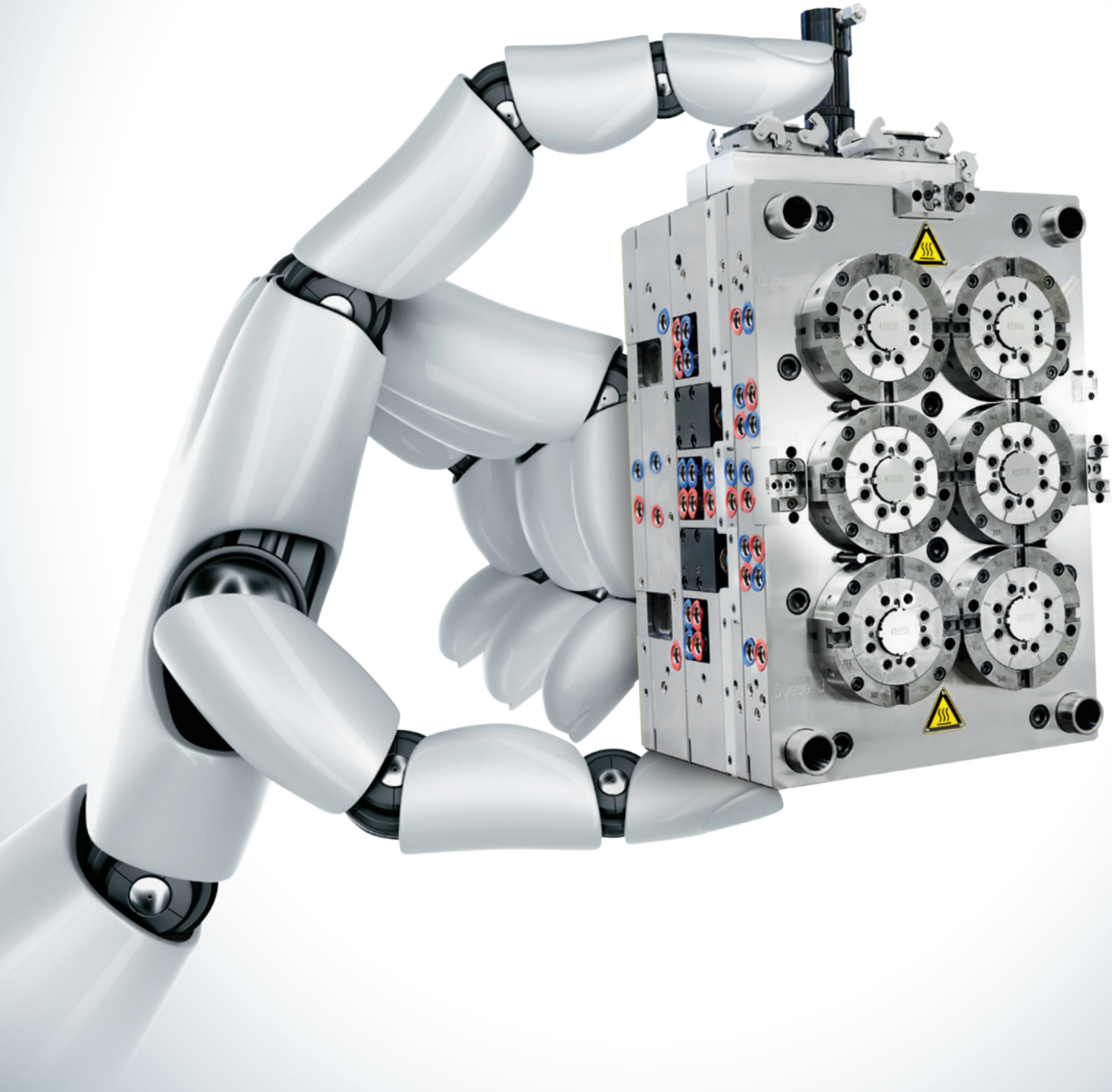

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