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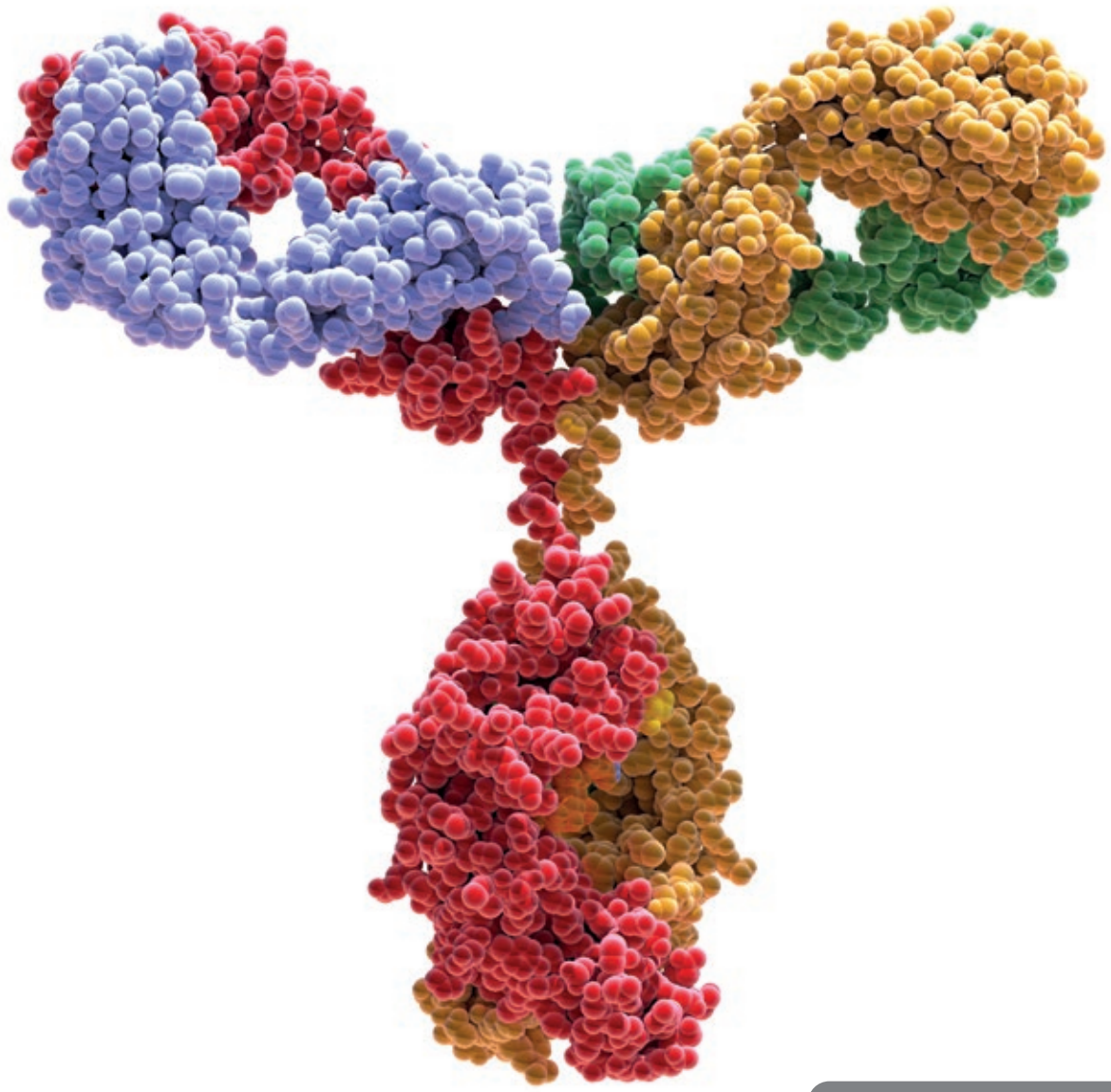

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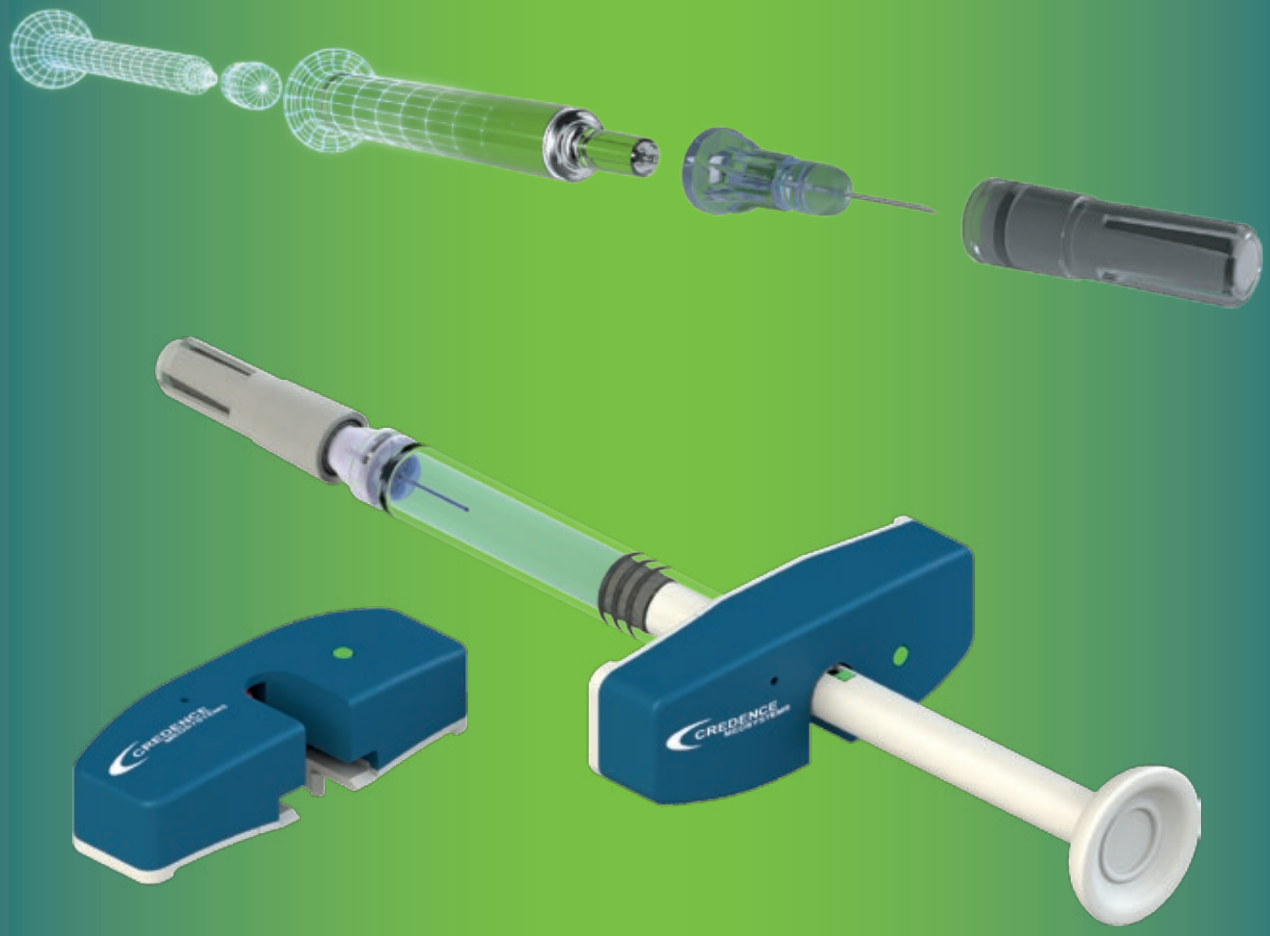

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Contents

ONdrugDelivery Issue N° 105, February 5th, 2020

PREFILLED SYRINGES & INJECTION DEVICES

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.

EDITORIAL CALENDAR

Apr 2020	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Drug Delivery
Dec	Connecting Drug Delivery
Jan 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles
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ADDRESSING COMPLEX BIOLOGICS WITH RATIONAL DRUG DEVICE DESIGN

In this article, Gene Rhode Fuensalida Pantig, RPh, Resident Molecular Biologist and Pharmacist at SHL Medical, reviews drug development over the years, the discovery of biologics as therapeutic agents and the emergence of autoinjectors. In correspondence, Hans Lin, PhD, a Research Fellow from Academia Sinica in Taiwan – who has interests in protein biology and drug discovery – discusses the inherent properties of biologics that should be of prime consideration to pharma companies and drug delivery device developers. With complex biologics moving the field of medicine further into a more personalised approach, the article also discusses the need for an even tighter collaboration from drug research through to development of the combination product.

The many advances in molecular biology and biotechnology – from the advent of recombinant DNA technology to the use of panomics[1] – have significantly furthered our understanding of the human body's molecular landscape. At present, scientists and clinicians steer the direction to deliver not just targeted but also truly personalised medicine.

This targeted approach in medicine has come a long way. From the classic antibiotics and antineoplastics, non-selective cytotoxic drug classes that often involve adverse effects for patients, we now shift to biologics – therapeutic molecules which try to correct biochemical pathways or inhibit aberrant cells or proteins. Alongside the development of biologics is the need to develop novel delivery systems that not only consider the molecule but also the end receivers of drug therapy – the patients. As well as the standard prefilled syringes for the assisted administration of biologics, recently developed prefilled pen and autoinjectors for patient self-administration have also found their space in molecular medicine.[2]

THE CLASSICAL APPROACH TO DRUG DISCOVERY AND DESIGN

In the past, drug development and discovery have mainly focused on small molecules, primarily owing to their oral bioavailability and their affinity to bind a druggable target. For a compound to be considered a lead in rational drug discovery, a classic requirement would be to satisfy Lipinski's "rule of five" (Ro5).[3]

The Ro5 is a set of physicochemical properties that allows the compound to be absorbed in the gastrointestinal system.[4,5] In general, the rule outlines that a lead compound should be relatively small in molecular size and, owing to its chemical properties, lipophilic in nature. While the rule has always been considered to determine the fate of whether a drug can even reach its site of action, most compounds that do not satisfy it are left unstudied.

ORAL SMALL-MOLECULE DRUGS AND THE DRUGGABILITY DILEMMA

Druggability,[6] on the other hand, refers to the likelihood of a target – oftentimes a protein involved in disease states – being modulated by a drug. Thus, while a potential drug may be considered absorbable, it must then bind to its druggable target at

> "Of the many challenges in delivering precision medicine, the drug itself is still the rate-limiting step."

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the site of action. This binding is expected to elicit a cascade of events, eventually alleviating disease conditions – at least at the symptom level.

However, not all disease-specific molecules or proteins are said to be druggable.[7] In fact, of the ~21,700 proteins identified in the human proteome by the year 2002, only 3000 are estimated to be druggable.[8] Putting this into perspective, subset data published in 2006 states that only 186 human proteins have been targets of all US FDA-approved oral small-molecule drugs of the same year – a number which is less than 10% of the druggable, potentially disease-related proteins.[9]

With only around 10% of the druggable human proteome addressed, there has been a spark of interest in discovering novel treatment modalities. After all, the remaining ~90% accounts for proteins and protein-protein interactions that are involved in various important biochemical pathways. At such a molecular level, any aberration would almost always result in a very specific disease state.

Simply put, a large portion of the druggable proteome is "undruggable" for oral small-molecule drugs. Taking a fast track into 21st-century therapeutics, biologics – molecules administered in recently developed delivery systems such as prefilled syringes and autoinjectors – have been reigning supreme to address the task.[2]

OVERCOMING THE RATE-LIMITING STEP IN MEDICINE

Of the many challenges in delivering precision medicine, the drug itself is still the rate-limiting step. In recent years, what remained elusive for small-molecule therapy has been taken over by biomolecules as therapeutics.[10] Scientists have started tapping into the potential use of large-molecule biologics.

In general, biologics are defined as pharma compounds synthesised or extracted from a "living" or biological source.[11] For the purpose of this article, we are focusing on biologics for therapeutic purposes – monoclonal antibodies (MAbs) and recombinant proteins, most of which are the result of harnessing recombinant DNA technology. While the first recombinant biologic was approved for clinical use in the 1980s, it was not until the dawn of the 21st century that we witnessed a steady trajectory in the research, development and use of these compounds.[12]

"With only around 10% of the druggable human proteome addressed, there has been a spark of interest in discovering novel treatment modalities."

The successful use of biologics in clinical applications has come a long way. Since the 1982 FDA approval of human insulin – the first recombinant biologic – development of biologic compounds has continued to be met with failures and triumphs. As early as 2005, researchers predicted the shift from organic chemistry to protein biology in medicine.[13] Since the concept of druggability has been discussed earlier, it is important to put on record that the field recognises that protein biologics are required to modulate and disrupt disease-related proteins and protein-protein interactions, which are often characterised with low druggability.[14] You could say the undruggable then becomes druggable through biologics.

With the current approach, caveats in druggability are circumvented by using biologics to modulate disease-specific proteins and their pathways.[7] From a symptom-based alleviation of the disease, now the molecular underpinnings of diseases are addressed, with recent biologics indicated for cancer, inflammation-related conditions, diabetes and migraine, to name but a few.

Biological medicines, especially proteins and antibodies, hold various advantages over small-molecule therapies. Proteins are highly specific in nature and function, and thus their action towards biological processes are precise and do not cause adverse effects.[12] The same is true for antibodies – versatile molecules that play a huge role in targeted therapy of diseases.[12,15] Biologic drugs, however, don't come without limitations and challenges.

UNDERSTANDING THE DELIVERY OF BIOLOGICS

The knowledge of the general physicochemical properties of biologics is of vital importance in translating these drugs into deliverable formats for effective patient administration. Since biological therapeutics are usually highly ordered but complex assemblies of long-chain peptides, they are of significantly high molecular weight and viscous in terms of their chemical and physical nature. In a discussion with SHL on this subject, Dr Hans Lin, a Research Fellow in the Institute of Biological Chemistry at Academia Sinica in Taiwan, communicates the inherent properties of biologics that should be of prime consideration to pharma companies and drug delivery device developers.

A researcher in the field of protein biology and drug discovery, Dr Lin points out that knowledge of the general pharmacokinetic properties of biologics is important. Further, he explains that it is during the preclinical and clinical studies when the biological drug's potency and effective dose, dosing frequency requirements and effective administration route is identified. With biological drugs varying in dosing and dosing frequency requirements, foresight is thus imperative for the success of a combination drug product strategy that is not only effective but acceptable for the patient.[2,13,15,16]

For example, clinical studies on the first systemic therapy for atopic dermatitis – an mAb – indicated the need for a higher concentration of the drug to achieve pharmacological efficacy. In terms of formulation, this translates to a biological drug that would require a higher volume in solution. The delivery format, on the other hand, would then require one that could be administered by patients without the need for intervention by a healthcare professional and with less drug administration frequency.

Case in point, a 2.25 mL autoinjector based on the Molly® platform could be one of the first to be approved by regulatory agencies as part of a combination product for the treatment of atopic dermatitis, asthma and a few other indications.[17] Molly® is an example of a single-use autoinjector that can accommodate complex biologics in the 0.1-2.25 mL range. For many years, 1.0 mL was considered the maximum volume for a subcutaneous injection, a measure adjusted to 1.5 mL by Mathaes and colleagues. Now, we are starting to see the first drugs in the 2 mL volume range being provided to patients in autoinjectors for self-treatment.[17,18]

The case for Molly® 2.25 as a combination product comes as a precedent in the evolving self-injection delivery of complex biologics for therapy. Along with the increasing development of biologics, it is of equal interest to note that this is one of the first autoinjectors for self-injection in the higher volume range – a precedent to consider for future development of drugs for self-injection.

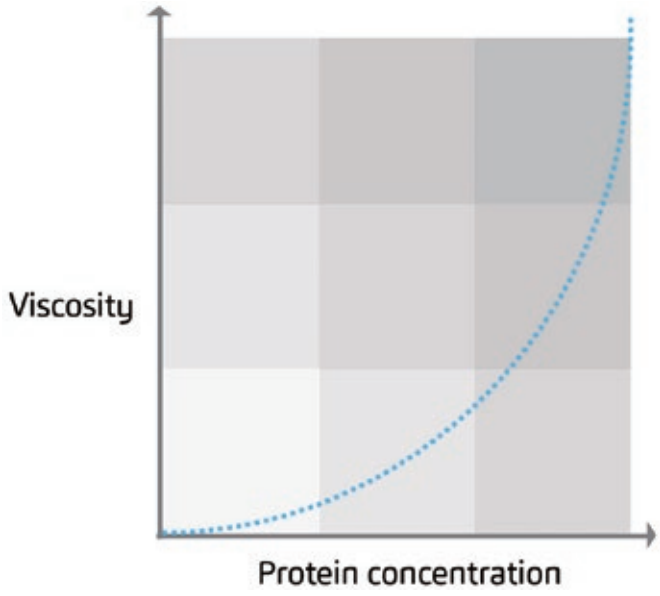

Figure 1: Generalised graph of the relationship between protein concentration and viscosity.

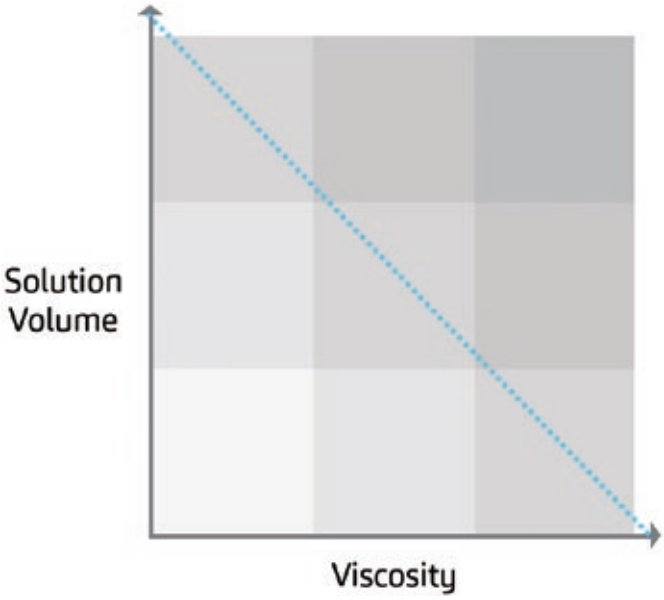

Figure 2: Generalised graph of the inverse relationship between protein viscosity and solution volume.

COMBINATION PRODUCTS ON A FORMULATION PERSPECTIVE

From a formulation perspective, it is important for researchers and drug device design engineers to understand the characteristic nature and properties of biologic drugs. The bioavailability of these large molecules – or the amount of the drug which reaches the body's systemic circulation to elicit an effect – is absolutely compromised in the oral state. Biologics require carefully designed medical devices to ensure proper parenteral drug administration and absorption into the body's systemic circulation. As such, this understanding is a crucial cause for the recent development of biologics in autoinjector delivery formats[2,16] by pharma companies and drug device developers, wherein acceptance of the format by patients is increasing.[27]

Complex biologics, like monoclonal antibodies (mAbs), typically require higher concentrations to produce clinically relevant effects. For such molecules, viscosity exponentially increases as a function of protein concentration (Figure 1).[18] Therefore, for a combination product to succeed in therapy, one must delineate drug device design in relation to the properties of the drug while considering patient-related factors in terms of drug administration.

In the medical device field, the Bertha® autoinjector is an example of a device that has been designed to address higher viscosity drug preparations. High protein concentrations that are characterised by viscosities of up to 60 centipoise can be delivered by the device, and its two-step operation is indicative of simplicity for patient self-injection.

On the other hand, concentrated protein biologics may require specific excipients to prevent aggregation and the addition of an optimal volume of diluent to increase drug stability. The increase in dose volume, in turn, may positively affect protein stability and lower viscosity. This could be illustrated in the inverse proportionality of protein viscosity and volume of the solution (Figure 2).[18] For biologics that may require volumes beyond 2 mL, cartridge-based devices may prove to be helpful for successful drug delivery. The Maggie® autoinjector, for example, uses a standard 3 mL cartridge.

On the basis of the intrinsic nature of protein biologics, the need for delivery devices that can accommodate higher fill volumes of biologics is implicit (Figure 3). In theory, biologics such as mAbs require higher quantities to reach the therapeutic dose.[18] On account of its concentration, this means that such biologics should be packed in a volume acceptable for patient administration but interspersed enough to prevent physicochemical challenges.

As was exemplified earlier by the case for Molly® 2.25, explorations of therapeutic volumes for biologics beyond 2 mL are underway. With the rise in the development of bigger and more complex protein biologics, delivery devices addressing these biologics and optimised for self-treatment – like Maggie® – are crucial.

> "From a patient standpoint, the practical aspects surrounding a combination product are critical, with usability as the prime focal point."

CURRENT AND FUTURE DIRECTIONS FOR COMBINATION PRODUCTS

With the current field of medicine approaching a more personalised way of treating disease conditions, interest in the development of biologics will remain. Since the core of precision medicine – which is to understand and address the underlying cause of diseases in individual patients[19] – is addressed by biological treatments, the research to discover biologics, biobetters and biosimilars will continue.[20] With patients as the end receivers of these treatment modalities, the continued success of biologics as combination products will depend on even tighter collaborative efforts between the researchers and developers involved.

From a patient standpoint, the practical aspects surrounding a combination product are critical, with usability as the prime focal point. In retrospect, some of the usability challenges related to small-molecule, oral treatments included difficulty opening tablet

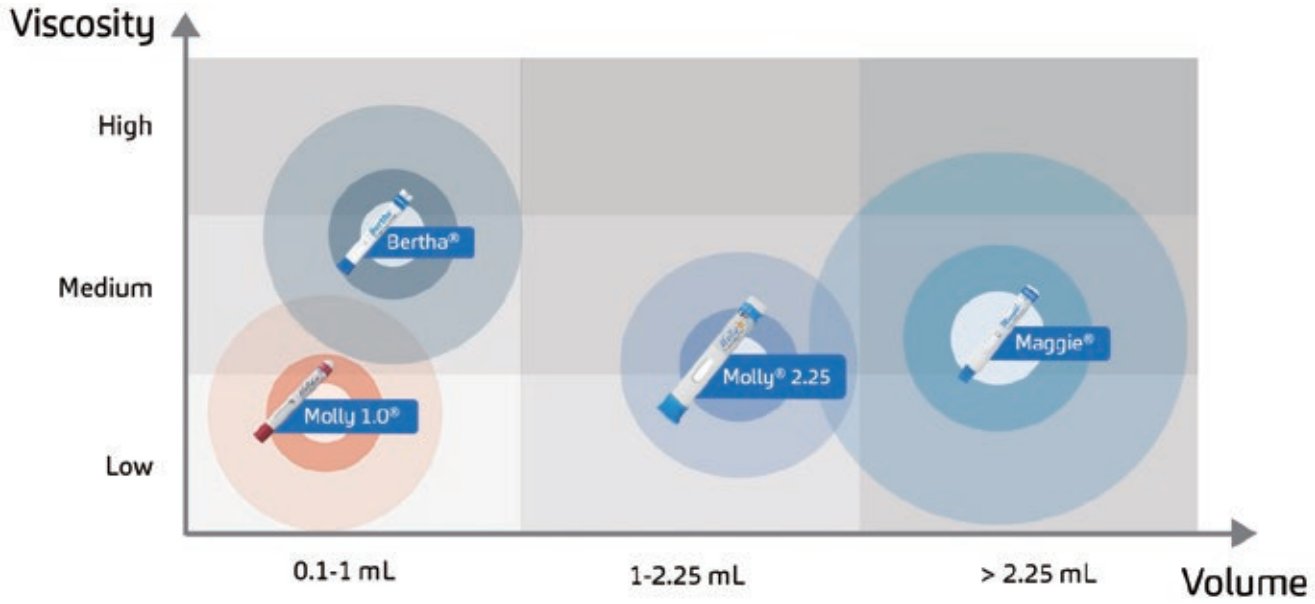

Figure 3: Examples of currently available drug delivery modalities for complex biologics.

containers and blister packs. While these challenges were identified through research, there are few published papers about this aspect of medicine.[21,22]

For biologics, now finding their space in targeted medicine, their success as combination products will depend on even tighter collaborative efforts between the researchers and developers involved. This means a well-thought-out and concerted development of the combination product – from research and formulation, primary packaging and secondary packaging through to patient usability, where the final product ideally would have an optimal balance between viscosity, volume and injection frequency. Thus, in translating these biological molecules that have varying intrinsic properties such as potency, viscosity and volume into a deliverable format, the need for their co-development with autoinjectors that complement these varying requirements will continue.

CONCLUSIONS

The field of therapeutics has certainly progressed through discoveries in molecular biology and biotechnology. These discoveries have made the development and production of complex biologics possible, and interest in biological therapeutics is strong (Figure 4).[10,23,24]

Along with rational drug design – a longstanding concept in pharmacological science – the success of a combination product for effective patient therapy relies on the rational design of drug devices. The significance of autoinjectors as drug delivery modalities for complex biologics will continue, as it delineates drug device design with the intrinsic properties of drugs and drug administration by patient self-injection. With the advent of digital technologies, it is also of interest that adaptation of medical software and digital implementations for self-injection devices are underway.[25,26]

Historically, medical devices were not perceived by the healthcare field with the same significance as that of the drug itself, as evidenced by the previous regulatory stipulations for devices.[27] Now, it could be said that therapeutics in the era of biologics require drug delivery devices as indispensable patient tools. Firstly, these drug devices serve to administer complex drug formulations targeted for specific patients. Secondly, with the advent of connected therapeutics – these devices serve to connect the patient to healthcare professionals and patient support programs in order to optimise therapeutic outcomes.[25,26]

Further development in drug delivery devices and combination products will truly allow the generation of populated patient data to inform pharma companies, drug-device developers, regulatory agencies and the patients about the absolute value of the drug.

For combination products, the interplay of the drug delivery device in relation to the drug's pharmacokinetics is evident, as the drug device plays a role in the fine tuning of drug formulation, dosage, dose

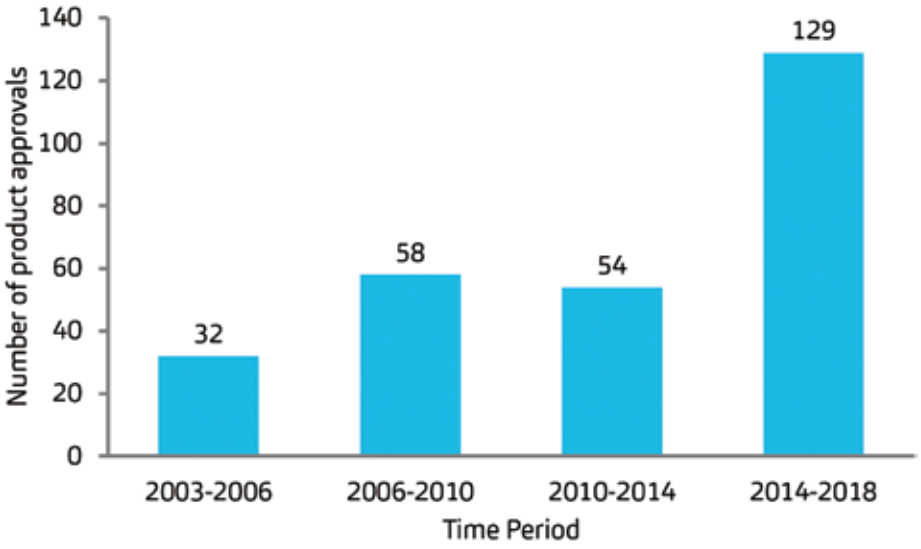

Figure 4: Regulatory approval of biopharmaceuticals over the years. The numbers pertain to the US and European Union regulatory approvals of recombinant biologics over the survey period.

administration and periodicity of injection. As patients are the end receiver of these combination therapeutics, evaluation of patient acceptance is of importance. Recently, an in-depth review has positively reported on patient compliance with self-injection devices such as autoinjectors.[28] Finally, as researchers discover novel biological compounds, the need for injection devices addressing the varying viscosities and formulation volumes will continue.

Our correspondent in this article, Hans Chun-Hung Lin is a Research Fellow at the Institute of Biological Chemistry, Academia Sinica – Taiwan's national research academy. He has a PhD in Chemistry from the Scripps Research Institute (CA, US), and from 1995 to 1997 pursued his postdoctoral fellowship at Harvard Medical School (MA, US). Dr Lin's multidisciplinary research interests include protein biology, particularly enzymology and glycobiology, as well as drug discovery. At present, he serves as the Director of Academic Affairs at Academia Sinica.

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DEVELOPMENT OF A NEW HIGH-PERFORMANCE AUTOINJECTOR

In this article, Tom Oakley, Director of Drug Delivery Device Development at Springboard, and Sigrid Saaler-Reinhardt, PhD, Director of Corporate Project Management at Midas Pharma, discuss the development of the Midas Pharma's NIS cartridge-based autoinjector.

Prefilled syringes have become the standard format for delivering new biologic drugs. However, they suffer from various issues, such as:

1 People do not like seeing needles.
2 There is a risk of contamination and injury via needlesticks.
3 They can be unsuitable for self-injection by people with hand tremors or dexterity issues from rheumatoid arthritis and suchlike.
4 The force required to deliver viscous drug formulations through an acceptably thin needle could be too high either for the user or for the syringe.
5 The drug formulation can interact with the silicone lubricant, the steel needle, the adhesive used to attach the needle or the tungsten used to form the hole for the needle.

"Standard" autoinjectors, which are based on a compression spring pushing on the plunger of a prefilled syringe, can solve the first three issues. But the fourth issue is a growing challenge for standard autoinjectors because certain biologics – notably monoclonal antibodies – need to be administered in high concentration for subcutaneous self-administration. This can lead to an increased viscosity of the formulation, which requires greater spring force.

Most autoinjector designs hold the plunger rod back away from the plunger when the device is in storage. When the device is triggered, the plunger rod accelerates forward rapidly until it impacts the plunger and creates shock through the system which can break the syringe. Another source of impact is where some device designs insert the needle into the

Syringe	Cartridge
✘ Limited volume	✔ Volume limited only by length
✘ Fragile flange and shoulder	✔ No flange, and a strong shoulder
✘ Tungsten and adhesive around needle	✔ No tungsten or adhesive around needle
✘ "Wet" needle in storage	✔ No needle contact in storage
✘ Sprayed-on silicone oil	✔ Baked-on silicone oil
✔ Used in early clinical trials	✘ Not typically used in early clinical trials

Table 1: Comparison of syringes and cartridges.

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patient using the main power spring. This can accelerate the syringe forward at high speed and cause impact when the syringe is decelerated again.

There are some innovative devices tackling these problems – such as the Oval Medical (Cambridge, UK) ArQ-Bios, which uses a custom primary drug container, or the Consort Medical (Hemel Hempstead, UK) Syrina AS, which uses a liquified gas propellant in place of a spring. Both have their merits but require the pharmaceutical company to support either a non-standard primary drug container or a non-standard power source, respectively.

Another way to manage the increasing viscosity is to dilute the formulation back to a more reasonable viscosity and deliver a larger-volume injection. Several platform autoinjectors are now available in 2.25 mL syringe formats. However, the change from the 1 mL to the 2.25 mL syringe formats tends to require substantial changes to the device. Changing the computer-aided design (CAD) models and manufacturing a new set of tools for almost all components entails an increased risk, time delay and cost. Further, in general, they cannot support injections greater than 2.25 mL.

There is, therefore, the need for a new autoinjector which:

- Avoids the problems associated with prefilled syringes (drug interaction, limited volume, etc)
- Uses a standard primary container that is already widely used widely for injections
- Uses well-proven components (springs, needles, packaging, etc) that are already derisked and low cost
- Can deliver higher volumes and/or viscosity than other low-risk autoinjectors.

WHY USE A CARTRIDGE IN AN AUTOINJECTOR?

Pharmaceutical cartridges are widely used to deliver drugs such as insulin, fertility hormones and growth hormone. They differ from the staked-needle syringe in that cartridges have an elastomeric septum seal at one end rather than a needle. Also, cartridges do not have the flange seen on syringes. The main differences relevant to this discussion are summarised in Table 1.

Cartridges are not typically used in early clinical trials for many new biologics, such as monoclonal antibodies. However, they could be used by either fitting an adapter to add a needle and plunger rod or by using the autoinjector that we will introduce in this article.

WHY PRESSURISE THE DRUG IN STORAGE?

Most spring-powered devices cause an impact when the spring is released. This could be avoided entirely if the spring was already pushing on the plunger, thus pressurising the drug during storage. The advantages of this approach are:

- Impact is avoided, so stronger springs can be used without risk of impact breakage, which in turn means that higher viscosity and/or larger volumes can be delivered through a given needle diameter.
- Air bubbles have been shown to cause degradation of proteins (Christian Dechant, SMi Prefilled Syringes Europe Conference, London, UK, January 17-18, 2018). When the drug formulation is pressurised in storage, air tends to dissolve into the solution. In addition, any remaining bubbles are compressed, thus reducing their surface area available for interaction with the drug formulation.
- The plunger does not move when ambient air pressure is changed, for example during air freight.
- The triggering mechanism can be very simple and completely independent of the rear end of the autoinjector. The injection can be started by inserting a needle through the cartridge's septum seal.

But could storage under pressure damage the drug? Testing at a pharma company has shown that there has been no degradation in their drug when stored at maximum pressure over the three-month period studied. There is no reason to believe there will be a different effect with longer duration. In fact, the reduction in bubble number and volume discussed above should reduce degradation.

Figure 1: 3 mL NIS autoinjector.

THE NIS AUTOINJECTOR

The NIS autoinjector from Midas Pharma (Figure 1) is a cartridge-based autoinjector wherein the spring is always pushing on the plunger. The simplicity of the NIS design (Figure 2) means that:

- A 1.5 mL or 3 mL cartridge can be used with only minor changes. For example, the same tool could be used for the main body, which is unique amongst autoinjectors.

Figure 2: Section view of NIS autoinjector.

- For a given cartridge diameter, a change in drug volume or viscosity needs only a change in the spring and plunger rod length.

Figure 3 shows two use steps for the NIS autoinjector. However, the design is so simple that it is even possible to do away with the step of removing a cap, which would make the NIS autoinjector the first "one-step" autoinjector on the market.

HOW CAN WE PREDICT AUTOINJECTOR PERFORMANCE?

Our primary considerations are that the autoinjector should:

- Be safe – which means, for example, a low chance of breakage or underdose.
- Deliver the drug through a thin needle in a reasonable time.

In order to answer the second point, we would like to know the maximum viscosity each autoinjector design can deliver through a given needle gauge in the maximum allowable injection time limit. The injection time is dominated by the drug formulation being pushed through the needle. Flow through the needle is governed by the Hagen-Poiseuille equation:

$$Q = \frac{\pi \Delta P d^4}{128 \mu L}$$

Rearranging to calculate injection time gives:

$$t = \frac{32 \mu L V D^2}{F d^4}$$

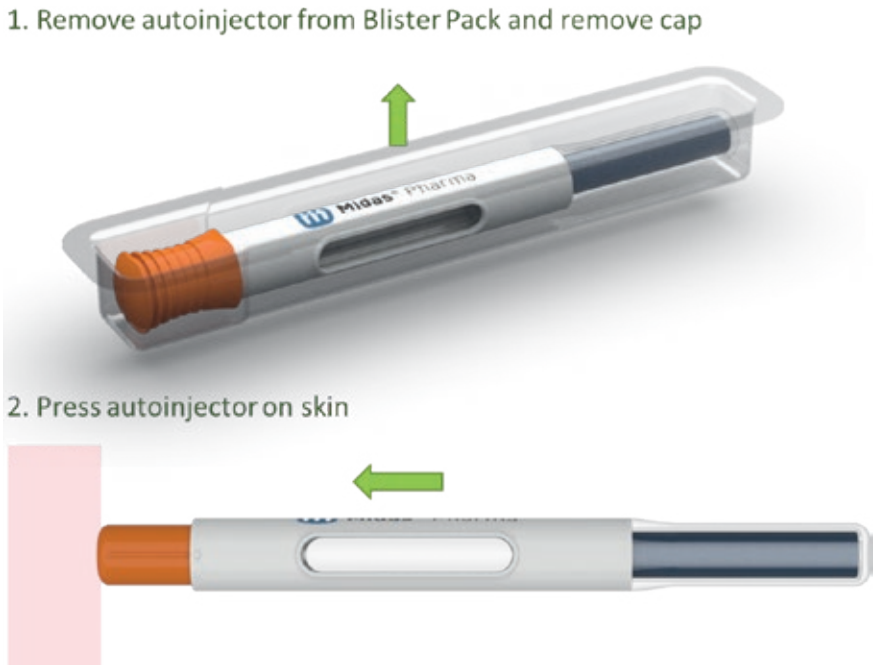

Figure 3: Use steps for NIS autoinjector.

Where Q is flow rate, π = 3.141, ΔP is the pressure drop, d is the needle inner diameter, μ is the dynamic viscosity, L is the needle length, t is the injection time, V is the drug volume, D is the syringe inner diameter and F is the force on the drug (which is spring force minus any friction).

Figure 4 shows the correlation between measured injection time and predicted injection time for an example autoinjector filled with calibrated 50 cP silicone oil, with an extra thin needle and weak spring to give greater injection time than the real device. The difference between measured and predicted injection time is not more than 1.5% so the model is good enough for our purposes.

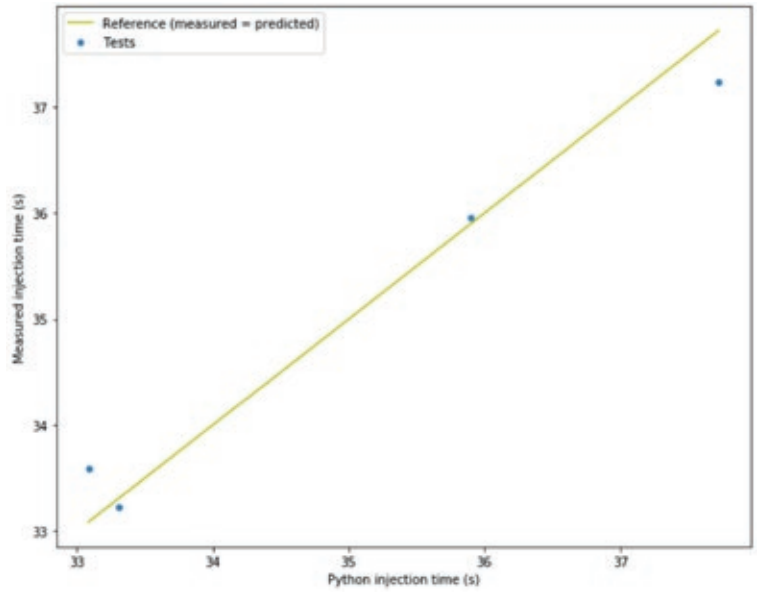

Figure 4: Actual injection times versus predicted injection times.

HOW DOES THE NIS AUTOINJECTOR COMPARE WITH COMPETITORS?

We could use the equation above to calculate the maximum viscosity which each autoinjector can inject in a given time through a given needle diameter – but that would assume that every parameter was at its mean value and would take no account of variation. Also, we want all injections to be under a given time limit – so we care about the slowest injections, not the mean. We need to calculate the distribution of injection times.

We could use algebraic manipulation but this is challenging and would become very challenging if any of the input distributions were not Gaussian. Instead, we can use a Monte Carlo simulation. For those who are not familiar with this method, the steps are:

1. Model the distribution of each input to the equation (drug volume, needle diameter, etc).
2. Take one sample at random from each input distribution.

"The NIS autoinjector could inject significantly higher-viscosity drugs than competitor devices."

3. Calculate one output value by putting the sample input values through our equation.
4. Repeat steps 2 and 3 until we have a suitably large number of output samples to represent the output distribution.

The validity of the Monte Carlo method depends on several factors being true:

- The inputs must be independent. For example, the needle diameter should not correlate with the needle length.
- The inputs should be representative. We have made our best efforts to use industry-wide tolerances and international standards.

Spring Force

- Each device platform has limited space for the spring.
- We calculated the strongest spring we thought could be designed into the space allowed.
- We used the industry standard tolerance of ±10% on spring force.

Device Friction and Plunger-Cartridge Friction

- Nominal friction was measured from device samples.
- Tolerance was estimated at ±70% (which approximates measurements from similar device developments).

Container Diameter

- Nominal diameter was measured from device samples.
- We matched the diameter to the nearest standard glass tube and used ±0.1 mm from ISO 13926-1:2004.

Needle Length

- Nominal was measured from device samples.
- Tolerance of ±1 mm was used because ISO 7864:2016 specifies maximum +1 mm and -2 mm.

We used the Monte Carlo method to calculate the maximum viscosity that could be injected by the NIS autoinjector and three competitors for various needle gauges, with no more than 1% of injections taking more than 15 seconds. The results (Figure 5) show that the NIS autoinjector could inject significantly higher-viscosity drugs than competitor devices. Alternatively, a similar viscosity could be delivered by the NIS through a smaller needle than competitors. Competitor devices would probably have unacceptable risks, such as plastic creep or glass impact, if they used the maximum force spring that could fit.

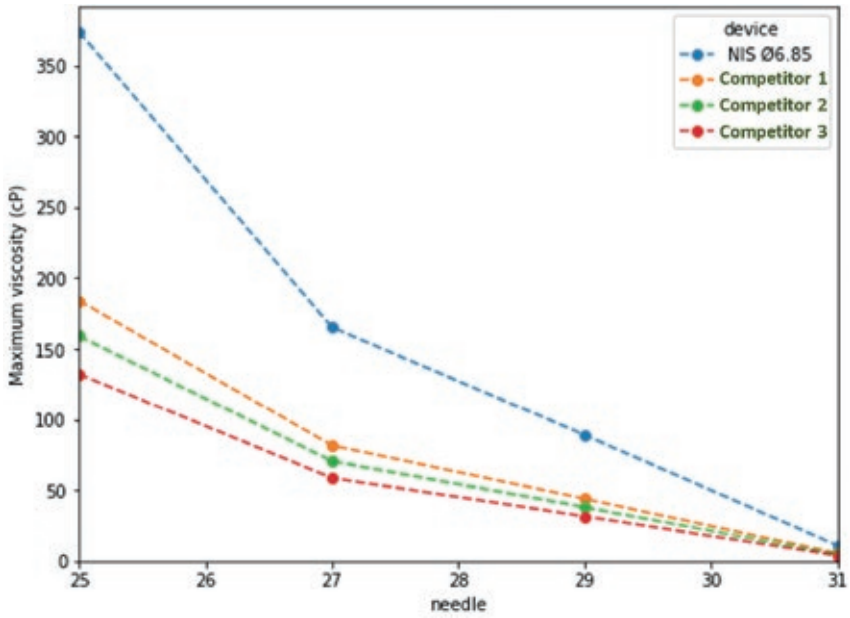

Figure 5: Maximum viscosity for the LARGEST SPRING for each device for given needle gauges. (The 31 gauge is regular wall, others are thin wall.)

SUMMARY

There are demonstrable advantages to using a cartridge over a syringe in an autoinjector, as described in Table 1. Furthermore, pressurising the drug in storage can eliminate impacts and reduce drug degradation. Elimination of impacts means that the autoinjector could be designed to deliver higher viscosities and/or volumes than competitors that are on the market. The NIS autoinjector embodies these ideas in a simple and low-risk design.

ABOUT THE COMPANIES

Springboard specialises in developing devices from concept to manufacture for regulated markets. It is expert at creating innovative yet robust designs and solving difficult technical problems quickly. It does not have internal projects so it is as fast and cost effective as possible, and the intellectual property generated belongs entirely to its clients.

Midas Pharma provides expertise, services and products across the full industry value chain, whether clients are looking for a manufacturing partner, support in regulatory affairs or plan to expand their business network. It is present in all major pharma markets worldwide.

ABOUT THE AUTHORS

Tom Oakley leads engineering and scientific teams developing new injection devices, pumps and inhalers. He has been the named inventor on dozens of patents throughout his 20 years' experience in industry. He is a regular speaker at various international conferences on innovation and medical device development, and mentors engineering and MBA students on innovation and device development at the University of Cambridge (UK) Engineering Department and the Judge Business School (Cambridge, UK).

Sigrid Saaler-Reinhardt's background is in biochemistry. She has a PhD in Cell Biology and Oncology and became a Professor of Molecular Genetics at the Johannes Gutenberg-University of Mainz (Germany) in 1997. She has published more than 50 papers, mainly in the field of cellular expression systems, nerve cell development and generation of monoclonal antibodies against various cell surface receptors and ion channels. Over the last five years, she has become a specialist in parenteral drug product development, selection of primary packaging, fill and finish and medical devices.

SCHOTT
glass made of ideas

FINDING THE RIGHT PACKAGING FOR BIOLOGIC DRUGS

Here, Christian Helbig, Head of Glass Syringes, SCHOTT, describes how the company's syriQ BioPure® prefillable syringes have been designed and developed to meet the specific requirements of the rapidly growing biologic therapeutics market, introducing a new 2.25 mL version, and – in partnership with WL Gore – a new silicone free version, the world's first silicone-free glass syringe system.

The pharmaceutical industry is witnessing a number of trends, which are increasingly influencing the development of new primary pharmaceutical packaging. One of these is the fast-growing market of biologics and another is the need to make the administration process as easy as possible for patients by enabling more convenient self-administration.

Biologics currently account for around two-thirds of >3000 drugs in the development pipelines of international pharmaceutical companies (Figure 1). In fact, these novel types of drugs offer effective treatment options for a number of complex diseases such as cancer. At the same time, biologics have become even more structurally complex than their predecessors. Their molecular structure is more sensitive not only to temperature and other environmental conditions, but also to extractables and leachables (E&L) that can be released from primary packaging materials. E&L present a risk of drug/container interaction and can diminish a biologic's purity and therapeutic effectiveness. As a result, the design of pharmaceutical containers for biologics is particularly challenging, as an innovative approach is required to ensure drug stability throughout the drug's entire shelf life. Furthermore, biologic drugs are often highly viscous, which makes them more difficult to administer.

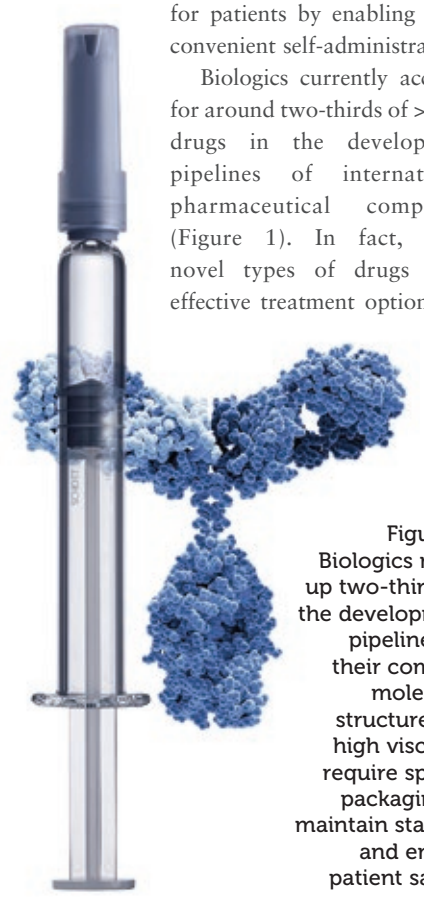

Figure 1: Biologics make up two-thirds of the development pipeline, yet their complex molecular structure and high viscosity require special packaging to maintain stability and ensure patient safety.

The second trend highlighted here is more closely linked to patient comfort and improving their overall quality of life. In the past, biologics have been administered as intravenous (IV) or subcutaneous (SC) injections in clinics or hospitals. This meant that the patient had to visit a doctor every time a drug dose was needed. In order to improve the patient experience, there is a shift to move the administration to the patient's home. While the option of self-administration allows patients to continue their treatment more independently, it also means that injection systems must meet patients' needs by ensuring a safe and easy administration process.

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"syriQ BioPure® syringes come with a range of coated plunger stoppers tailored especially for sensitive applications. In fact, more than 48 different combinations featuring premium quality elastomer components have already been successfully tested and approved."

SCHOTT, an expert in the field of pharmaceutical primary packaging, has responded to these trends by launching syriQ BioPure®, prefillable glass syringes designed specifically for the biologics market. The new syringes keep sensitive drugs stable over their shelf lives, shorten time to market by providing a full documentation package for the combination product requirements, while making administration much easier for patients.

STATE-OF-THE-ART PACKAGING OF IMMENSE IMPORTANCE

syriQ BioPure® syringe barrels, the primary containers, are made of highly inert FIOLAX® borosilicate glass, the gold standard in the pharmaceutical industry since its development in 1911. Thanks to its strong track record, its suitability for use with sensitive drugs has been thoroughly researched. In addition, to ensure that tight geometrical tolerances are met for the syringes, each individual glass tube is subjected to thorough inspection using advanced technology.

As highly sensitive drugs are prone to interact with the container and components, the syriQ BioPure® manufacturing process has been further improved to reduce the amount of tungsten and adhesive residues as well as to ensure a uniform silicone layer. All features are validated and documented in accordance with the latest US FDA guidelines.

syriQ BioPure® syringes come with a range of coated plunger stoppers tailored especially for sensitive applications. In fact, more than 48 different combinations featuring premium quality elastomer components have already been successfully tested and approved. Options include various closure systems, such as Aptar 4800, Aptar 4900, West 7025 and West 7028. The use of high-end materials further contributes to the superior E&L profile of the glass syringes.

Furthermore, the syringes can be used with most of the leading safety and autoinjector devices, thus meeting market demand for products that can be administered at home for greater patient comfort. Seamless integration into these devices is achieved due to the syringes' high dimensional accuracy. Additional dimensions that exceed ISO requirements and new geometrical tolerances are reached by employing cutting edge forming technology and by performing online inspections. This guarantees device compatibility by design and therefore leads to superior functionality in the patient experience.

syriQ BioPure® prefillable glass syringes are delivered pre-sterile in a standard nest and tub. The syringes can be filled on a wide variety of standard ready to use (RTU) filling lines and are easy to handle. Short time to market for the pharmaceutical industry is further supported as all required documentation is fully available.

The containers are available in both 1 mL long and 2.25 mL syringe formats – the latter being newly introduced to the market at Pharmapack 2020 (February 5-6, 2020 in Paris, France). This larger format was particularly developed for specific biologics, which are administered via autoinjectors.

Ensuring the efficiency of the treatment leads to an increase in the bioavailability, and therefore in a higher API concentration. This results in an increase of the viscosity of the API. The higher the viscosity, the more force is required to inject the drug, which may lead to the syringe breaking. Additionally, by nature, these large molecules in a high concentration can cause stability issues. In order to ensure an equally efficient treatment the glass syringe barrel has to be increased. While a standard 1 mL long glass syringe would be too small in volume for the increase in bioavailability, everything beyond 3 mL would be too big for a SC injection. Hence, a 2.25 mL glass syringe designed for these kinds of biologics is a suitable solution in terms of bioavailability and a SC injection to ensure the ease of administration and the efficiency of the treatment for the patient at the same time.

"Together, SCHOTT and WL Gore have presented the first prefillable glass syringe (PFS) system that completely eliminates the need for silicone or similar substances when administering complex biologic drugs."

THE WORLD'S FIRST SILICONE-FREE GLASS SYRINGE SYSTEM

Within the biologic drug market, an estimated 10-15% of the pipeline are biologics that are highly sensitive to silicone. Silicone has long been a necessary substance for helping to reduce the injection force needed to administer drugs via prefilled syringes to make the treatment more comfortable for the patient. Nevertheless, there are cases in which silicone can interact with and even harm a drug. For this reason, pharmaceutical companies are also in need of more advanced types of syringes that avoid siliconisation of the syringe barrel while maintaining consistent gliding force through the highly accurate geometry of the container.

SCHOTT has collaborated with the global material science company WL Gore to pair Gore's ImproJect™ plungers with syriQ BioPure® silicone-free syringes (Figure 2).

Figure 2: SCHOTT teamed up with WL Gore to introduce world's first silicone-free glass syringe system, syriQ BioPure® silicone free.

Together, SCHOTT and WL Gore (Newark, DE, US) have presented the first prefillable glass syringe (PFS) system that completely eliminates the need for silicone or similar substances when administering complex biologic drugs. The two components create a unique silicone-free glass syringe system, which is the first of its kind in the world today, thus changing the ways in which biologics can be protected during filling, storage and up until the moment of administration.

While pharma companies previously chose to use vials instead of prefilled syringes to avoid silicone contamination, with syriQ BioPure® silicone-free syringes, a new class of drugs can now be manufactured and stored in prefillable syringes. This offers a way to save time for clinicians, reduce healthcare costs and improve safety for patients.

syriQ BioPure® silicone-free syringes use no silicone inside the syringe barrel. To maintain consistent gliding force and injection duration over the shelf life of the product, but also to provide robust container closure integrity, great emphasis was placed on accurate geometry. The new syringes are made of FIOLAX® CHR glass tubing – named in accordance with its controlled hydrolytic resistance – that is 100% inspected with the help of a big data process to ensure tight dimensions and the high cosmetic quality of each barrel. In addition, syriQ BioPure® silicone-free also features ultra-low tungsten residuals as well as low cannula adhesive residuals to lower the extractible profile and reduce the risk of container/drug interactions.

The barrels are offered with Gore ImproJect™ silicone-free plungers, an industry-leading silicone-free plunger, to further eliminate the risk of container interaction with sensitive biologics. Designed for use in bare-glass (non-siliconised) barrels, these plungers help protect complex or sensitive biologics from silicone-induced aggregation and particulation while maintaining consistent injection performance over time.

This combined offering represents the only commercially available option for a silicone-free, prefilled syringe system (plunger and barrel) that protects sensitive biologics from potential interactions with silicone.

CONCLUSION

In summary, the rise of biologics presents an opportunity to treat numerous diseases, yet the structural complexity of molecules is simultaneously creating new complications when it comes to ensuring drug stability. Containers, moreover, need to support the trend towards self-administration by being compatible with autoinjectors and similar devices.

Innovations such as the extended syriQ BioPure® portfolio including the new 2.25 mL format and syriQ BioPure® silicone-free syringes offer solutions to ensure drug stability while enhancing the patient experience.

ABOUT THE COMPANY

SCHOTT Pharmaceutical Systems helps people around the world protect, access and use the medicine they need as safely and conveniently as possible. As market leader in primary packaging made of glass and polymer, SCHOTT safeguards and advances the integrity of injectable solutions and more. SCHOTT is a pioneer with unsurpassed quality, safety and reliability.

ABOUT THE AUTHOR

Christian Helbig is the business leader of the Strategic Business Field Glass Syringes at SCHOTT. He has more than 10 years of experience in pharmaceutical packaging sector, developing advanced pharmaceutical packaging i.e. surface modifications and coatings on glass and polymer, understanding of drug-container interaction investigations. Further, he has been working on development and commercialisation of prefilled glass syringes (syriQ®) and polymer syringes (TOPPAC®) including closure systems and compatibility with injection devices for various applications in various markets. Mr Helbig holds a biotechnology engineering degree with emphasis on process engineering from the University of Applied Sciences Emden (Germany).

SCHOTT Pharmaceutical Systems

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the ease-of use of her
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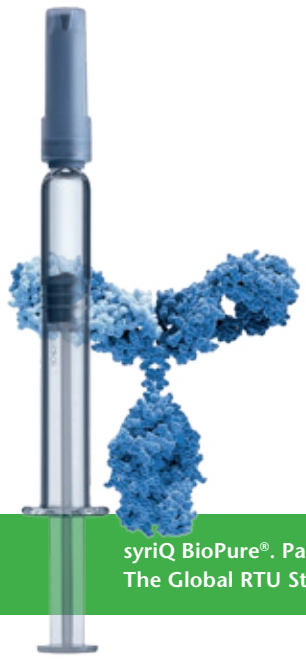

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HOW USERS DISTINGUISH BETWEEN SELF-INJECTION DEVICE PLATFORM VARIANTS

Ever-increasing interest in device platforms raises concerns around the broad availability of lookalike autoinjectors that may result in inappropriate medication usage and potentially put patients at risk. Here, Andreas Schneider, PhD, Innovation & Business Development Manager, Ypsomed Delivery Systems, summarises a recent empirical study[1] detailing how effectively various user groups distinguished platform device variants. The article highlights how patients, healthcare professionals and non-professional caregivers distinguished between device versions, provides insights into which device attributes drive device distinguishability, and then relates these attributes to user group-specific characteristics.

Self-injection device platforms have come a long way in disrupting the traditional device development process. In fact, they resolve long-standing industry challenges. Not only do platforms provide attractive cost structures and proven handling concepts across user groups but they also reduce technical risks and speed up time to market. A platform is referred to as a user-tested drug delivery system that, by design, enables the efficient development and manufacturing of drug-specific product variants. It comes as no surprise that most of the recently approved handheld autoinjectors are derived from device platforms (Table 1).

The significant interest in self-injection device platforms, however, conceals certain reservations. One concern raised by industry experts is that the increasing adoption of platforms may heighten the risk of medication errors. Much is at stake. The emergence of lookalike devices might, experts worry, provoke preventable events causing inappropriate medication usage, potentially putting patients at risk.

On the one hand, patients with multimorbidity increasingly self-manage complex medication plans that could include more than one version of an injection device platform. On the other hand, the complexity of dosing regimens continues to increase and, for instance, may involve the same drug delivery device platform across dose strengths, often distinguished by label information and colouring only.

> "One concern raised by industry experts is that the increasing adoption of platforms may heighten the risk of medication errors."

Unfortunately, we know very little about how users distinguish between self-injection devices. Although research has repeatedly put labelling and packaging of solid oral dosage forms under the microscope to avoid inappropriate medication use, there is limited empirical evidence on what drug delivery device attributes drive users' ability to distinguish between platform device versions.

We also lack understanding of how various user characteristics – such as professional background, age, dexterity or visual impairments – shape their perceptions and similarity ratings. This matters because platform devices are increasingly used across chronic disease states where device differentiation should be carefully adjusted to specific patient needs and characteristics.

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<2011	2012	2013	2014	2015	2016	2017	2018	2019
Aranesp® Amgen	**Sumatriptan** Sun Pharma	**Otrexup®** Antares	**Bydureon®** AstraZeneca	**Cosentyx®** Novartis	**Benepali®** Biogen	**Benlysta®** GSK	**Actemra®** Roche	**Copaxone®** Teva
Enbrel® Amgen/ Pfizer		**Rebif®** Merck	**Plegridy®** Biogen	**Praluent®** Sanofi	**Erelzi®** Sandoz/ Novartis	**Kevzara®** Sanofi	**Aimovig®** Amgen/ Novartis	**Cyltezo®** Boehringer Ingelheim
Neulasta® Amgen			**Tanzeum®** GSK	**Repatha®** Amgen	**Orencia®** BMS	**Makena®** AMAG	**Amjevita®** Amgen	Epinephrin/ Teva
			Trulicity® Lilly		**Sumatriptan** Antares		**Emgality®** Lilly	**Fasenra®** AstraZeneca
					Taltz® Lilly		**Hadima®** Merck	**Gvoke HypoPen®** Xeris
					Zembrace® Promius		**Hulio®** Mylan	**Nucala®** GSK
					Zinbryta® Biogen		**Hyrimoz®** Novaris	**Teribone™** Asahi KASEI
							Imraldi® Biogen	**Vyleesi®** AMAG
							Xyosted® Antares	

Table 1: Non-exhaustive list of approved platform-based disposable single-use autoinjectors (compiled in December 2019).

"We undertook a non-interventional simulated usage study[1] where participants assessed the similarity of autoinjectors."

THE STUDY DESIGN SEARCHING FOR ANSWERS

In searching for answers, we undertook a non-interventional simulated usage study[1] where participants assessed the similarity of autoinjectors. 74 participants among patients across chronic disease states, non-professional caregivers and healthcare professionals rated the similarity of eight autoinjector platform variants.

These device variants differed across four design dimensions that are typically adjusted during customisation work between device manufacturers and pharmaceutical firms: the colour of the label (grey, yellow, orange), the colour of the needle shield (grey, orange, yellow), the overall size (1.0 mL and 2.25 mL prefilled syringe formats) and the device shape (round or square). Eight different autoinjector configurations were included. Each participant thus assessed the similarity of 28 device pairs.

Multidimensional scaling analysis then transformed these individual ratings in solution spaces to empirically derive the attributes driving how participants distinguish platform device variants. Fuelled by a powerful computational algorithm, this statistical technique allows determination of the underlying dimensions on the basis of individual similarity perceptions – without the need for participants to articulate the rationale for their rating.

Much like drawing a map using the distances between pairs of cities, the algorithm produced solution spaces where the distance between devices corresponds

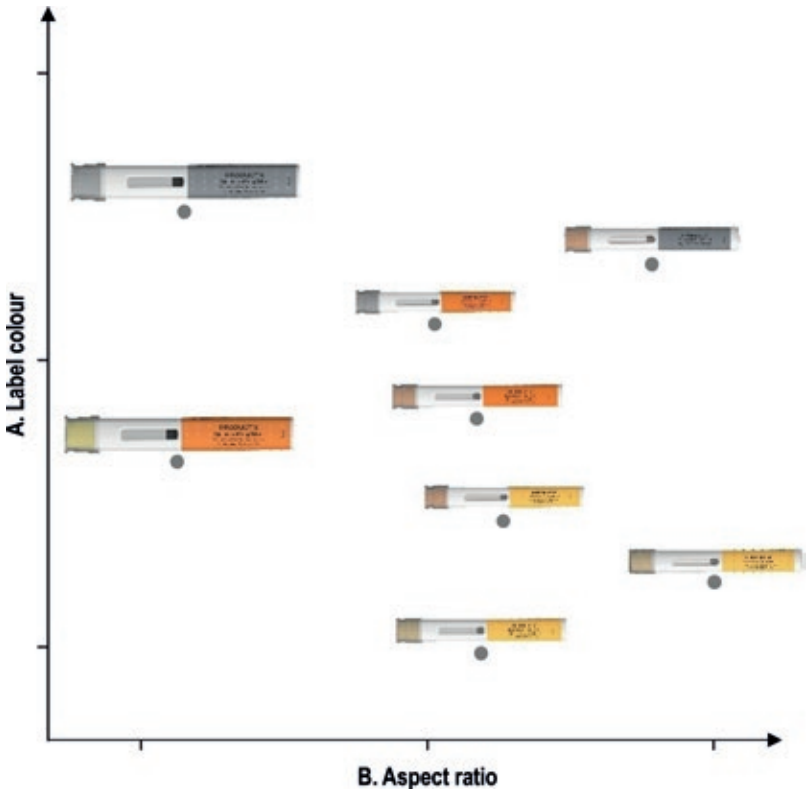


Figure 1: Typical solution space where the distance between autoinjectors reflects participants perceived device similarity. The two dimensions correspond to two design attributes – label colour and aspect ratio – empirically identified to drive device similarity (total sample, n=74).

to their perceived similarity: the closer the devices were positioned, the higher their perceived similarity. Figure 1 shows a typical solution space generated by the study. Using a systematic multi-step coding procedure, we then assigned a specific device attribute, or a combination thereof, to each of the emerging dimensions for each resultant solution space.

FIVE DEVICE ATTRIBUTES DRIVE AUTOINJECTOR DISTINGUISHABILITY

First and foremost, the results show that, regardless of their apparent similarity, users are still moderately-to-well able to distinguish between platform device variants. More than half of the similarity ratings (50.3%) were above four on the nine-point Likert scale. Moreover, the simulated use study empirically derived five attributes driving device distinguishability across user groups: the label colour, the size and shape of the device, its aspect ratio and chromaticity. Table 2 illustrates the empirically derived device attributes relevant for device distinguishability.

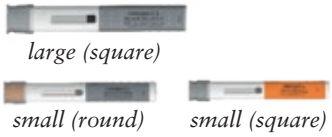
Device attribute	Description	Illustration	Does the attribute drive device distinguishability?					
			G1. Healthcare professionals	*G2. Non-professional caregivers*	*G3. Adolescent patients*	*G4. Adult patients*	*G5. Elder patients*	*G6. Visually impaired patients*
Label colour	Plain colouring of the label	 *grey* *yellow* *orange*	No	Yes	Yes	Yes	Yes	[weak]
Size	Small versus large size of the device	 *large (square)* *small (round)* *small (square)*	Yes	Yes	Yes	Yes	Yes	Yes
Shape	Square versus round shape of the device	 *round (small)* *square (large)*	[weak]	No	Yes	No	Yes	Yes
Aspect ratio	Compound device shape and size	 *small / round* *large / square*	Yes	Yes	Yes	Yes	No	No
Chromaticity	Compound label and needle shield colour (overall hue)	 *grey / grey* *yellow / yellow*	[weak]	Yes	No	Yes	No	[weak]

Table 2: Empirically derived device attributes driving platform device distinguishability.

Figure 2: YpsoMate Design leverages the autoinjector platform advantages while offering high industrial design flexibility on the basis of product-specific design shells.

Although label colour, size and shape were anticipated to drive users' similarity ratings, aspect ratio and chromaticity did not correspond to single design features but highlighted interaction effects between them. First, aspect ratio was the combination of the autoinjector size and shape. Second, chromaticity represented the overall device hue or brightness along the continuum, with the configurations "grey label and needle shield" and "yellow label and needle shield" as its two ends.

These findings hold important implications for device development. The participants did not necessarily distinguish user interface elements but used the overall device appearance, such as its chromaticity, as a basis for similarity ratings. Future device design development thus should integrate different units of analysis, considering potential interaction effects between distinct user interface elements.

The results also show that colouring of the needle shield did not emerge as a single device attribute driving device distinguishability. Although needle shield colour is typically modified as part of the routine customisation work, participants did not use this element in isolation to distinguish platform device variants.

Overall, the study suggests geometric features take precedence over tested colour schemes of a specific attribute driving distinguishability. Future device development programmes thus may not only differentiate through colouring a single user interface element, such as the needle shield, but also more holistically adjust colour schemes – including colouring of the label, housing and needle shield – or even pursue individual industrial design options. For instance, YpsoMate Design offers fully customised autoinjectors with specific individual outer shapes produced on the standard platform manufacturing line. From a device development perspective, YpsoMate Design offers the best of both worlds: leveraging the proven platform while enabling full differentiation with the help of unique design shells (Figure 2).

> "YpsoMate Design offers fully customised autoinjectors with specific individual outer shapes produced on the standard platform manufacturing line."

USER CHARACTERISTICS AND USE CONTEXT MATTER

The study provided insights into user group-specific patterns and how device similarity was perceived. Table 2 summarises which design attributes were found to drive similarity ratings per user group. Interestingly, some patterns were linked to user group characteristics (e.g. age, professional education, dexterity and visual impairments) and device usage context.

Elderly patients, for instance, did not use aspect ratio – an attribute linked with the user's sense of touch and perceived ease of holding the device – as the basis for recognising the device. Their emphasis on visual instead of tactile attributes may be linked to decreasing dexterity with age. Elderly patients may well be aware of, and thus compensate for, decreasing dexterity, thereby prioritising visual over tactile attributes. Similarly, visually impaired patients largely excluded device attributes related to colour (i.e. chromaticity) as the basis for device distinguishability.

The results also detail how educational backgrounds and situational factors influence how users distinguish autoinjector variants. Unlike non-professional caregivers, healthcare professionals primarily used geometric features to assess device similarity. Neither label colour nor chromaticity was relevant for healthcare professionals. These findings re-emphasise prior work where this user group raised concerns over limited time to become familiar with label colouring schemes to identify drug products correctly.

These challenges are particularly pronounced in the context of complex clinical trials where label colouring may be used to convey information about investigational drug type or dosage strength. Here, innovative auxiliary technologies may foster not only effective but also efficient device identification at the point of use.

For example, the reusable cloud-connected sensor module SmartPilot for YpsoMate (Figure 3, next page) automatically identifiesthe drug product using near-field communication (NFC) tags embedded in the autoinjector label. Using both visual and acoustic feedback, the connected system then notifies users about the correctness of the drug product at hand, thereby reducing the administrative burden at clinical trial sites and confirming allocation of the correct investigational drug to the correct treatment arms.

CONCLUSION

The study summarised here offers much-needed insights into how user groups distinguish potentially lookalike platform-derived autoinjectors. The results guide future device development toward device attributes that support device distinguishability – namely device size, shape, label colour, aspect ratio and chromaticity. The methodology provides the pharmaceutical industry with a novel toolbox which helps to avoid medication errors through effective device differentiation.

Revealing user group-specific patterns to device distinguishability, the study also suggests it is worth adjusting device differentiation to the intended user population, bearing in mind their characteristics (e.g. age, educational background, dexterity or vision

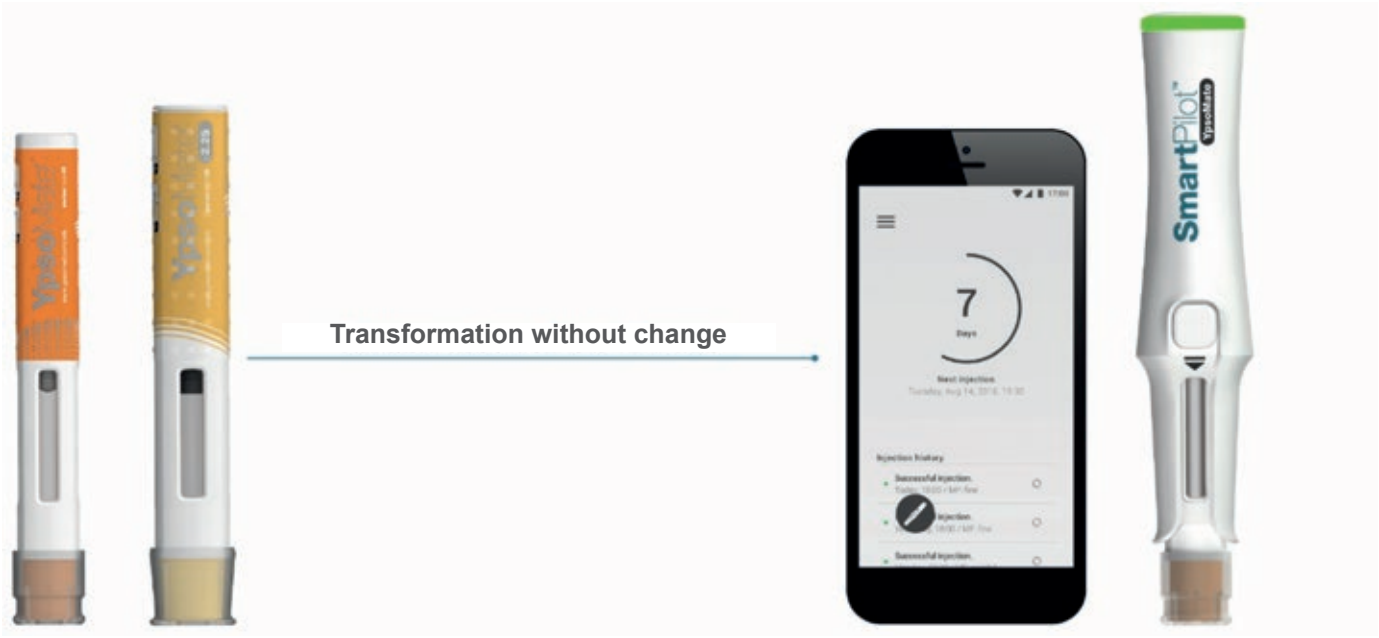


Figure 3: SmartPilot for YpsoMate is a reusable monitoring add-on to transform the marketed disposable two-step autoinjector into a cloud-connected system. It not only tracks injection events and provides real-time guidance to patients but also authenticates the drug product at the point of use.

impairments) and the context of device usage. In so doing, it provides the basis for more informed decision making to improve platform device distinguishability and mitigate inappropriate medication use.

The empirical study summarised here was funded by Ypsomed and conducted in collaboration with HFC Human-Factors-Consult (Berlin, Germany).

As a leading developer and manufacturer of mechanical and cloud-connected autoinjectors and pen systems for self-administration, Ypsomed has established the *Scientific Research & Communications* programme. Its objective is to advance new insights into self-injection devices relevant to industry and academia. The results regularly appear in peer-reviewed scientific forums such as *Expert Opinion on Drug Delivery* and *Medical Devices: Evidence and Research* and are presented at leading medical device and drug delivery conferences.

ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms comprise autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pen injectors, ready-to-use prefilled wearable patch injectors, and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio.

With more than 30 years of experience and pioneering spirit in the development and manufacturing of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested into the development of connected solutions and therapy-agnostic digital device management services.

Anticipating future needs of patients, pharmaceutical customers, payers, and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases, and integrating these insights with third-party digital ecosystems. Ypsomed leverages unique in-house capabilities in electronics, software and connectivity for the development of new devices and digital product systems.

Ypsomed is ISO 13485 certified and all processes comply with design control and cGMP guidelines with operational QA/QC experts on-site at each of its locations.

Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by both pharma customers and regulatory agencies to supply devices for global markets including the US, Europe, Japan, China and India.

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Andreas Schneider is Innovation & Business Development Manager with Ypsomed Delivery Systems. His responsibilities include the definition and development of new platform devices with a particular emphasis on connected and smart device systems. As such, he has been actively involved in the design and development of SmartPilot for YpsoMate, a reusable connected add-on that transforms the proven two-step autoinjector into a connected system. Dr Schneider has published various articles and held presentations in the areas of innovation management and drug delivery. He received his PhD in Innovation Management and Organisation Sciences from ETH Zurich, Switzerland.

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LEVERAGING THE PATIENT JOURNEY TO OPTIMISE DEVICE USE AT HOME

In this article, Séverine Duband, Global Category Manager, and Mark Tunkel, Director of Business Development, Insight Innovation Center, both at Nemera, discuss the importance of device optimisation to increase patient safety during self-administration of medication.

Self-administration at home is becoming increasingly common for parenteral drugs, leading to needlestick injuries becoming a growing patient safety concern.

> "More than three million needlestick injuries are reported every year globally."

The growing prevalence of chronic diseases, along with the evolution of patients' lifestyles, is driving new ways of administrating parenteral drugs. Novel treatments have become available, with the majority arising from biological molecules. Biologic drugs are predominantly administered via injectable devices, using prefilled syringes as a base.

In addition, pharmaceutical companies are striving to move injectable drugs from intravenous (IV) to subcutaneous (SC), hence avoiding hospital time for patients who largely prefer self-administration at home, instead of long and cumbersome hospitalisation. Home administration brings many benefits – lowering the cost of treatment for all stakeholders and increasing adherence to treatment regimens.

However, more than three million needlestick injuries are reported every year globally, according to the WHO – resulting in serious health, psychological and cost challenges. To boost protection for both healthcare professionals and patients, global regulations are progressively enforcing the use of safety systems for injectable drugs:

- In 2000, the US FDA issued the Needlestick Safety and Prevention Act – and the US was the first country to adopt and actively enforce legislation requiring healthcare facilities to use safety syringes
- In the EU, the new Medical Device Regulation 2017/745 (MDR) becomes mandatory this year, clearly stating as a key principle that protection of users and patients when injecting a medication with a syringe-based device is a must.

Self-administration at home therefore translates into a need for safer, easy-to-use and ergonomic devices. Having patients (or caregivers who are not healthcare professionals) injecting a drug means increased risks of use errors and needlestick injuries. Protecting users from sharps injuries, whilst optimising the injection experience, has become a must.

UNDERSTANDING THE PATIENT JOURNEY TO PROVIDE BETTER OUTCOMES

At the earliest stages of establishing the requirements and user needs for a delivery platform, Nemera works with customers to fully understand the patient journey by using a technique called applied ethnography (Figure 1). This method relies on a combination of interviews and in-context observations of practices, processes and experiences within the patient's home or natural environment.

At this stage, potential use cases are looked at broadly – from when a patient receives their device, through the entire process of preparing, administering and

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Figure 1: Applied ethnography can help designers learn about the context of use in self-administration through observations and interviews to get a broad understanding of the patient journey.

disposing of that particular device. This gives the most natural view of the patient experience in use and in context. It is equally important to gain an understanding of the experience of healthcare professionals, as well as conducting applied ethnography in relevant settings in acute care or clinical environments in cases where patients may be treated in a clinic and also self-injecting at home. This is critical in helping with device selection and training for a specific patient population.

Understanding both the patient and healthcare provider experience enables development of these patient journey and clinical environment process maps (Figures 2 & 3), which demonstrate the complete process patients go through in managing their disease – both from an administration standpoint and from a longitudinal perspective – as they progress with their condition and treatment.

This can be of critical importance in applications where care is being migrated from a clinical environment such as an oncology ward – with built-in support systems – to an environment of self-administration where clinical personnel are not present and the burden of support falls to a family member or caregiver. These cases are often driven by a migration in drug-delivery modality such as from IV to self-administered SC that need to be considered in a programme. The ability to gain a significant understanding of the

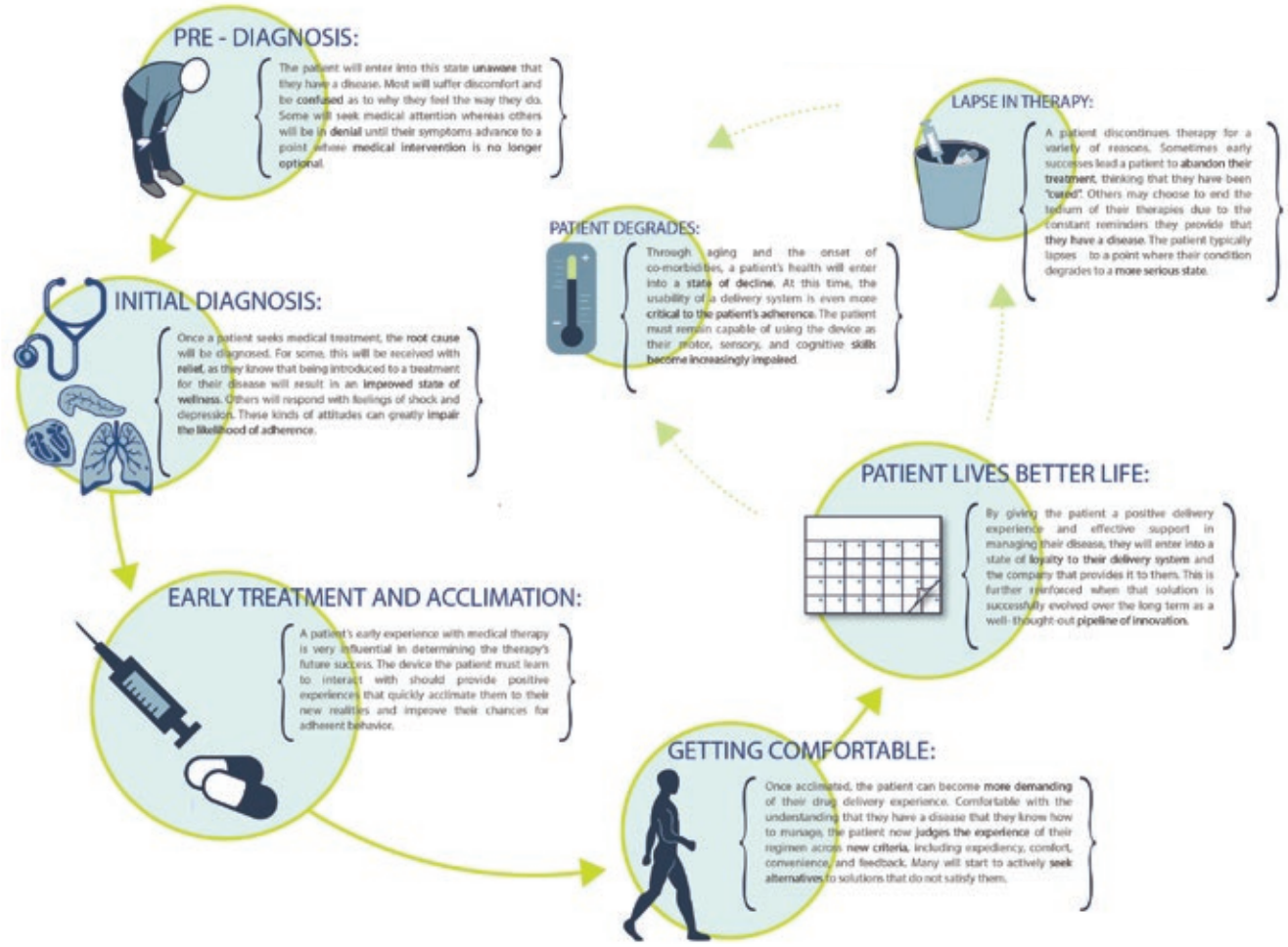

Figure 2: The output from applied ethnography is a patient or clinical journey map that allows the development team to identify opportunities for improving the user experience or mitigating risk.

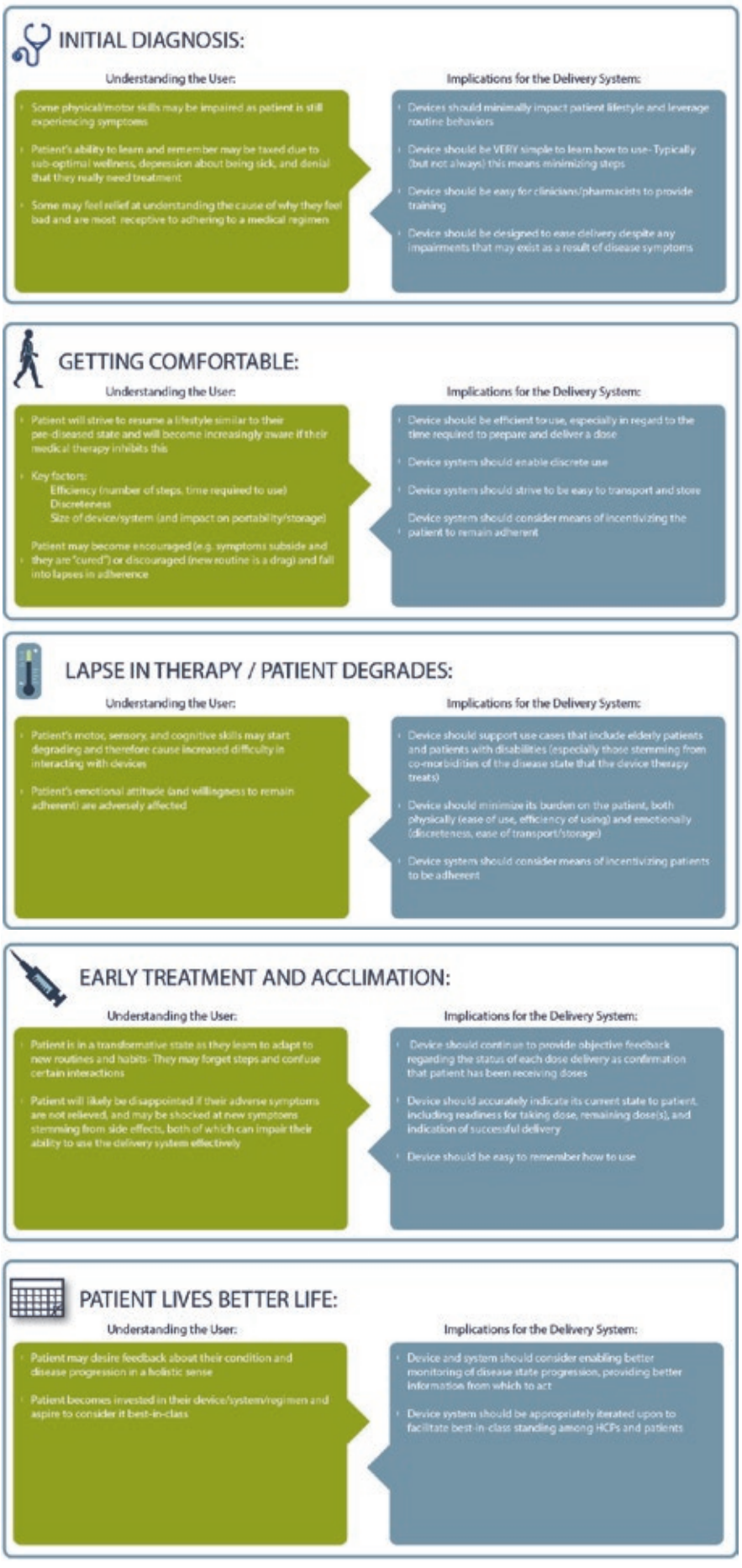

Figure 3: An intimate understanding of the patient journey can be leveraged to identify opportunities for innovation across all stages of the patient experience.

environment, social/emotional contexts and all the other factors that influence a patient's use of a self-injection device can be incredibly powerful in addressing these challenges.

Thoroughly understanding and mapping the patient journey and inter-relationship with healthcare provider processes can then be leveraged as an early-definition road map to help:

- Determine where customisation of a device may be warranted to address user needs further with certain patient populations
- Identify experiential gaps at an early stage, which can then be addressed through the development of instructions for use (IFU), novel training methods such as resettable trainers, value-added packaging or other methods to support clinical work as well as drive commercial differentiation
- Uncover patient engagement and adherence opportunities that can be supported with connectivity and other methods to support value-based care, which is increasingly a focus of payers and providers in the US in particular
- Identify potential areas of user-based risk that may be present in clinical trials and in market so they can be mitigated as early as possible in development.

A NEW GENERATION OF PASSIVE ADD-ON SAFETY DEVICES

Regulation and recommendations are evolving to improve patient and health worker safety. In this context, Nemera's Safe'n'Sound product range matches the need for safe and easy-to-use self-deliveries – this passive safety device for prefilled syringes provides increased safety for patients and healthcare professionals.

Biologics have become a significant driver for new treatments, with more than 2,700 remedies in development as of mid-2017 – three times higher than in 2013.[1] These new biologic drugs, such as monoclonal antibodies, are good candidates for the treatment of the aforementioned chronic diseases.

Biologic drugs are very often needed in high concentration. This can be driven by the nature of the molecule, composition of the final drug and the effort to decrease the frequency of treatment for the patient. Their viscosity sees a power law increase as the antibody concentration rises. Thus,

to be injected, these molecules need to be diluted, which leads to higher injection volumes and lower (but still high) viscosity. As a result, larger-dose drug deliveries are a growing segment, with volume shifting towards 2 mL.

The Safe'n'Sound needle safety device platform is now available to accommodate 2.25 mL fill volume prefilled syringes. This new 2.25 mL size (Figure 4) is specifically relevant to administer complex, high-value drugs such as monoclonal antibodies or other biological therapies. It offers a reliable and intuitive design for user safety, and is compatible with any type of ISO standard 2.25 mL prefilled glass syringe, including various flange types.

The platform is suitable for low fill volumes and high-viscosity formulations. It is robust against shocks and vibrations, and can run with manual and fully automated assembly lines. Safe'n'Sound is a passive, one-handed safety device and is intended to be used by non-experienced users for self-administration as well as healthcare professionals.

With its ergonomic benefits, it helps patients throughout the injection without compromising on safety or robustness. Activation of needle shielding is easy and intuitive, it has a large thumb pad and extended finger flanges to optimise the injection experience, and the clear, visible tip enables easy drug inspection.

The Safe'n'Sound product range has been fully validated through user studies and is commercially available. In addition, in order to answer patients' needs in self-administration settings, Nemera offers a fully customisable platform. For example, for patients with conditions resulting in disabilities or dexterity issues, Nemera can offer "soft touch" material to improve gripping, as well as an overcap to ease rigid needle shield removal. Colour customisation for a safer drug or dose identification is also available.

Figure 4: Nemera's Safe'n'Sound add-on safety device is now available for 2.25 mL prefilled syringes with many customisation options.

DEVELOPMENT OF SAFE, EFFECTIVE AND DIFFERENTIATED COMBINATION PRODUCTS

Using this foundation, Nemera works with customers to provide technical support, human factors and patient experience activities (Figure 5) necessary for a successful drug-device combination product development process. Customers often assume that all the human factors, risk management and characterisation of performance activities relative to their specific drug and patient attributes have already been completed as part of the platform device development.

However, this is not the case as, ultimately, pharma companies are responsible for their own drug-device combination and the platform device at that stage is really only half the picture. It's incumbent on the pharma company to ensure their selected device, in combination with their drug, is appropriate, safe and effective for the target population. This also extends to

Figure 5: To support human factors submissions, evaluate the impact of innovative packaging, instructions for use, etc and differentiate with a platform device, it is necessary to work with patients.

"It is very important to understand patients' needs and to provide them with better solutions to administer their treatment."

executing the earlier stage road map to optimise the patient experience to create competitive differentiation and to ensure adherence and engagement with patients and clinical stakeholders. This may be of particular interest to customers in the biosimilars or generics markets, where many competitors are targeting the same reference drug or devices, and differentiation wherever possible is critical.

Through capabilities in design research, human factors engineering, user experience design, engineering, lab services and regulatory support, Nemera is positioned to offer all the support customers require through an integrated device platform and service programme that includes:

- Lab and analytical services to support characterisation and compatibility of drug products, syringe candidates and devices such as Safe'n'Sound to optimise their integration
- Leveraging the Insight Innovation Center's consulting expertise to help define user groups/populations and early use-related risk analysis activities to define the human factors and usability programme necessary for the client's regulatory/filing strategy and identified clinical risks
- Developing instructions for use, value-added packaging, connectivity add-ons to support patient engagement/adherence, and integration of resettable training devices into the patient services model to create commercial differentiation
- Conducting formative and summative usability testing globally for all aspects of the device and supporting assets in alignment with the human factors programme definition through human factors engineering report documentation for use in regulatory submissions
- Programme management excellence to ensure all elements of the programme are integrated to drive efficiency and proactively mitigate any programme risks.

This capability, combined with Nemera's device platforms and manufacturing expertise, helps customers achieve the outcome of a successful regulatory submission and commercial launch of safe, effective and differentiated combination products while mitigating the risks associated with multiple partners who may not have expertise and experience in all the aspects critical for success.

CONCLUSION

Thanks to the increased early-stage development capabilities offered by the recent integration of newly acquired capabilities with the Insight Innovation Center, the Nemera teams in Europe and the US can now be a single partner for device platforms and integrated services – from front-end innovation, design research, human factors and design engineering to strong l ate-stage development, as well as clinical and commercial manufacturing capabilities.

These enhanced capabilities help in gaining a full understanding of the patient journey that can be leveraged to support user-experience-driven optimisations of the injection experience, to create competitive differentiation and increased patient engagement. This also extends to satisfying human factors engineering requirements for a specific drug/device combination product using Safe'n'Sound, as well as other device platforms offered by Nemera. This service offering eliminates the need for customers to use multiple resources and can result in a more efficient process and speed to regulatory filing and commercial supply.

Especially in the parenteral industry – where the evolution of patients' lifestyles has been changing the way of administrating drugs – it is very important to understand patients' needs and to provide them with better solutions to administer their treatment. That's why Nemera has developed Safe'n'Sound, which is fully customisable and available in 1 mL and 2.25 mL sizes. Its robust and ergonomic design helps prevent needlestick injuries, providing user-friendly protection for healthcare professionals or inexperienced users. This design optimisation is also key for pharma companies as it has an impact on treatment efficiency and drug overfilling.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacturing of drug delivery devices for the pharma, biotechnology and generics industries. It offers a portfolio of products and services across ophthalmology, nasal, inhalation, dermal, transdermal and parenteral delivery. Nemera's vision is to be the most patient-centric drug delivery device company. Its newly branded Insight Innovation Center, with offices in the US and Europe, provides consultative services to support clients' overall device strategy. Providing user research, human factors, user experience design and design for manufacturing expertise, the Insight Innovation Center helps clients navigate device strategy for both novel and platform solutions.

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ABOUT THE AUTHORS

Séverine Duband is Category Manager at Nemera in charge of the parenteral range of proprietary products including Safe'n'Sound, the passive safety device platform for prefilled syringes. Ms Duband joined Nemera in 2018. She has 10 years' marketing experience in fast-moving consumer goods, with key competencies including strategic planning, new product development launches, project management, brand communication and team leadership in an international environment. Ms Duband has an MSc in Business Marketing from Emlyon Business School (Lyon, France).

Mark Tunkel is Director of Business Development for Nemera's Insight Innovation Center. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharma industry, Mr Tunkel has advised many of the world's leading companies on their product development and innovation strategies, with an emphasis on driving realisation and the most favourable business outcomes.

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ENHANCING THE PATIENT EXPERIENCE FOR SELF-INJECTION SYSTEMS

The complexity of injectable treatment regimens for chronic disease sufferers means onboarding aids can be integral to the disease management process. In this article, Joe Reynolds, Research Manager at Noble, an Aptar Pharma company, discusses the role of demonstration devices in improving the patient experience and adherence.

Diagnoses of chronic illnesses such as rheumatoid arthritis (RA), Crohn's disease and osteoporosis are expected to skyrocket in the coming decade, resulting in growing use of patient-centric drug delivery devices – including autoinjectors, prefilled syringes with safety features, and on-body and respiratory devices.

Because of the complexity of injectable treatment regimens, onboarding aids – such as reusable demonstration devices – can be integral to the disease management process, from improving compliance to enhancing the patient experience and easing their emotional responses to disease-related changes in their lives. Yet, nearly half (49%) of patients do not receive in-office training when prescribed self-injection medication.[1]

When patients are properly trained and given the tools for success at the time of their therapy prescription, they can become more adherent – receiving the full benefit of their therapy, leading to longer, healthier lives. What is striking is the lack of training that healthcare professionals (HCPs) provide. Studies reveal that, after prescription, 84% of patients incorrectly use their autoinjector at home.[2]

> "Retention and recall worsen over time without practice and repetition."

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

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"As biologics become more advanced and require less-frequent dosing, the longer down-time between injections may allow for non-adherent patient behaviours to arise."

Another phenomenon working against patient adherence is the forgetting curve theory that suggests retention and recall worsen over time without practice and repetition. This theory postulates that 50% of the information HCPs give to their patients when prescribing a self-injection is forgotten within one hour, 80% is forgotten in two days and 90% is forgotten in a week (Figure 1).[3]

As biologics become more advanced and require less-frequent dosing, the longer down-time between injections may allow for non-adherent patient behaviours to arise. This is especially troublesome for patients who are tasked with self-injecting without the support of an HCP — or even a demonstration device — week after week throughout their therapy.

Demonstration devices closely replicate actual prefilled syringes and autoinjectors but without the needle or medicament. This allows patients to learn how to use a specific device and potentially improve familiarity, increase confidence and build adherent behaviours with the true drug delivery device and medication. This intermediate step in the self-injection journey may not only increase health outcomes for the patient but also can reap benefits for HCPs, pharma companies and payers in the form of decreasing healthcare costs.

With so much to gain, both therapeutically and financially, when patients are properly trained on the use of self-injectors, it is incumbent on the healthcare community to determine how best to ensure this adherence.

DEMONSTRATION DEVICES IN CLINICAL TRIALS

Successfully developing and launching combination products is an intricate process. As compounds mature through early-stage clinical trials, profiles and formulations are analysed to determine the optimal route of administration and presentation for product candidates. When it comes to biopharmaceuticals, this commonly includes selection of the drug delivery systems that will be used to distribute and administer the medications.

Manufacturers often conduct market research and human factors studies when designing and developing delivery systems to select a device that satisfies the needs of patients, HCPs and other stakeholders.

"Testing drug delivery devices with the end users in the early stages can help facilitate greater success downstream."

During this process, outputs from these workstreams provide valuable insight into patient needs – from prescription and onboarding through the entirety of their use of the therapy. The insights gathered and examined during this process should be leveraged to help define and prioritise requirements for demonstrators and other educational resources for patients as they embark on their new therapy.

When this process occurs in the early stages of clinical trials, there is opportunity for pharma companies to use demonstration devices during human factors studies to determine the best route of administration to aid patient comfort and, more importantly, long-term adherence. Testing drug delivery devices with end users in the early stages can help facilitate greater success downstream.

Demonstration devices may be used in human factors studies during early-phase clinical trials to create best-in-class user experiences by:

- Better understanding the needs and expectations of patients and HCPs to create robust and impactful training and onboarding solutions that support patients from prescription of their new self-injectable through their at-home treatment and beyond.
- Educating users and helping promote the efficient progression of programmes and collection of quality data.

For demonstration devices to be used effectively during these early-phase clinical trials, best practices should be established to ensure their use brings the most value to the study and to patients, HCPs,

pharma companies and payers long term. As such, it is important to create a framework that dictates the use of demonstration devices in these, to:

- Train sponsor personnel and site investigators on the use of devices to ensure they are correctly administering agents and training patients, where applicable. Ensure sponsor personnel understand the difference between various self-administration devices and the benefits and potential drawbacks of each
- Qualify study participants by allowing them to experience how various devices operate and ensuring they can self-inject as directed. It is important to ensure subjects begin on an even playing field in terms of their knowledge of device usage
- Allow trial subjects to build their confidence in self-administration and to gain hands-on experience in using a drug delivery device
- Provide ongoing training to subjects and study personnel in order to mitigate learning erosion – as per the forgetting curve theory – and improve the recall and application of skills, particularly for at-home dosing
- Use resettable demonstrators rather than real drug delivery devices during the clinical and device development process to minimise waste
- Improve user safety by reinforcing proper injection behaviours through resettable devices.

A great deal of useful information can be gleaned if these recommendations are followed, including patient and/or HCP preference for one drug delivery device over another, patient knowledge gained from using a training device, understanding how hands-on experiences using a demonstration device can successfully change the way patients self-inject, and how well training can help mitigate learning erosion. These insights can enlighten the pharma industry in near limitless applications (Figure 2).

Figure 2: Patient using the Noble demonstrator of the BD UltraSafe to practise a self-injection.

NOBLE AND BD COLLABORATE ON BD ULTRASAFE™

Although BD has not yet used demonstrators in clinical trials, one example that supports this use is Noble and BD's partnership for the BD UltraSafe™ needle-guard product family. Noble and BD established a collaborative development framework in an effort to:

1. Help pharma companies increase touchpoints through access to and use of demonstrators in a variety of settings by patients, caregivers, HCPs, pharmacies and product-specific channels
2. Support patient adherence and confidence with self-injection therapies across the board.

The two companies understood the importance of providing demonstration devices to pharma companies as a method to enhance patient education programmes for the rising number of at-home self-injectable therapies. They also understood that, with this rise, comes a growing number of patients who are expected to administer their therapies without the support of an HCP – which has the potential to lead to decreased patient adherence.

Noble and BD's collaboration for the BD UltraSafe includes a customisable demonstrator platform for manufacturers developing and launching drug delivery systems. BD UltraSafe is increasingly used to deliver self-injections across a breadth of therapies for diagnoses ranging from RA, osteoporosis and psoriasis to asthma and migraines, among others.

> "Demonstration devices are vital components of the patient self-injection experience."

ABOUT THE DEMONSTRATOR

The Noble demonstrator of the BD UltraSafe system is designed for repeated patient use. It is true in form and function to the actual BD UltraSafe system – producing a realistic injection experience – and comes with various needle options.

To facilitate at-home patient engagement with the product, the demonstration device comes with its own instructions for use that teach patients not only the proper injection steps but also how to reset the device for repeated use. Additional videos and how-to material can also be included to bolster patient engagement with the product further and thus support therapy adherence and confident self-injection.

The Noble demonstrator platform for the BD UltraSafe system can be slightly modified for brand specifications and other nuances, as required, but otherwise facilitates provision of demonstrators that are ready for market. The benefits of Noble's platform devices for pharma companies interested in deploying a demonstration device with their BD UltraSafe passive needle guard include:

- Speed to market: demonstration devices are off-the-shelf ready for market
- Accurate simulation: BD device design specifications form an integral part of the demonstration device creation
- Proprietary design: patented technologies provide repeatable and reliable training experiences
- Quality: demonstration devices are tested against Noble's stringent quality standard
- Low cost of entry: there is no tooling expense.

Figure 3: The Noble demonstrator of the BD UltraSafe product line.

These products are tested and validated through tooling and process validation, design verification testing, including lifecycle testing, and product functionality testing.

When compared with non-platform demonstration devices, the Noble demonstrators of the BD UltraSafe system differentiate themselves by being market ready, making it even more important for pharma companies to know which type of delivery device will be used for their drug very early in the development process. Once that is understood, a demonstration device can be deployed to market concurrently with the drug and its delivery system, supporting the launch and solidifying the demonstration device – in the eyes of patients – as an imperative tool for treatment success (Figure 3).

CONCLUSION

Demonstration devices are vital components of the patient self-injection experience. But determining the correct device requires specialised planning, co-ordination and expertise. When properly implemented, along with other patient support services, demonstrators and injection training can help improve patient adherence.

When patients stay on their therapies longer and more consistently, it is a win-win for all involved, including HCPs, pharma companies and payers. Achieving these benefits requires deliberate planning early in the product lifecycle, starting as early as the clinical trials. Doing so increases the contributions of demonstration devices throughout the product lifecycle, from use in clinical trials through to the patient use feedback loop.

To read more about BD and Noble's collaboration on the BD UltraSafe™ passive needle guard product family and the importance of utilising demonstration devices in clinical trials, please visit: bit.ly/EnhancingPatientExperience.

BD and BD UltraSafe are property of Becton, Dickinson and Company.

Noble's demonstrators are multi-use. BD UltraSafe™ devices are single-use medical devices.

ABOUT THE COMPANY

Noble is an Aptar Pharma company focused on fostering healthy patient outcomes for those who self-administer drug therapies, through the development of robust training devices and onboarding solutions for the world's top pharma brands and biotech companies. Noble manufactures and commercialises training devices that mimic the exact feel, force and function of drug delivery devices such as autoinjectors, prefilled syringes, and on-body and respiratory devices in order to increase patient adherence and confidence and decrease usage errors.

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Joe Reynolds is Research Manager at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximise value for stakeholders. Mr Reynolds earned his Bachelor of Science in Business Administration from the University of Central Florida, a Master of Science in Marketing from the University of South Florida, and a Master of Science in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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ADDRESSING THE EVOLVING NEEDS OF VARIABLE DRUG DELIVERY REGIMENS

In this article, Temitope Sodunke, PhD, Strategic Innovation Leader, BD Medical – Pharmaceutical Systems, introduces the BD Evolve™ On-body Injector and describes how the device is designed specifically to address the rapidly evolving needs of the pharma industry and meet patient requirements.

The pharmaceutical industry is rapidly evolving and experiencing a diverse set of competing challenges. These challenges include a changing healthcare landscape and transition of care out of the traditional clinical settings to alternative sites, including patients' homes.[1] Several biologic blockbusters have expiring patents,[2] increasing pressure on pharmaceutical companies to maximise revenue and stay ahead of competition. There is also an emergence of biosimilars fuelling the need for effective drug product differentiation. Lastly, patient demands and expectations are changing as they seek a greater role in their own care.[3]

"With the introduction of the BD Evolve™ On-body Injector, we now give pharma companies a wearable solution that is designed to enable new delivery formats in alternate settings."

To address these challenges, innovative pharmaceutical companies continue to advance their clinical development pipelines to develop new and more sophisticated biologics. Other companies are revisiting their lifecycle management strategies and general market entry approaches to compete more successfully (identifying new use cases, alternative delivery formats, and promoting value-added services that boost patient engagement). Some companies are riding new technology trends towards a more cost-effective and patient-centric healthcare delivery model.[4]

Figure 1: The BD Evolve™ On-body Injector with Bluetooth connectivity for remote and secure one-way communication.

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Pharma Strategy	Key Supporting Strategy	BD Evolve™ Features
Deliver novel biologic	**Innovate new products** with delivery characteristics that improve patient experience and acceptance	**Customisable to support different treatment** regimens (pulsatile, continuous, episodic, or single bolus delivery)
	Leverage key clinical data to benchmark versus standard regimens	**Programmable** for delayed or timed administration up to 3 days
Maximise value via lifecycle management	**Maximise clinical differentiation** against intensifying competition	**Designed to enable new delivery formats** in alternate settings and to support treatment conversions (IV to SC, IM to SC, bolus to basal)
	Improve line of sight to patient compliance with unobtrusive measurement and monitoring	**Equipped with connected capabilities** – Bluetooth for remote and secure one-way communication with additional options to enhance injection data capture.
Differentiate a biosimilar	**Differentiate biosimilar** combination products	**Designed for effective SC delivery** of up to 3 mL of medications
	Provide access to viable treatment regimens	**Flexible to support adjustments** to existing formulations and variations in treatment regimens
Optimise the standard of care	**Augment value proposition** of an asset around convenience and clinical efficacy	**Convenient for at-home medication delivery** which may improve adherence
	Reduce healthcare costs while improving the patient experience	**Adaptable to enable reduced cost** of patient care (reduced hospital visits and transportation)
	Give providers an option that may improve outcomes and patient experience	**Flexible to support adjustments** to existing formulations and variations in treatment regimens

Table 1: Benefits associated with the BD Evolve™ On-body Injector.

To be successful with the above strategies, pharmaceutical companies will need to rely on drug delivery systems that:

1. Address the complexity and variability around novel drug delivery characteristics
2. Enable drug product differentiation through solutions centered on the patient experience
3. Are designed to optimise the standard of care.

At BD, we understand these challenges and are developing solutions that will enable the delivery and successful commercialisation of complex biologics. With the introduction of the BD Evolve™ On-body Injector (Figure 1), we now give pharmaceutical companies a wearable solution that is designed to enable new delivery formats in alternate settings and is designed for customisation to support adjustments to existing formulations and variations in treatment regimens. Table 1 aligns key pharma strategies with supporting strategies BD can provide its pharma partner, together with specific beneficial features of the BD Evolve™ On-body Injector relevant to each strategy.

1. Addressing the Complexity & Variability Around Drug Delivery Characteristics

The number of biological drugs continues to increase rapidly (>900 biologics currently in development)[5] as pharma companies seek novel formulation strategies as a way to treat challenging conditions more effectively and to retain their market position in the face of competition. Therapeutic formulations are progressing through development and becoming more complex as research continues to yield new types of drug products. Biologic attributes can range in dimension for volume, viscosity, dosing frequency and type of administration. In addition, some medications now require a more tailored delivery approach depending on the therapeutic area and unique requirements of individual patient populations.[6] The drug may need to be delivered in a single bolus format, turned on, off, or even modulated over time to enable more complex delivery profiles – continuous, episodic, timed, delayed, or delivery over multiple time frames.

For innovative pharmaceutical companies looking to commercialise a challenging biologic successfully, an advanced drug delivery device that is customisable and programmable to support different treatment regimens (across a range of delivery volumes for extended wear durations) can be beneficial. The BD Evolve™ On-body Injector is designed to be customisable to support different drug and delivery attributes and is designed to be programmable for delayed or timed administration of medications.

2. Enabling Differentiation Through Solutions Centred on the Patient Experience

A shared goal of both pharmaceutical companies and healthcare providers is to improve patient experience and outcomes. Today's patients are at the centre of the healthcare ecosystem, inspiring new research and delivery approaches, while becoming savvy consumers of health information. With the shift of care from hospitals to the home, patients are required to take a more active role in their care and demand more user-friendly, more convenient interventions. To address this trend, pharmaceutical companies are shifting formulations typically meant for intravenous (IV) delivery or intramuscular (IM) delivery to subcutaneous (SC) delivery formats.[7]

SC delivery offers patients greater convenience, flexibility for at home treatment, and greater control over their own treatment administration versus IV delivery. In addition, clinical researchers are looking at alternatives to intermittent bolus injections as a way to improve patient tolerability and elicit a more physiologically relevant response. For example, a recent NIH study in children with severe congenital hypoparathyroidism showed clinical advantage with medication delivered using a slow basal rate versus twice-daily injections.[8]

"BD Evolve™ enables effective SC administration of up to 3 mL of medication."

Pharmaceutical companies seeking to differentiate their combination drug product can benefit from a device that enables effective SC administration of medications across a range of delivery volumes for extended wear in alternate sites. Such an advanced delivery device could also support value-added adjustments to existing formulations and improve the overall patient experience. The BD Evolve™ On-Body Injector is designed to enable new delivery formats in alternate settings and support various treatment conversions, such as IV to SC, IM to SC, and bolus to basal. BD Evolve™ also enables differentiation with smart capabilities to support remote and secure one-way communication of dosing information via Bluetooth.

3. Providing Solutions that Optimise the Standard of Care:

Healthcare systems are seeking solutions that enable providers to flex how treatment is delivered to the patient.[9] With the shift to home-based care, providers are changing their perspectives to consider patients as partners in their care, whereby a patient is empowered to self-administer their medication and more empowered as part of the overall treatment decision making process. For many patients, the care journey can be cumbersome. From frequent hospital or care centre visits to managing multiple medications, patients are often loaded with all the extra steps involved in taking care of their health.

As an example, patients undergoing fertility treatments are often burdened with more than just the physiological and emotional stress of their treatment.[10] These patients have to manage the organisational and logistical aspects of continuing their treatment including the need to make multiple trips to the clinic, sometimes over the weekend and in distant clinic locations.

> "BD Evolve™ is filled at the time of use, designed to provide flexibility to support adjustments to existing formulations and variations in treatment regimen and can be worn for up to three days."

> "Providers are changing their perspectives to consider patients as partners in their care, whereby a patient is empowered to self-administer their medication and more empowered as part of the overall treatment decision making process."

An advanced delivery device that can be pre-programmed to deliver the hormone treatment within the specified delivery window in the comfort of the patient's home could mean that the patient no longer needs to go into the clinic over the weekend. These patients can be empowered to self-administer their medication at home and providers can have the assurance that the right amount of medication will be delivered within the required therapeutic window.

Aside from patient convenience, these benefits can potentially lower the overall cost of patient care – reducing follow-up visits to the physician, clinics no longer have to open at the weekend or after hours to accommodate the specific timing of injection – thus reducing the total overhead costs for the providers. Patients can also save on the cost of transportation (to and from the clinic) and minimise lost wages, in cases where work is missed and wages are unpaid.

BD Evolve™ is filled at the time of use, designed to provide flexibility to support adjustments to existing formulations and variations in treatment regimen and can be worn for up to three days; allowing for convenient at-home medication delivery which may improve adherence as well as reduce the cost of care.

BEYOND TRADITIONAL DELIVERY BOUNDARIES

As an industry leader in parenteral delivery devices that help treat chronic disease, BD continually explores new ways to advance the standard of care for various conditions and healthcare challenges. An area of focus has been the delivery and successful commercialisation of complex biologics, a priority underserved by current delivery formats.

Our solution is designed to incorporate preferential attributes for our pharmaceutical partners, providers, and patients with the goal to improve the patient experience and lower the overall cost of care. With the introduction of BD Evolve™ On-body Injector, we now give pharmaceutical customers an innovative solution for customisable and programmable SC administration of biologics. It is a system that is flexible, allowing for continuous, episodic, or delayed delivery across a range of volumes for extended wear and durations in alternate sites.

The BD Evolve™ On-body Injector goes beyond traditional delivery boundaries to address the changing needs of combination drug products:

- BD Evolve™ is designed to enable the delivery of novel biologics, support different drug and delivery attributes, and is programmable for delayed or timed administration of medications
- BD Evolve™ is designed to enable differentiation with connected capabilities to support remote and secure one-way communication of dosing information via Bluetooth
- BD Evolve™ enables effective SC administration of up to 3 mL of medication and provides greater flexibility for adjustments to existing formulations and variations in treatment regimens with up to three-day wear allowing for convenient at-home medication delivery which may improve adherence, reduce the cost of delivery, and optimise the standard of care.

In summary, the BD On-Body Injector System is a new solution that pushes traditional boundaries of drug delivery formats to serve the delivery demands of combination drug products.

BD Evolve™ On-body Injector is a product in development; some statements are forward-looking and subject to a variety of risks and uncertainties.

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Temitope Sodunke is Strategic Innovation Leader for BD Medical – Pharmaceutical Systems, responsible for identifying and assessing new areas of opportunities (product, solution, and services) around delivery systems for injectable drug therapies. She has over 15 years of experience across multiple industries (pharma, defence, finance, and medtech). Her areas of expertise include innovation, strategy, and new product development. Dr Sodunke received her BSE in Biomedical Engineering from the University of Rochester (NY, US) and completed her graduate studies (MSE in Chemical Engineering and PhD in Mechanical Engineering) at the University of Pennsylvania (PA, US) and Drexel University (PA, US). She then completed a post-doctoral fellowship in Radiation Oncology at Harvard/MGH (MA, US).

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LARGE-VOLUME INJECTORS: RISE IN BIOLOGICS BRINGS CHALLENGES

Developing devices capable of delivering highly viscous biologic drug formulations at high volumes does not come without its challenges. In this article, Paolo Fiorini, PhD, Senior Design Engineer; Gerard Linnane, Engineering Services Director, Michael Kiely, Senior Device Development Engineer; Maciej Grygorczuk, Design Control Specialist; and Joshua Coyne, Product Development Engineer; all at Jabil Healthcare, discuss these challenges and the merits of various drive solutions.

It is anticipated that the market size for large-volume injectors (LVIs) will be US$8.1 billion (£6.2 billion) by 2025.[1] This demand is largely being driven by growth in the biologics sector – one-third of annual drug approvals are now in biologics.[2] Typically, these drugs are highly viscous and require large-volume injections to achieve the required therapeutic dose.

Capability for the patient to deliver these drugs at home using an autoinjector would bring many advantages. There is a huge psychological benefit to the patient in administering their medication at home, in an environment that is comfortable and familiar to them, leading to improved patient outcomes. This also lessens the burden on the health system through reduced hospital visits and outpatient procedures.[3]

WHY SO CHALLENGING?

One of the primary challenges in developing LVIs is the large injection forces required. Some of the main factors that impact the injection force are:

- Drug viscosity
- Drug volume
- Injection time
- Syringe barrel internal diameter
- Needle internal diameter
- Needle length
- Friction forces (including stiction).

These relate to the required injection force (F_{inj}), as modelled by the Hagen-Poisseuile equation, for non-Newtonian fluids (Figure 1).

$$F_{inj} = \frac{128\,Q\,L\,\mu\,A}{\pi\,D^4}$$

Figure 1: The Hagen-Poisseuile equation for non-Newtonian fluids.

> "One of the primary challenges in developing LVIs is the large injection forces required."

For example, moving from a low viscosity 1 mL injection to a high-viscosity 5 mL injection will first require an increase in the flow rate (Q) to maintain a similar injection time. The viscosity value (μ) will increase with increased viscosity formulations. Furthermore, barrel diameter (A) can be increased to maintain the overall length of the device. The needle characteristics of length (L) and inner diameter (D) will typically stay the same so as not to adversely impact patient comfort. All these changes will contribute to a significantly higher injection force (Figure 2).

NON-NEWTONIAN FLUIDS

Another factor to consider when assessing the interaction between the drug and the device are shear rates. Many biologics behave in a non-Newtonian manner and do not adhere to the standard Hagen-Poisseuile model. Commonly, they exhibit shear-thinning properties such that their viscosity during injection reduces for increased flow rates – corresponding to a lower injection force than predicted in the standard model.

> "The four most common solutions are spring drives, gas drives, electromechanical drives and chemical drives."

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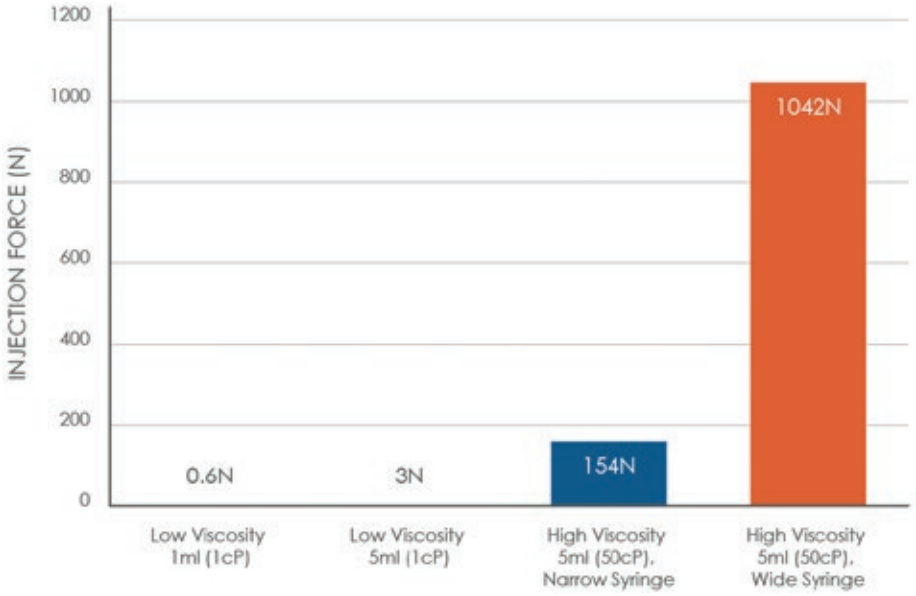

Figure 2: The impact of viscosity and volume on injection force.

Each drug formulation should undertake a rheological assessment to understand its behaviour during injection. This would avoid potential over-engineering of the device to provide an injection force that is above requirements. From a drug viability perspective, it is important to understand the impact of high shear rates during injection on drug integrity and performance – for example, to avoid damage to the drug.[4]

WHAT ARE THE OPTIONS?

Having established the need for a high force to drive the injection, what are the main options out there to achieve this? The four most common solutions are spring drives, gas drives, electromechanical drives and chemical drives. Here, a brief overview of each option is provided along with benefits and challenges of each.

Spring Drive

The most widely used energy source for autoinjectors is the spring drive (Table 1). This solution has many advantages, with a wide selection of established suppliers to the medical device industry, well understood automated assembly methods and a relatively low cost. However, the high force required for LVIs introduces several challenges for spring mechanism designs.

Typically, the spring driven mechanism will need to be stored in a compressed state for a long period (more than three years). The force in this compressed state is driven by the maximum injection force, along with the force required to compress the spring to its starting position (Figure 3).

It will be necessary for the components used to maintain the spring in a compressed state to be highly resistant to creep. A cost-effective solution here would be to use high-performance polymers such as liquid crystal polymer. However, it would require extensive finite element analysis and materials testing to understand the material performance over the required storage time.

A potentially more expensive but lower-risk solution would be the use of metallic components. For these, careful consideration should be given to the optimal manufacturing method at an early design stage. For a pen injector device, deep drawing and impact extrusion can be cost-effective methods for producing metallic parts with hollow, cylindrical geometries. Part geometry should be optimised at an early stage to suit the chosen manufacturing method.

An additional challenge with spring-driven mechanisms is maintaining the overall length within an optimal form factor for usability. For a standard compression spring, there is a minimum compressed length that can be achieved based on the maximum force required, the length of travel required and the k-factor of the spring. This could potentially be reduced by using novel spring designs such as volute springs – a conical spring with a short, compressed length – or dual springs.

Benefits	Challenges
Lower cost solution	High load during storage
Non-complex assembly	Variable injection speed
Low risk for drug compatibility issues	Device size

Table 1: Spring drive benefits and challenges.

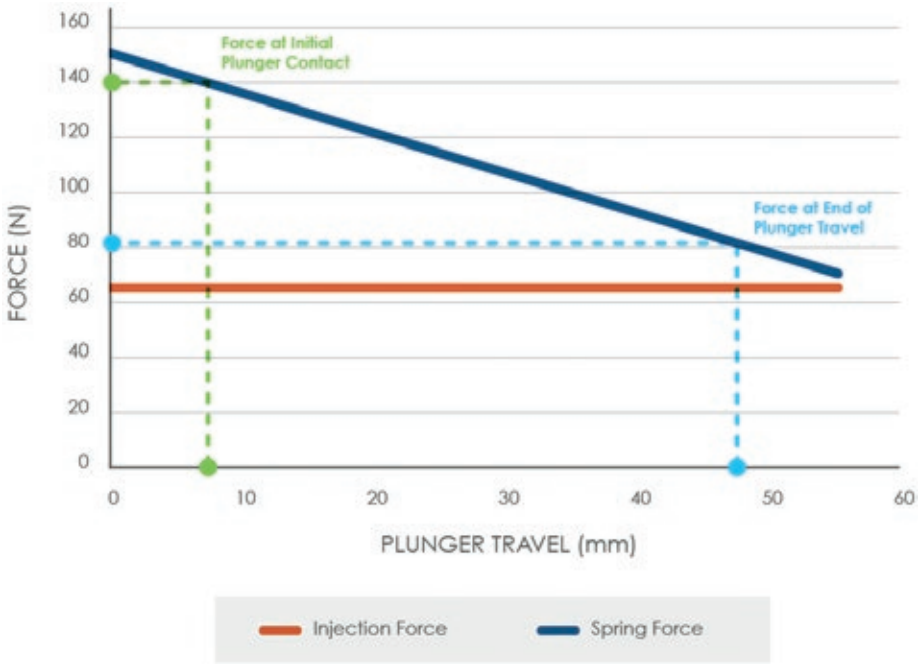

Figure 3: Injection versus spring force.

Clock springs could also be used in this application, which would give the added benefit of maintaining a constant force over the injection travel.

Gas Drive

Compressed gas has many advantages as a drive mechanism (Table 2). It can generate a very high force output within a small form factor. It requires very few components to operate and exhibits low noise during operation.

However, selecting the appropriate gas for the application can be challenging. Principally, there are two main options – single-phase gases and dual-phase gases (including refrigerants). As refrigerant gases are typically being phased out due to their environmental impact, single- and dual-phase gas options excluding refrigerants are discussed here. Two of the more challenging aspects of a gas drive design are discussed in further detail here – pressure output stability and leakage.

Single-phase gases will have a reduction in pressure output from beginning to end of delivery and exhibit a relatively low sensitivity to temperature. Dual-phase gases will provide a relatively constant pressure over the drug delivery; however, the pressure output is highly sensitive to ambient temperature (Figure 4). Understanding operational temperature range, required injection time and expected injection force profile are critical in selecting the correct gas solution for the application.

It is also important to consider leakage from the container over the device lifetime. What detections should be put in place at production to mitigate against leaking canisters? – i.e. weighing the gas contents at various stages through production, adding tracer elements to the gas for detection or temperature testing to raise the internal pressure of the gas and stress test the canisters. Isolation of the gas from the drug and venting of the gas are other design features that it is critical to assess and implement into the design.

Benefits	Challenges
High power density, only applying force when actuated	Gas sensitive to pressure and temperature
Can provide a constant pressure	Leakage and exhaust gas management
Quiet during use	Limited supply chain options

Table 2: Gas drive benefits and challenges.

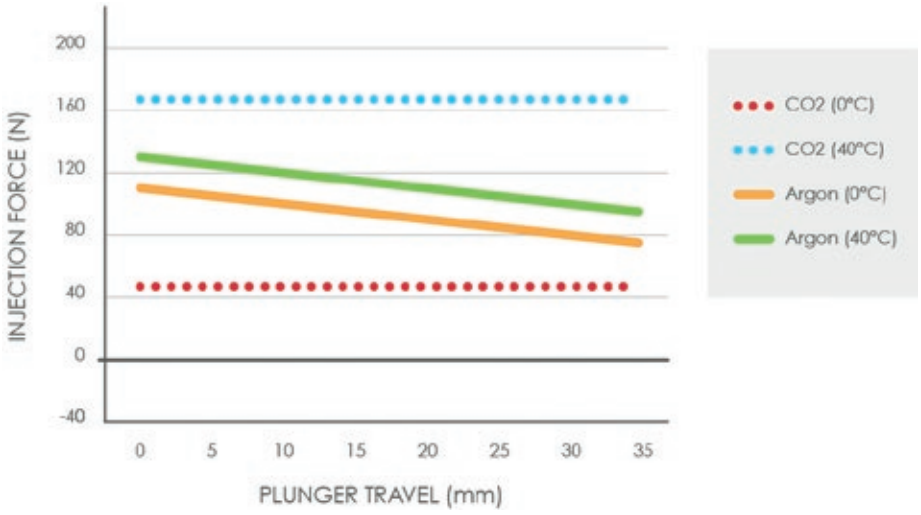

Figure 4: Injection force versus plunger travel.

Electromechanical Drive

For a platform injector device, an electromechanical drive mechanism (Table 3) can provide the flexibility and tunability required to deliver a range of drug viscosities and volumes with customised drug delivery profiles. It also has the advantage of adding connectivity to help with patient monitoring and compliance. There are, however, some challenges for electromechanical drives.

Integration of the electronics and the componentry into the overall mechanical design is a significant challenge. This requires a strong systems-level engineering approach to ensure a robust device at production volumes. Here are some examples (Figure 5) where a motor and printed circuit board assembly (PCBA) must be assembled into the plastic bottom housing of an injector pen. The motor has negative and positive terminals on its undercarriage that are to align with contact pads on the PCBA. This contact will require an interference fit to ensure a robust electrical connection. Both the PCBA and the motor will be heat staked into position using posts in the bottom housing.

For a successful assembly, it is critical to understand the PCBA requirements – namely, the manufacturing tolerances, the cut-out tolerances and the component placement tolerances. Assembly tolerances for placing the PCBA and the motor into the housing are also important. Finally, the moulding tolerances on the plastic housing need to be considered. In a typical project, components will be sourced from multiple suppliers (Figure 5). Systems-level planning and execution are critical to ensure the final device will assemble correctly and function as intended when these components are brought together in the final device.

By adding electronics to the device, there is also additional complexity in testing that will need to be completed on the device to meet stringent electrical safety standards. The firmware development will also need to be managed in conjunction with the PCBA design and validated to ensure it meets requirements.

Benefits	Challenges
Hugh flexibility as a platform device	Potentially high cost solution
Potential to add connectivity	Meeting power requirements
Low risk for drug compatibility	Firmware development

Table 3: Electromechanical drive benefits and challenges.

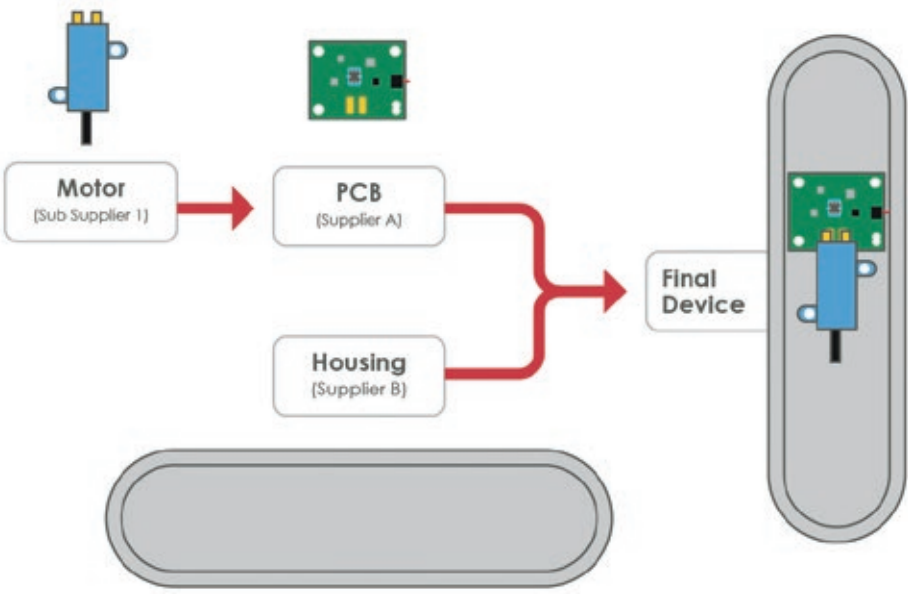

Figure 5: PCB assembly.

Benefits	Challenges
Very high potential power density	Force profiles susceptible to environmental challenges
Low number of moving parts	Environmental disposal challenges
No stress / pressure in stored state	Development time (novel technology)

Table 4: Chemical drive benefits and challenges.

Chemical Drive

Using the energy created from a chemical reaction can be a novel approach to generating the required injection force for an LVI (Table 4). Some of the advantages to this method include the high energy density achievable in a compact size and the potential to control the reaction to meet your requirements – i.e. a lower initial force to mitigate against high impact on the drug container. However, there are some challenges to this method that will need to be overcome.

When one considers the use of chemical energy, the risk that frequently comes to mind is an out-of-control reaction. This is a very real issue but there are many ways to use the energy from a chemical reaction in a controlled, safe and regulated manner.

One such possibility is the use of an electric source to stimulate and thus regulate the chemical reaction through electrochemical interactions. This gives greater flexibility to the designer in creating a delivery profile that matches the device requirements. With the addition of a PCBA, programmable delivery profiles can be created to offer greater flexibility as a platform device.

Other possibilities include mechanical pressure release valves to regulate the progression of pressure build-up or bypass mechanisms that attenuate the reaction once it has progressed outside of the desired parameters. This occurs either through the release of a regulator or through reduction of an active component in the reaction.

A major factor that must be accounted for in the control of chemically driven devices is sensitivity to the environment, particularly temperature, which will directly impact the reaction. Any successful control mechanism must adequately account for this. Other factors for consideration include isolation of the chemical element from any contact with the drug container or the drug itself and understanding the variation of the force output within the operational conditions of the device.

CONCLUSIONS

Developing a handheld injector to deliver large volumes (>1 mL) of highly viscous drugs in a short time period (<30 s) poses some challenges. The main consideration is generating the high injection forces required. Discussed above are some of the potential options to generate the required force using either spring, gas, electromechanical or chemically driven mechanisms. There are benefits and challenges for each mechanism that should be assessed against the specific device requirements.

ABOUT THE COMPANY

Jabil Healthcare (formerly Nypro) is one of the world's largest, most comprehensive healthcare solutions and capabilities providers. Its customers have access to an array of engineering, design and manufacturing solutions across multiple sectors in the healthcare industry. Jabil Healthcare understands the challenges and potential solutions associated with each LVI mechanism. It has specific project experience across all the potential drive solution options from concept selection through to final manufacturing.

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ABOUT THE AUTHOR

Paolo Fiorini joined Jabil Healthcare in 2018 with more than 10 years of experience in project management, process and product development for novel and disruptive technologies in challenging and highly regulated industries. Dr Fiorini completed both his Mechanical Engineering degree and PhD with University College Dublin (Ireland) and is a chartered engineer with the Institution of Mechanical Engineers (CEng, MIMechE)

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DRUG DELIVERY DESIGNED TO IMPROVE THE PATIENT EXPERIENCE

In this article, Jennifer King, Marketing Manager at Enable Injections, looks at the delivery challenges of many novel therapies for chronic diseases, using a specific patient's story as an example, going on to highlight the ways in which a novel device approach, like the company's enFuse wearable platform, could make all the difference for patients.

Chronic illness touches everyone, it seems. Whether it is a family member, friend or co-worker, many people have some understanding of how difficult life can be while managing a chronic disease. The biotech revolution has led to many novel therapies that are changing lives. But these new therapies may come with delivery challenges that make it difficult for a patient to receive treatment. When a patient shares stories of the rigours they endure to manage their disease, it highlights the motivating factor behind novel technology like the enFuse on-body infusor platform (Figure 1).

Figure 1: The enFuse, on-body infusor.

A REAL PATIENT WITH A REAL STORY

The Enable Injections team recently spent time with a patient who introduced an interesting perspective on her infusions. Megan has managed a chronic autoimmune disease for more than 15 years. She is passionate about helping others who live with similar autoimmune diseases – especially young people, because she was diagnosed at the age of 18.

Megan was initially prescribed 28 pills per day for treatment, which proved to be difficult to manage and ineffective. While planning her life around her dosing schedule, she lived in a mental fog due to fatigue and was unable to travel or do other activities she loves.

At the age of 23, she began seeing a new doctor who said to her: "You are a young person and you deserve to live your life." Megan said hearing those words was life-changing, as she thought she would never feel well again. Her new doctor prescribed a new therapy via IV administration, and she began feeling better. Even though she was required to take an afternoon off work for each treatment, she didn't mind the inconvenience. She began to think of the three hours tethered to the IV as "me time" because the hospital infusion centre was comfortable and, over time, she came to know the staff. However, each infusion had the potential for its own challenges.

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"In a survey of patients receiving IV enzyme replacement therapy, 40% felt that hospital-based ERT is disruptive, causing loss of days at school and work, stress and family issues."

For an IV infusion to go well, the medicine needed to arrive at the correct location at the correct time, the IV had to be placed at the site without complications, her vitals had to be in the right range and her body had to respond properly to the treatment. In addition, to receive her treatments, Megan often had to work with her insurance company to gain the proper approvals to ensure her treatments were covered.

Recently, Megan's insurance payer interrupted her IV infusion routine by informing her that it now requires home infusion for her IV therapy. In Megan's words, setting up the home infusion was a disaster. The home infusion nurse showed up hours late, the supplies and medicine arrived a day late and, when they did arrive, she had to spend three hours sitting on the couch with a stranger in her home. This was uncomfortable for Megan because she lives alone.

Megan asked the infusion nurse what she would do if there was a reaction. The nurse responded that she wasn't sure and mentioned calling the 911 emergency number. Megan felt uncomfortable with the arrangement to get emergency care in the event of a reaction.

As a result of her concerns, Megan's insurance now allows her to receive her IV infusions at the home infusion company site. However, she receives her infusion in a windowless cinder block room, and still faces the same logistical challenges, such as missing time at work, as she did when she was treated in a hospital. With no alternative treatment options, she feels stuck and lacking control over her treatments.

CURRENT INFUSION OPTIONS AND CHALLENGES

From the patient's perspective, the potential move of infusions from healthcare clinic to provider-administered at home has many challenges. In a survey of patients receiving IV enzyme replacement therapy (ERT), 40% felt that hospital-based ERT is disruptive, causing loss of days at school and work, stress and family issues. However, 93% of patients had the perception that receiving ERT in the hospital had the advantage of greater safety, closer monitoring and more support from health professionals compared with at-home treatment. A total of 55% were willing to receive ERT at home but 33% were against it.[1]

While home infusion options bring benefits to the payer insurance companies through savings in overall treatment costs[2], as reimbursement changes, patients may experience an increased burden from medical versus pharmacy benefits. These challenges may force other choices onto the patient – including, ultimately, whether to continue care. In the end, for real people with conditions that require energy to manage, the patient usually needs to remain on their therapy to experience the benefits that come with improved health.

DESIGNING TO ALLEVIATE CHALLENGES

Enable Injections has focused on the patient right from the start – it was originally founded to help improve the way children receive vaccinations, in conjunction with research being conducted at Cincinnati Children's Hospital (OH, USA). Soon after work began, Enable's key objective shifted to focus on an even more pressing matter – a way to help patients receive their injectable medicines outside of a healthcare facility. To support the emergence and growing importance of biologics therapies, which often require administration in large volumes, the enFuse technology was born.

Through dozens of human factors studies, Enable Injections honed the enFuse design to simplify patient interaction with the device and target a large range of patient users. Using feedback from pharma and biotech companies, Enable Injections worked to incorporate one of the most pressing requests from pharma into the design – to use the original primary container closure to load the device for delivery for infusion via the enFuse system (Figure 2).

"Enable's key objective shifted to focus on an even more pressing matter – a way to help patients receive their injectable medicines outside of a healthcare facility."

Figure 2: The enFuse 25 mL on-body vial transfer system.

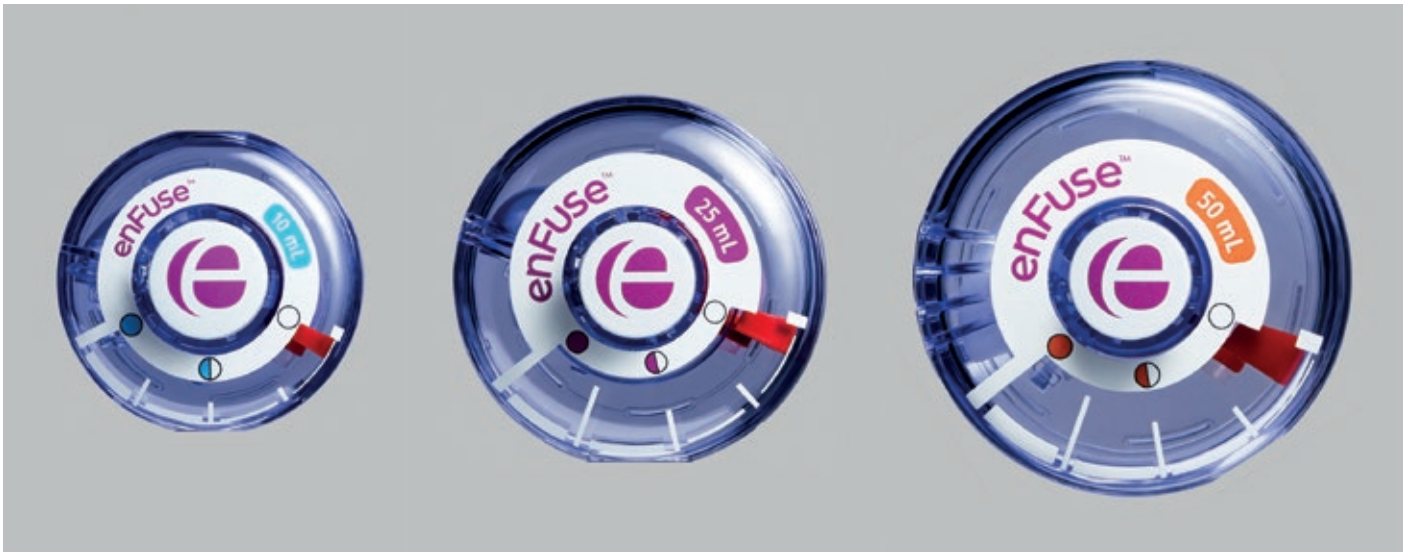

Figure 3: The enFuse portfolio of on-body infusors is being developed in 10, 25, and 50 mL sizes.

"Patient preference studies indicate most patients prefer home-based treatment over treatment at a healthcare facility."

The enFuse platform is designed to leverage existing primary container closure systems, which eliminates the need for additional drug compatibility testing, additional filling and manufacturing lines, and additional stability testing risk. EnFuse is under development in 10, 25 and 50 mL variants (Figure 3).

BENEFITS OF SELF-ADMINISTRATION

Patient preference studies indicate most patients prefer home-based treatment over treatment at a healthcare facility.[3,4] Home-based treatment is associated with fewer days of missed work and school compared with administration in a healthcare clinic.[5,6,7] Patients report home-based treatments are more comfortable, less stressful, more effective and have less impact on family life.[8]

In a 12-month prospective evaluation of outcomes in patients with primary immunodeficiency, patients reported fewer limitations with work and daily activities, improved vitality and better general health after switching to subcutaneous home infusion from IV infusion. The majority reported they preferred the subcutaneous route of administration and home-based therapy over IV infusion.[9]

Studies also report economic benefits and cost reductions in home-based treatment versus hospital or clinic treatment. The cost savings have the potential to be realised from both a healthcare payer perspective and a patient and societal perspective.[5]

With self-administration, treatments may be more easily accessed by the patient. Patients may no longer be required to travel to a healthcare facility to receive treatment or schedule appointments with healthcare providers for in-home treatment. In addition, patients may be more likely to adhere to treatment regimens, as administration may not require additional time away from other activities.

Payers, policy makers, physicians and employers may appreciate the potential positive impact on the healthcare system. However, even with the benefits, the shift to home-based self-administration will require significant effort and collaboration between technology providers like Enable Injections, pharma innovators, payers, prescribers, pharmacies and providers to truly improve the patient experience.

THE GOAL OF MAKING A DIFFERENCE

At Enable Injections, our goal is to help make a difference for people. The enFuse is designed to help improve the patient experience. Enable Injections will continue to stay engaged with patients like Megan to help inform the development of the enFuse.

When asked about whether she would prefer her "me time" at the hospital sitting in the infusion clinic for hours or to regain time through the potential for home self-administered infusion, Megan said she would choose to have her time back. She wouldn't have to stop working or travelling, invite a stranger into her home or arrange her life to accommodate infusion if she could self-administer at home. She would have more control over an aspect of her life that so often feels that it lacks control. For Megan, and other patients like her, that is what makes all the difference.

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 drug delivery platform uses standard container closure systems to deliver large-volume, high-viscosity pharma and biopharma therapeutics.

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Jennifer King serves as Marketing Manager for Enable Injections. She has more than 20 years of experience with marketing in the media, electronics and pharma industries. Ms King has a BS in Mechanical Engineering from Purdue University (West Lafayette, IN, US).

NEXT-GENERATION WEARABLE DELIVERY DEVICES FOR LARGE-VOLUME BIOLOGICS

Thomas Mayer, Business Development Manager, Sonceboz, discusses the Swiss quality behind Sonceboz's platform of wearable injection devices for large-volume biologics. These devices can follow drugs from clinical trials to commercial phase through lifecycle management, which reduces risk and speeds time to market.

Demand for biologics such as monoclonal antibodies continues to bring growth opportunities to the large-volume wearable injectors market, with some researchers estimating the global market to reach US$1.5 billion (£1.2 billion) by 2030. Interest in the devices is being driven by their ability to deliver high volumes between 3 mL and 20 mL – or higher – into subcutaneous tissue. The sweet spot regarding delivery volumes seems to be around 10 mL.

Novel drug delivery technologies such as co-formulated hyaluronidase go some way to making high volume delivery possible.

> "The wider the span of applications, the more challenging it is to find the right technical solution."

But delivery of high volumes of drugs into subcutaneous tissue – especially when intended for home use/self-administration also requires new delivery device technologies, such as on-body injectors, so as not to limit a patient's freedom to live life.

Figure 1: Sonceboz's electromechanical wearable injector is designed around an omnidirectional pump module.

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MULTIPLE DRUGS, ONE TECHNOLOGY SPEEDS TIME TO MARKET

From a platform point of view, in an ideal world, a pharma company with multiple drugs would want one technology to leverage across different drug products. But the wider the span of applications, the more challenging it is to find the right technical solution.

Sonceboz is currently developing an electromechanical wearable injection device platform (Figure 1) designed around an omnidirectional pump module. This makes it possible to connect to various primary drug containers of capacities up to 20 mL or even higher – such as vials or cartridges – without the need for changing the overall system architecture. This is possible by separating the pump module from the drug reservoir – making the two independent of each other.

The advantage of this is that one can rely on one proven system architecture but also leverage already established and proven primary drug containers – and thereby accelerate development and time to market.

Figure 2: The Sonceboz wearable injector platform offers different delivery volumes, programmable pump delivery profiles and container options.

These characteristics are important in achieving the goal of having a drug delivery platform that a pharma company can use from clinical trials to commercial scale to lifecycle management, and have confidence that the system is reliable, taking a level of risk out of development.

By offering different delivery volumes, programmable pump delivery profiles and container options (Figure 2), pharma companies can multiply the platform across different drug products. The advantage is reliance on one proven system, thereby accelerating development and time to market.

THE FAMILY OF WEARABLE INECTION DEVICES

Sonceboz devices are designed to be easy for patients to use, and device prep is completed

by a series of simple and intuitive steps. All the wearable injection devices use the company's electromechanical pump system with dynamic soft-cannula insertion. The Sonceboz platform includes five single-use dedicated variants that enable use from clinical trials to lifecycle management.

The large-volume injector (LVI) comes in two versions. One is cartridge-based, whereby the user inserts a prefilled cartridge into the device at the point of use. This version comes in different sizes to accommodate cartridges from 3 mL to 20 mL. The second LVI variant has an internal reservoir and uses a standard vial adapter that automatically transfers the contents of the vial or syringe inside the on-body device prior to injection. A temporary drug container inside the device is designed for short-term storage. This device is intended for clinical trials or cases where a pharma company wants to keep the vial as a primary container but still provide a delivery device solution to its patients.

The LVI-V is for vial transfer with standard vials/syringes up to 20 mL; the LVI-U is for prefilled cartridges up to 20 mL and is optimal when cold storage is required since it allows for separate storage of drug and device, which in turn reduces the package footprint; and the LVI-P is a prefilled, preloaded version.

The dual-cartridge injector (DCI) uses the same pump architecture to independently inject APIs from two separate containers, either sequentially or simultaneously. This is an ideal solution for combination therapies or lifecycle management where the API is already filled in a smaller volume cartridge such as a standard 3 mL. DCI is well suited for combination therapies in oncology or in cases when one wants to maintain an existing drug container but double the delivered payload.

> "The dual-cartridge injector (DCI) uses the same pump architecture to independently inject APIs from two separate containers, either sequentially or simultaneously."

> "The entire Sonceboz wearable platform comes with built-in connectivity using Bluetooth Low Energy as the communications and connectivity interface."

The auto-reconstitution injector (ARI) is intended for automatic reconstitution of lyophilised drug products. In biologics, there is often a need to store a drug in a powdered state because it will not remain stable over its intended shelf life in a solution. But manual reconstitution of lyophilised drug formulations is a complex procedure and challenging for caregivers and even more so for patients.

With ARI, a prefilled and loaded diluent is automatically transferred into the vial containing the lyophilised drug product. When the transfer is complete and the drug reconstituted, the pump retransfers the resolved drug product back into the device. Once this step is completed, the vial adapter is removed and the device used on-body. This simplifies the use of lyophilised products and supports self-administration. A built-in sensor suite monitors proper handling and orientation during transfer and mixing.

The entire Sonceboz wearable platform comes with built-in connectivity using Bluetooth Low Energy as the communications and connectivity interface. This enables pharma companies to include data from the on-body devices into a dedicated digital-health solutions suite.

INCORPORATING THE MOTION OF MECHATRONICS

Mechatronics is what makes the Sonceboz devices so flexible. Mechatronics is at the crossroads of electronics, mechanics and computing, with a variety of applications. For more than 25 years, millions of mechatronic drives from Sonceboz have been used in hospitals, clinics and laboratories around the world in the form of blood pumps and syringe pumps for dialysis machines, and motors or actuators for diagnostic equipment. The company produces 70 million mechatronics systems annually, all of which are manufactured in Switzerland.

Now, the company is applying precision mechatronics to its wearable injection device platform in the form of its GentleTouch piston pump. Its integrated three ports allow drug transfer and mixing across a range of delivery volumes, speeds and viscosities without the need for design changes.

The electronically driven pump goes through two stages during its cycle. In the first stage, the pump fills itself by applying a vacuum to whatever primary container it is connected to. The second phase uses positive displacement to pump the drug into the patient or, if required, to another container. The fluid path is completed by the dynamic needle insertion and retraction system, which features a thin 27G soft cannula and built-in needle-stick injury prevention.

This design and the ability to command the direction of flow allows for the previously described flexibility in terms of use cases and therapeutic applications. The pump system is independent of the drug container so one can connect both small and very large containers. And the pump is constructed with materials and coatings that are compatible with large-molecule biologics; the pump's lubrication system has been designed to be in line with biologic drug product requirements. Also, the motion that the drug fluid is subjected to is not damaging to the drug product.

LEVERAGING AUTOMOTIVE EXPERIENCE IN PHARMA AND MEDTECH

Situated in the heart of the Swiss Watch Valley, since 1936, Sonceboz has been focused on mechatronics, beginning with industrial time-keeping equipment and

transforming into a leading supplier of actuation for the passenger and commercial vehicles industry.

Adherence to stringent quality standards and cost pressures in the auto industry is something Sonceboz has been able to leverage in the medical device sector, and now in pharma drug delivery. In the auto industry, it is expected that a mechatronic system function 100% of the time, and Sonceboz leverages its expertise in high-quality and high-volume automated manufacturing to provide the utmost safety and reliability standards to drug delivery devices.

The wearable injector platform follows design for manufacturing (DFM) guidelines, enabling top-down automated assembly of all components at top quality. And, by implementing complete end-of-line control, every functional element of the wearable platform is then tested according to specifications to ensure the device performs its job as intended from a technical point of view. From a user point of view, the device is intuitively designed so that a user will know how to use the unit just by looking at it.

Sonceboz is currently in the engineering verification phase with the platform to fully characterise the design prior to design verification testing. The device platform is expected to be ready for clinical trials in late 2021.

The future of drug delivery is technology that allows patients to receive their medication at home, not in a hospital or outpatient clinic. Mechatronics, building on a long and rich history, is writing a new chapter in the medical field, particularly in drug delivery.

ABOUT THE AUTHOR

Thomas Mayer is responsible for business development at Sonceboz Medical. Prior to joining Sonceboz in 2016, he held various management positions at Boston Scientific's Cardiac Rhythm Management division. His first interactions with the pharmaceutical industry came early during his apprenticeship at Uhlmann Pac-Systeme in Laupheim, Germany. Mr Mayer holds an advanced degree in Medtech and Pharma Management from EPFL Lausanne (Switzerland) and a diploma degree in Medical Engineering from Furtwangen University (Germany) as well as an MBA with honours from FOM University in Munich (Germany).

ABOUT THE COMPANY

Sonceboz's core competencies consist of design, development and production of mechatronic drive systems. Since 1936, the company's focus has been on innovation, and best-in-class quality and service. Sonceboz is ISO 13485 certified and active in wearable drug delivery, medical devices and laboratory industry. Customised technology modules like motor drives, electronics, pumps and needle insertion systems are available for medical device manufacturers. Sonceboz's activity in medical devices is based on long experience in the automotive sector, where top quality, reliability and cost effectiveness is key.

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HOW TO DESIGN A BODY-WORN INJECTOR

Body-worn injectors require you to understand your user, your drug and your technology – and there are numerous pitfalls for the unwary. In this article, Stephen Augustyn, Head of Mechanical Engineering Group at Team Consulting, gives some insights into how to design a successful body-worn injector – or select a device that is suitable for your needs.

Body-worn injectors are tricky little beasts – they aim to combine the convenience of an autoinjector with the precision of an infusion pump but aren't quite either of these devices. There is a wealth of devices and technologies on the market – or about to reach the market – all vying for your attention. But how can you make sure you're choosing the correct product or making the right design decisions?

It really comes down to three key points – understand your user, understand your drug and understand your technology (Figure 1). If you have secure knowledge of these three areas, your chance of creating – or selecting – the right device increases enormously. Team Consulting has spent the last six years designing and identifying the right body-worn injectors for clients and contributing to the new ISO standard to help regulate these products. This article offers a distillation of some of the key things that we have learned.

There are some excellent products in this space but there is no single device that will be the optimum choice in all applications. A body-worn injector intended to treat a patient recovering from surgery will have a very different set of requirements from one intended to help a patient manage a chronic condition.

"A body-worn injector intended to treat a patient recovering from surgery will have a very different set of requirements from one intended to help a patient manage a chronic condition."

UNDERSTANDING YOUR USER

There are many reasons why you may wish to use a body-worn injector over an autoinjector – you may be delivering more drug than an autoinjector can comfortably hold, you may wish to spend longer delivering the drug or you may even want to delay, or modulate, the drug delivery. However, the single biggest driver for body-worn injectors has been the requirement to deliver larger drug payloads. Most autoinjectors on the market have a prefilled syringe (PFS) at their heart – a rigid glass or polymer syringe, with a sterile needle, storing 1-2.25 mL of drug product.

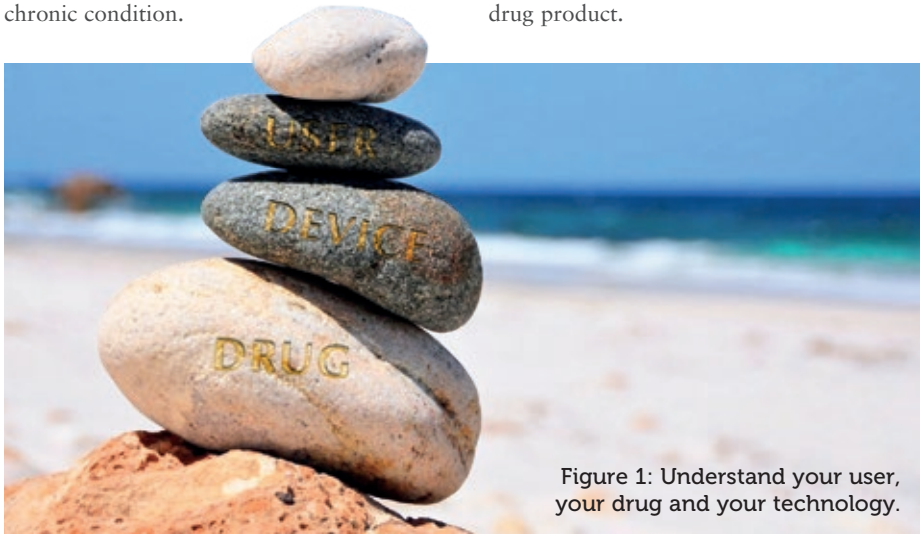

Figure 1: Understand your user, your drug and your technology.

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Figure 2: How the injector will attach to the body is a key consideration.

"The design of the patch and careful consideration of the removing features is also critical."

The principal difference between an autoinjector and an on-body injector is that the patient holds the autoinjector throughout the delivery sequence whereas, with a body-worn injector, the user attaches the device, begins the delivery and removes the device once delivery is complete. This aspect of on-body injectors should result in a more comfortable and consistent injection experience for the patient but it does require a more sophisticated and expensive device.

ATTACHING AND REMOVING THE INJECTOR

Precisely how the injector will attach to the body should be a key consideration for the designer. If the device is a single-use disposable product, adhesive would be the obvious choice but even that solution requires some deeper consideration. The requirements for an adhesive that only needs to work for 10 minutes whilst a patient is stationary are very different from the adhesive that needs to work on an active user and stay in place for hours.

The profile of the patient will also make a big difference – young children and the elderly can have very delicate skin, and some conditions or drugs may make the skin more susceptible to damage and irritation. The design of the patch (Figure 2) and careful consideration of the removing features is also critical – the patch should allow the user to stabilise the skin around the patch, get a secure grip on the patch and remove it with a gentle peeling action. 3M has a useful "find my adhesive" facility on its website that can help you identify a suitable material but be prepared to do some testing and evaluation work.

"One of the key questions that can impact the design of a body-worn injector is whether the device will come prefilled or not."

If you have a device with an integral needle or cannula, you will have no option but to affix the product directly to the skin – but there is the option of remote delivery. This is the model used by most continuous subcutaneous insulin infusion (CSII) pumps and can be practical for disposable pumps as well. Patients with chronic conditions may present problems when asked to adhere a pump to the same area of the body day after day, so separating the pump from the infusion site may offer a real advantage.

USER INTERFACE

On-body injectors will often feature electronics as part of the delivery system and this will then come with the temptation to give ever more feedback to the user, add smartphone integration and offer "helpful" advice on use of the product. This is a huge area to explore, and beyond the scope of this article, but every new feature must justify its place on the product and what may seem like an incredibly helpful and smart feature in the design office may be very confusing to patients. It's worth dedicating significant time and effort to investigating and testing products with target users as it will reveal challenges you didn't see coming. Get your product concepts in front of representative users as early as possible and let your decision making be based on evidence.

CO-MORBIDITIES AND COMPLEX TREATMENTS

It is increasingly the case that users present to their healthcare practitioners with complex conditions – e.g. diabetes, high blood pressure and diabetic neuropathy. These are precisely the patients who could most benefit from a body-worn injector and their needs will have to be considered if they are your target group. If the device is not sold prefilled and the user needs to transfer or reconstitute a drug, how is the patient going to manage this process?

The ISO Committee ISO TC84 examined the challenges that visually impaired users have with injectors when it created ISO 11608-7:2016. The design guidance in ISO 11608-7 has many useful recommendations that may assist designers developing new on-body devices.

UNDERSTANDING YOUR DRUG

One of the key questions that can impact the design of a body-worn injector is whether

the device will come prefilled or not. If the device will be prefilled, there will be a fundamental impact on the design of the primary container, the environmental storage of the drug/device combination and the stability studies undertaken. Storing the injector below room temperature will have an impact on the materials and power sources in your device. Even a few degrees' change can make plastic materials more brittle and less flexible. This could mean that the critical fluid seal on your device no longer works as it did during your development testing, your injection forces become larger or fluid lines don't flex as they should.

The effect of temperature on drug behaviour should also be examined in detail and testing should reflect real-world use of the product. If the drug and device will be stored at low temperatures and then brought up to room temperature for delivery, the test programme should reflect this. A lower temperature drug may have a much higher viscosity which would require more force to be delivered than the mechanism can produce. Similarly, testing with a drug or mimic at a higher temperature than intended may result in a false positive in the testing programme – putting the health of patients at risk.

Aiming to deliver a larger drug payload or a high-viscosity drug is one of the benefits of using an on-body injector. The challenge comes with using a suitable model fluid during development testing. Some of the drugs destined for these devices are extremely expensive or highly toxic. But if you leave your device testing with the real drug – or a very accurate mimic – until the last moment, you can guarantee that it will have some surprises for you.

BACK TO PRIMARY SCHOOL

Primary container selection will be at the heart of the device design. There are hundreds of filling lines available in the world's major economic areas that have been configured to fill standard cartridges and prefilled syringes – and if your container will fit on this line, you have an immediate commercial advantage. There may be a compelling reason for adopting a novel primary container but if your pharma clients are very reluctant to re-run stability studies in new containers, you will need to apply careful consideration as to how you get the drug from a vial or cartridge into your on-body injector.

> "The intellectual property landscape around these drive and sensing technologies is extremely crowded and identifying freedom to operate can be a significant challenge."

Experience from running dozens of verification studies on different parenteral products suggests that ageing products and introducing a live drug for the first time always have an impact on device performance. So, start testing with either the active drug or a highly representative placebo as early as you can in the development as you don't want to be making fundamental discoveries on device behaviour when you get to your design verification programme.

UNDERSTANDING YOUR TECHNOLOGY

In addition to your primary container, you will need to provide a source of power to deliver the drug. On most autoinjectors this is performed using a compressed spring and there is no reason why a spring can't be used on a body-worn injector. Compression springs are cheap, accurate, reliable and easily made to your specification. They are also large, need to be stored in a compressed (highly loaded) form, can't be controlled after release and lose power as they expand.

If you have a highly variable injection force (for example, a high break-free force and a low glide force) then springs may not be ideal. Also, if you need a device with a slow infusion of drug, you'll need to control this action through flow restrictors in the fluid path and this can lead to variable behaviour as the drug viscosity changes or as the manufacturing tolerances change.

Many of the restrictions of using springs don't matter for autoinjectors where you are just trying to deliver the contents of the

Figure 3: Displacement pump technology is at the heart of Sensile's range of pumps.

primary container as quickly as possible. However, in body-worn injectors, springs may be too much of a compromise. If you need to provide active control of the delivery of the drug, you are almost certainly looking at an electronic drive system with rate control. This can be done with no feedback (where you may just be driving a pump or plunger at a defined rate) or you may use active feedback to precisely control the delivery rate.

Active feedback, measuring displacement or fluid flow, offers the best control of delivery rate and it will also provide a mechanism to detect occlusions or alert the user to any errors in the device. This would necessitate having an electronic drive system which could be a displacement pump like the SenseCore pump at the heart of Gerresheimer subsidiary Sensile Medical's (Olten, Switzerland) range of pumps (Figure 3) or a plunger-based system as used in West Pharmaceutical Services' (Exton, PA, US) SmartDose device. The SMT-101 pump from United Therapeutics subsidiary SteadyMed Therapeutics (San Ramon, CA, US), uses a novel expanding battery design and there are many other competing technologies that different manufacturers are promoting. The intellectual property landscape around these drive and sensing technologies is extremely crowded and identifying freedom to operate can be a significant challenge.

The use of electronics does come with one significant headache that pharma companies aren't used to – supply management for electronic components. The electronics industry works on a very short lifecycle, driven largely by the rise in mobile consumer technology. Resolving the tension between having a stable design (as expected in a lot of pharma applications) and a key piece of technology in your product, such as a sensor or a drive system, that will be going through generational changes over the life of your product – which is likely to take years to get to market – presents real challenges. Speaking directly to the supplier of these parts and committing to holding stock of components may be the only real strategy for a device builder.

INJECTING OR INFUSING?

Selection of a drive technology will be influenced by your intention to deliver an injection or an infusion. The difference is that an injection is based on delivering a volume of drug in a manner tolerable to the patient – and an infusion is based on delivering drug at a controlled rate to create a pharmacokinetic effect. This is the critical difference that has been identified in the draft of ISO 11608-6, the new standard for on-body delivery systems.

> "If you only ever test to your device specification limits, you'll never know if a subtle change in component tolerances or manufacturing process may result in a huge spike in device failures."

For example, CSII pumps must deliver basal and bolus quantities of drug at a precisely controlled rate and, for this reason, their performance requirements are best described by IEC 60601-2-24. This also applies to the Insulet (Acton, MA, US) Omnipod, which can superficially appear to be a large-volume injector but is in fact an infusion pump. Whilst a product that acts as an infuser or an injector will face many of the same challenges, it is vital that the device manufacturer recognises what is important to them. This required performance will have a dramatic effect on the architecture of their device and the verification that they will have to evidence.

GETTING THE 'MEOST' OUT OF YOUR TEST PROGRAMME

One of the key approaches to mitigate hazards from unknown drug behaviour or technical design risks is to use multiple environment over stress testing (MEOST) or highly accelerated life testing (HALT). Both methodologies will help to stress your product by pushing the testing outside the specification range for the device. This testing should not be part of your verification programme but part of an engineering test programme or a small-scale pre-design verification test (DVT) study.

This approach to testing will help you to be confident that the design space you have defined is well within the capabilities of your device. If you only ever test to your device specification limits, you'll never know if a subtle change in component tolerances or manufacturing process may result in a huge spike in device failures.

You can also use analytical modelling to identify vulnerabilities in the design by running multiple simulations of the way the product will operate to help understand your design space. These analytical modelling approaches do not need to be limited to complex 3D simulations that rely on heavy computing power – something as simple as a Monte Carlo analysis of tolerance stacks or activation loads may save a lot of time and samples in the test lab.

CONCLUSION

On-body injectors offer some significant benefits for patient care, including management of chronic symptoms and less time in hospital. The key to delivering a successful product is all about putting the patient experience at the centre of the design, building the device to deliver that experience and knowing exactly how your drug and device technology will behave. Whilst, superficially, these products can look a lot like infusion pumps or autoinjectors, they come with their own challenges – and having a rigorous test and development programme in place is your very best chance of creating a robust product.

ABOUT THE COMPANY

Team Consulting is an award-winning medical device design and development consultancy. For more than 30 years it has worked closely with clients at many of the world's leading pharma and device companies to develop better medical devices.

ABOUT THE AUTHOR

As one of Team's Mechanical Engineering Heads , **Stephen Augustyn** is responsible for the delivery of Team Consulting's capability in device engineering. He has more than 20 years' experience in the design and development of drug delivery devices, and is also member of the ISO/TC84 – the ISO committee focused on standardisation of devices for administration of medicinal products and catheters.

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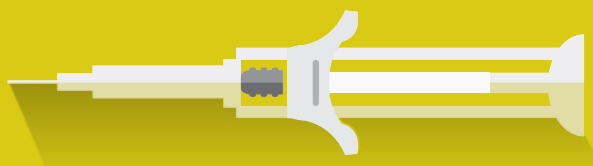

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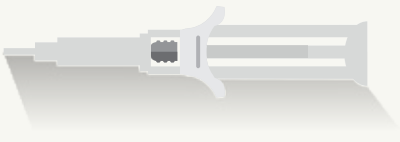

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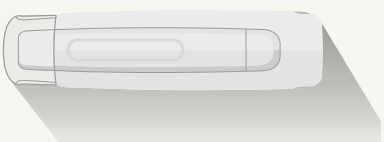

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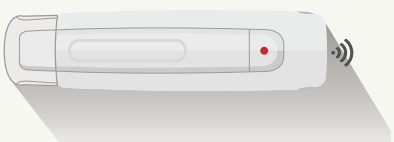

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PRODUCT SHOWCASE: ZwickRoell Parenteral Device Testing Platform

In 2020 several billion prefilled syringes (PFSs) were sold worldwide and the market continues to grow. Anticoagulants and vaccines dominated the PFS market, but the number of biologics stored and administered in PFSs is steadily increasing. These PFSs are also used in autoinjectors. Due to the sensitivity during storage and the complexity of their action mechanism for administration, they must meet high requirements, for which ZwickRoell offers a wide variety of standardised test fixtures.

TESTING PFS TO ISO 11040 -4, -6 & -8

ISO 11040 for PFSs (Part 4: Glass barrels for injectables and sterilised sub-assembled syringes ready for filling, Part 6: Plastic barrels for injectables and sterilised sub-assembled syringes ready for filling, and Part 8: Requirements and test methods for finished PFSs) describes 10 mechanical tests. ZwickRoell has a complete portfolio of products to satisfy the requirements of ISO 11040 -4, -6 and -8. The variable test fixtures are suitable for a wide range of syringe types and geometries. Some tests require a testing machine with additional torsion drive. The universal test fixture for syringes can also be used for tests on carpules by means of suitable adapters. Torsion and leakage tests are described in ISO 80369. An overview of the tests:

Figure 1: Glide force test.

- C1: Flange breaking resistance
- C2: Luer cone breaking resistance
- E: Glide force test for evaluation of syringe lubrication (Figure 1)
- F: Needle penetration force test
- G1: Needle pull-out force
- G2: Closure system liquid leakage test
- G3: Luer lock adapter collar pull-off force
- G4: Luer lock adapter collar torque resistance
- G5: Luer lock rigid tip cap unscrewing torque
- G6: Pull-off force of tip cap or needle shield

TESTING OF THE LUER/LUER LOCK CONNECTIONS

The Luer cone is a standardised connector system used in tube systems in the medical industry. It is used with items such as cannulae, syringes, catheters, three-way stopcocks, and infusion tubes. The seal is achieved through use of a cone-shaped fitting, called a Luer cone. Furthermore, the Luer lock connector has a threaded sleeve to achieve a tight connection so fluids cannot escape.

For quality control of these components, a materials testing machine with superimposed torsion drive is used. The ISO 80369 Part 7 and Part 20 standards are used to test a Luer system or Luer lock connection for stability through various tests. The superimposed axial/torsion drive of a zwickiLine torsion materials testing machine enables easy determination of torques under static axial load. The test fixtures also allow for leak tests.

SERIAL, PARALLEL AND FULLY AUTOMATIC SYRINGE TESTING

If it is necessary to test a large number of syringes in a short time a materials testing machine with a carousel or an X-Y table can be used. A large number of specimens can be fed to the machine via a magazine and automatically tested one after the other. Operator influence on the test is reduced, resulting in greater stability in MSA/Gauge R&R studies.

Reliable test results are a basic requirement when testing medical and pharmaceutical products. Extensive automation improves test-result reproducibility, minimises operator influence and simplifies validation using measurement system analysis studies. In addition to the automated test sequence, various handling systems provide automatic specimen feed. Another application concerns, for example, syringes used in syringe drivers. In this case the syringe plungers are depressed over a lengthy period.

TRACEABLE, TAMPER-PROOF TEST RESULTS

Ever-increasing demands are placed on software used in the medical and pharmaceutical industries to document the traceability of completed actions, and guarantee data integrity. The testXpert III testing software's traceability option enables logging of actions and changes before, during and after the test, making test results and documentation traceable and safeguarding them against tampering. Integrated user management and functions including electronic records and an electronic signature ensure that test results are protected against manipulation at all times. Together with the organisational measures and procedure instructions that apply to the individual companies themselves, the requirements of US FDA in 21 CFR Part 11 are fulfilled.

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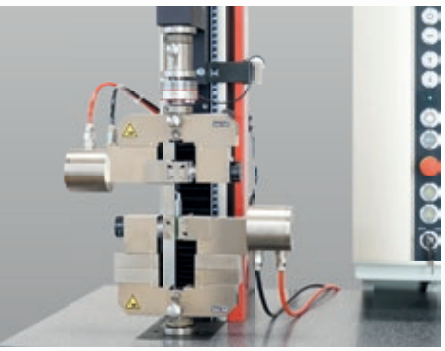

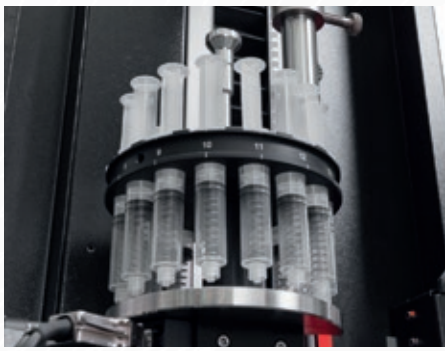
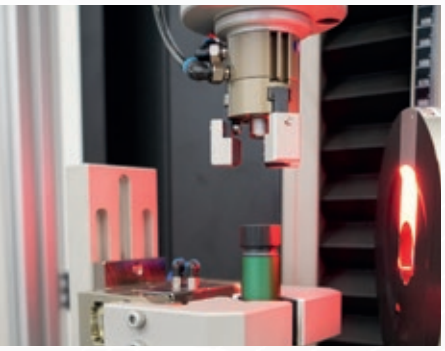
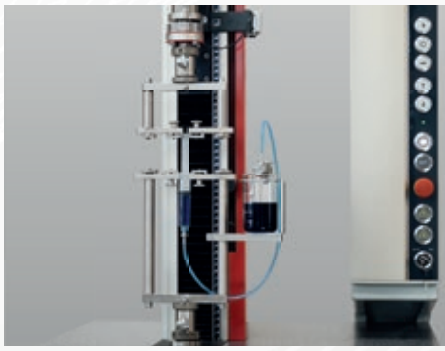

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THE NEED FOR CSTDS IN BOTH MANUAL AND AUTOMATED COMPOUNDING

In this article, Marino Kriheli, Co-Founder of Equashield, discusses the benefits of using closed system transfer devices (CSTDs) in both manual and automated hazardous drugs compounding.

Healthcare workers may be exposed to hazardous drugs (HDs), often chemotherapy medications, at many points during their manufacture, distribution, storage, transport, compounding and administration, as well as during waste handling and care of treated patients.[1] The risk of exposure is, therefore, not limited to those directly involved with the drugs, such as pharmacists or nurses. It extends to all workers, including those involved in the maintenance and repair of equipment in the compounding and administration environment.

> "The consequences for not properly protecting staff members can be severe."

This has been confirmed in a clinical study which found drug contamination on select surfaces at every stage of the medication system, which it said indicated the existence of an exposure potential throughout the facility – potentially leaving "up to 11 job categories per site [that] may be at risk of exposure at some point during the hospital medication system".[2]

According to the US National Institute for Occupational Safety and Health (NIOSH), approximately eight million US healthcare workers are at risk of exposure to HDs, while the European Commission estimates that some 20 million European healthcare workers are at similar risk.

The consequences for not properly protecting these staff members can be severe. NIOSH has demonstrated that exposure to HDs can produce negative health outcomes, including abdominal pain, nausea and vomiting, diarrhoea, hair loss, dermatitis, irritation of skin and eyes, irritation of mucous membranes and menstrual cycle disruption. In more extreme cases, exposure can result in birth defects, miscarriages and even some forms of cancer.

As a result, health agencies worldwide have created safety guidelines for interacting with HDs. NIOSH recommends that, in tandem with other safety measures, healthcare workers use a CSTD, throughout the HD-handling process. And the US Pharmacopeia (USP) recommends that CSTDs be used as supplemental engineering controls in USP 800, which came into effect in December 2019.[3] The UK's Health & Safety Executive (HSE) recommends the use of fully closed systems where reasonable[4] and EU-OSHA in the EU lists closed systems in its "hierarchy of prevention".[5]

The importance of CSTD use was further demonstrated in a study by Vyas in 2013 which showed that CSTDs can reduce HD contamination – and CSTDs are increasingly becoming the standard of care. However, the need for better protective measures will increase over time as the number of patients requiring these drug therapies continues to grow.

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Figure 1: The Equashield CSTD, with encapsulated syringe barrel and a metal plunger rod.

ONLY FULLY CLOSED SYSTEMS ARE EFFECTIVE

CSTD use is becoming standard practice across healthcare markets as global bodies follow US examples, including NIOSH and USP in championing the use of CSTDs, especially given the improvements in the available products over time. The original design of CSTDs took the correct approach by mechanically preventing escape of hazards out of the system as well as stopping environmental contaminants entering the device. These original "barrier systems" isolated people from hazards while also protecting the sterility of HDs.

Subsequently, alternative filter-based systems have emerged. However, this design approach is inherently flawed due to the reliance on filtration to separate hazardous materials from non-hazardous. For example, even the largest drug vapour is at least 1,000 times smaller than the filter paper used in many filter-based systems. Such systems also tend to rely on the inclusion of a charcoal filter. However, use of charcoal filters includes a number of variables and, while they may be effective at absorbing certain substances, they may not be effective in preventing other materials passing through. An additional concern with charcoal filters is that, over time, they become saturated – which will further impact their effectiveness. Furthermore, while NIOSH concedes that filter systems can be effective for certain drugs that have no potential to generate vapour, there are currently more than 200 drugs identified on its list of HDs, the majority of which do release vapours.

The Japanese NIOSH and the International Society of Oncology Pharmacy Practitioners (ISOPP) have similarly stated that filter systems can become saturated and have varying efficiencies.[6] Both bodies have concluded that filter-based CSTDs do not meet the definition for what should be considered a closed system.

> "If an automated compounding system does not use CSTDs throughout the process, the same dangers of environmental contamination in manual compounding still exist."

In contrast, barrier systems have several distinguishing advantages which set them apart from filter-based devices, with the most obvious being that closed systems are completely sealed and do not allow dangerous vapours to escape. Being completely closed also includes needle safety, as the needle is not exposed at any point of connection and disconnection – preventing the risk of needlestick injuries.

EQUASHIELD'S KEY INNOVATIONS

When Equashield entered the CSTD market over a decade ago, the company's goal was to streamline and improve the original CSTD design concept, offering superior safety and ease of use for the compounding and administration of HDs.

The Equashield CSTD was developed to cover more routes of exposure than alternative systems. It features an airtight encapsulated syringe barrel and a metal syringe plunger rod which runs through the centre of the syringe chamber to prevent contamination from drug residue on the syringe barrel wall. The plunger rod is also wiped clean before being withdrawn from the barrel at the encapsulation point (Figure 1).

Equashield's key innovation compared with the original CSTD design can be seen in its pressure equalisation mechanism. Rather than using an external balloon to store sterile or contaminated air, Equashield designed the syringe barrel itself to store sterile air before use and to contain hazardous materials within the chamber after the HD has been injected. This air-to-liquid exchange and containment is possible through the two needles placed within the syringe.

To prevent leaks at connection points, Equashield uses a double membrane locking system to prevent liquid droplets escaping between connections. The rubber membranes are located at the end of the CSTD and on the vial adaptor, locking together first and then allowing the needle to pass through

the double layer to reach the drug in the vial. The needle then retracts through the double membrane upon removal and is never exposed throughout the process (Figure 2).

Lastly, just a single motion is required to connect and disconnect any Equashield components, which enables quick transfers with minimal force for significantly improved ease of use by pharmacists and nurses who handle the compounding and administration of HDs.

CRUCIAL FOR SAFE AND EFFICIENT AUTOMATION

As in many other industries, automation has entered the drug compounding space, bringing added benefits such as increased efficiency and patient-specific dose preparation. However, while it has been established that CSTDs are an integral component of manual HD compounding, integration of CSTDs is often overlooked in robotic compounding, as the assumption is that the robot contains any escaped hazards within.

However, just as there would be issues of HD exposure without using a CSTD working in a biological safety cabinet or within an isolator, if an automated compounding system does not use CSTDs throughout the process, the same dangers of environmental contamination in manual compounding still exist.

While traditional compounding robots are a step in the right direction, they are not able to prevent contamination. Residue has been found on intravenous therapy bags, syringes and working surfaces for a number of reasons, such as the syringes being open at certain points in the compounding process. Prior to attaching the needle to the syringe, or before a syringe with a full dose is capped, HDs are fully exposed and able to escape into the environment. Therefore, the prepared doses that are produced by these systems may be saturated in HD residue, presenting considerable risk to healthcare workers in the vicinity.

With this in mind, both manual and automated compounding need to be treated equally when it comes to HD exposure, and CSTDs must be incorporated for both manual and automated processes to minimise environmental contamination.

Figure 2: Equashield's "needle-free" connections.

"While traditional compounding robots are a step in the right direction, they are not able to prevent contamination."

Figure 3: The Equashield PRO fully automated compounding system.

Figure 4: The Equashield PRO vial-grabbing mechanism and verification system.

NEW GENERATION OF SAFE AND EFFICIENT AUTOMATED HD COMPOUNDING

This is why we think the Equashield PRO – the first ever CSTD-enabled fully automated compounding system – is the safest and most efficient HD compounding robot on the market. Unlike earlier systems, which not only fail to prevent contamination but also tend to be slow and inefficient, the PRO was designed to address these shortcomings and reimagine the automation process safely and efficiently (Figure 3).

A major shortcoming in the design of the original compounding robots is the reliance on one robotic arm alone to perform the majority of varied tasks. Equashield PRO was designed to operate more like a factory line, using eight simultaneous workstations to complete the compounding process. Each station is an effective "expert" in its role and performs its task quickly and efficiently, shortening the length of the entire process.

Another significant issue with traditional compounding robots is the "grabbing" mechanism. Because each drug vial is a different size, a robotic arm must spend extensive time identifying the right point to pick up the vial to safely withdraw a dose. This time-consuming process is compounded by the lengthy processes of needle insertion into the vial. When a traditional robot grabs a syringe or drug vial, it does not always pick up the piece in the same spot. As such, it takes more time for the robot to then determine where the needle is, where it needs to be inserted and how deeply to insert it to withdraw the right amount of the drug, without wasting any of the liquid.

Because the PRO uses CSTDs, the syringes and vials all use uniform vial adaptors. This allows the PRO to move much faster. It is able to pick up any size of vial in the same manner, thanks to the vial adaptor. The PRO is also able to verify the drug and dosage with visual verification software and efficiently bring it to the next station (Figure 4).

The PRO can be used for high-throughput, patient-specific dose preparation, as well as batch compounding. Equipped for both tasks, it can store more than 50 syringes and 70 drug vials, allowing it to produce over 60 individual doses per hour. The PRO also offers medication error control by using verification software for each dose and can detect any bubbles in the syringe, which could result in inaccurate doses. The PRO's factory-style line-up is all housed in a machine comparable in size to standard biological safety cabinets.

CONCLUSION

It is vitally important that healthcare facilities use clinical judgement when deciding on which closed system to implement in order to properly protect healthcare workers. After many years of research and education, we are at the stage when CSTDs are becoming a best practice in HD handling, supported by regulation. The future of compounding, however, is still developing as automation technologies begin to take the stage. As automation becomes more prevalent, we must ensure that the protective principles that are currently in place for manual compounding are retained with automation – with CSTDs as a central part of the compounding process.

ABOUT THE COMPANY

Equashield provides manual and automated solutions for compounding and administering hazardous drugs. Its products include Equashield II – its flagship CSTD – and Equashield PRO, the first ever CSTD-enabled automated pharmacy compounding system.

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ABOUT THE AUTHOR

Marino Kriheli, Co-Founder of Equashield, has more than 20 years' experience of industry project management, in both the industrial engineering and medical device manufacturing spaces. In 2010, he co-founded Equashield, a leading provider of a range of manual and automated solutions for the compounding and administration of hazardous drugs. Prior to founding Equashield, he co-founded medical device manufacturer Plastmed, an original equipment manufacturer for Johnson & Johnson.

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THE CHALLENGES OF A CHANGING MARKET & THE BENEFITS OF DEVELOPMENT FLEXIBILITY

In this article, David Fink and Sheila Trgovac, both Vice-Presidents, Strategic Development at Ximedica, describe how adopting a flexible development model in mid-to-late development brings benefits through to commercialisation, especially in the context of a changing market.

Today's pharmaceutical industry faces greater challenges to effective drug delivery, including a growing list of novel drugs like biologics, biosimilars and customised therapeutics, as well as the trend towards self-administered treatment. Additionally, the increasing focus on human-centred engineering in concepting and testing delivery solutions is emerging as a high priority driver in the development continuum. If applied successfully, human factors and usability engineering minimise use risk and increase treatment acceptance throughout the development, regulatory submission, and commercial launch stages.

NAVIGATE THE PATH TO MANUFACTURING

Traditionally, a long-term manufacturing strategy heavily influences much of the mid-to-late stages of the development process as it is planned in tandem with the initial commercial launch goal. A high-volume product model driven by commercial demand forecasts justifies this path but can also lead to a significant investment in capital equipment, automated assembly processes and design validation – increasing time to market and delaying revenues. Mistakes made here can be costly, extending commercialisation and further postponing revenue. But, if ignored, these mistakes may drive down adoption and, more importantly, forfeit an optimal treatment solution for patients.

Looking at new therapeutics, a more modest commercial volume forecast – or one that gradually ramps up – provides an opportunity for a less rigid development approach and better accommodates the evolving drug delivery field. Ximedica leverages a powerful ISO-certified quality management system that meets this flexible development strategy.

Consider the stages of development to put this approach into perspective: detailed design, design for manufacturability, verification and validation, clinical trial design and execution, and preparation for commercial launch. With a flexible model, the intent is to reduce risks further, through cycles of testing and iterating designs (e.g. performance, usability, manufacturing and commercial) and ensuring an optimal treatment solution is in place when the drug comes to market. This includes potential reductions in time to market and/or opportunities for market entry in a managed volume path.

FLEXIBLE DEVELOPMENT MODEL

Ximedica frequently employs a flexible development model in the mid-to-late stages of development. For example, in detailed design work, using rapid prototype mould tooling options frequently answers fundamental performance and assembly

> "Development teams should not lose sight of the benefits to challenging the usability of the product."

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> "Often, difficult trade-offs or compromises are made downstream that could have been easily corrected if the core needs and risks were addressed upstream."

questions. Progressing to more accurate and durable tooling resolves tolerance challenges in system performance, fit and assembly. Traditionally these activities, including initial design for manufacturability, have been the focus of the engineering and design assurance functions. However, development teams should not lose sight of the benefits to challenging the usability of the product.

MANAGE DEVELOPMENT RISK

Performing an early risk assessment with a clear understanding of the intended end user and how they will use the product successfully within the treatment regimen is an imperative for planning a successful regulatory and commercial development path. This foundational usability work, however, is often overlooked or frequently delayed to later stages – making corrections more time consuming and expensive. Often, difficult trade-offs or compromises are made downstream that could have been easily corrected if the core needs and risks were addressed upstream. Unfortunately, these trade-offs may manifest as use errors in validation studies – leading to a major programme setback.

> "Secondary packaging is emerging as a key element in a treatment's successful presentation to end users."

ADD VALUE WITH HUMAN FACTORS AND USABILITY WORK

Ximedica's human factors and usability team works alongside the engineering team, testing the product's usability against the design inputs generated from a solid user-requirements foundation. Frequent formative studies need not be expansive or costly. Such studies can ease uncertainties and build confidence in the end solution if used effectively. These frequent iterations also build confidence with the marketing and commercial teams as they participate in product testing with end users. For example, there may be hand dexterity challenges with the targeted patient population that can be tested and iterated in volume even at this development stage – ensuring a user-friendly solution and increasing product adoption.

After risks have been mitigated, Ximedica routinely uses bridge tooling for gaining confidence in the end product and putting an early, tangible device in the hands of end users and marketing and commercial teams. In particular, this gives marketing and commercial teams an in-depth look at the device to help prepare for product launch. Ximedica has successfully exploited quality bridge tools through validation, late-stage clinical study, regulatory approval and early commercial launch. This path is the stepping stone to developing a final manufacturing solution with shorter and less impactful development times and without excess capital expenditure.

Development of the assembly solution can follow a similar path, where teams commonly start with manual assembly and toggle to semi-automation before turning to full automation. Ximedica frequently uses this manual assembly process through clinical study and concurrently develops a semi-automated process. Performance, assembly and usability risks are addressed and mitigated in this manner.

BENEFIT FROM SECONDARY PACKAGING

Another example of flexibility in the mid-to-late stages of development resides with secondary packaging. Driven by regulatory pressures but, more importantly, human-centred engineering, secondary packaging is emerging as a key element in a treatment's successful presentation to end users. Primary packaging development starts early in the project or is leveraged from prior projects. Secondary packaging is developed concurrently with a develop-test-and-iterate approach for a successful treatment application. With usability in mind, this approach identifies potential use errors early, saving time and capital.

A solid understanding of the intended use flow of the solution can inform packaging and presentation of the entire treatment to users for successful end use. It should not fall entirely on the instructions for use (IFU) to inform the end user how to use the product properly. Appropriate placement of the IFU, sequencing the various device

components according to use flow, geometry and diagrams, and images printed on the package all enhance the secondary packaging and user understanding. Formative studies allow a chance to test the secondary packaging early and often with the intended users. Ximedica uses this path to test frequently, reducing the risk of use errors and significantly contributing to successful regulatory submissions.

The changing pressures of delivering an effective drug device are increasing in demand and require a more flexible development approach. Ximedica views this as an opportunity to evaluate options proactively where a finished manufactured solution is not necessarily the best product launch strategy. This flexible approach, combined with early usability considerations and optimised secondary packaging, will not only reduce regulatory risk and increase product adoption but also reduce time to market, contribute to greater revenue realisation and optimise the efficacy of the final treatment solution.

ABOUT THE AUTHORS

David Fink has more than 40 years of successful new product development experience in the medical device industry ranging from early-phase research, strategy and business development through detailed design to commercial launch. His role at Ximedica is working closely with client companies to align their project needs effectively with Ximedica's extensive development capabilities. Prior experience includes more than 20 years at Covidien/Kendall, most recently serving as Director of Research & Development, managing multiple development groups in the fields of cardiology, radiology, respiratory care and advanced wound care. Mr Fink's experience includes 12 years in antimicrobial device platform development.

Sheila Trgovac partners with clients to translate their strategic objectives into meaningful development of innovative and impactful healthcare products. She draws on her extensive experience in product development and marketing to help clients bring new products to market faster, more efficiently and with greater market potential and impact at every stage of the development process. She has 12 years' experience in medical device, pharmaceutical, business management, account management, marketing and, most recently, drug delivery device development. She has a BSc in Bioengineering from Penn State University (PA, USA) and a Masters in Management from Harvard University (MA, USA).

ABOUT THE COMPANY

Ximedica is a full-service design and development firm focused on medical devices, combination products and consumer health. Its drug delivery expertise includes topical, transmucosal, inhalation and injection. It is ISO 13485:2016 certified and US FDA registered.

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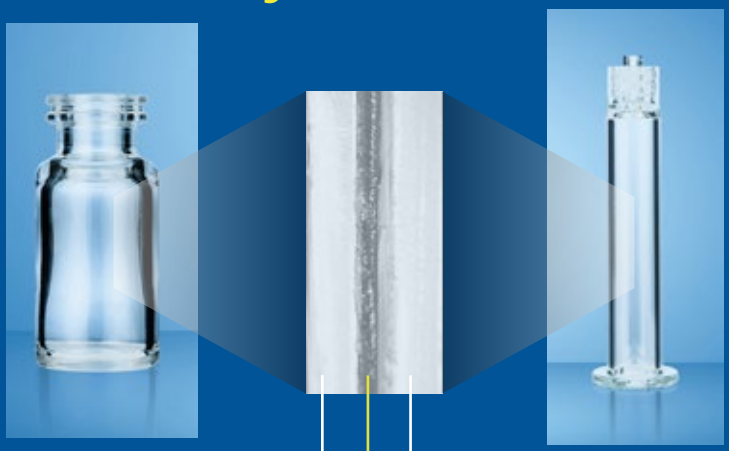
OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



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- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Regenerative Medicine

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OXYCAPT™ MULTILAYER PLASTIC VIAL AND SYRINGE

In this article Shota Arakawa, Assistant Research Manager, and Tomohiro Suzuki, Associate General Manager, both of Mitsubishi Gas Chemical, discuss the benefits of the OXYCAPT™ multilayer plastic vial and syringe for the rapidly growing field of biologics and regenerative medicines.

There are some problems with existing glass and plastic vials and syringes. For example, glass suffers from breakage and delamination, whereas plastic lacks sufficient oxygen and ultraviolet light (UV) barrier properties. Especially with glass, the US FDA has pointed out these problems, which have led to more than 50 recall incidents. To address these problems with glass, several suppliers have launched alternative plastic vials and syringes – but in some cases the inadequate oxygen barrier has meant they have failed to meet customer demands. Given this situation, Mitsubishi Gas Chemical (MGC) has developed multilayer plastic vials and syringes with an excellent oxygen barrier, a high UV barrier, very low extractables and high breakage resistance, among other features.

The OXYCAPT™ vial and syringe consists of three layers (Figure 1). The inner and outer layer are made of cyclic olefin polymer (COP) – the most reliable polymer in the pharma industry. The middle layer is made of a novel polyester developed by MGC. The characteristics of COP give OXYCAPT™ a high water-vapour barrier, very low extractables, high pH stability, low protein adsorption, high breakage resistance, etc. The new polyester plays a role as an oxygen and UV barrier to address the weaknesses of COP alone.

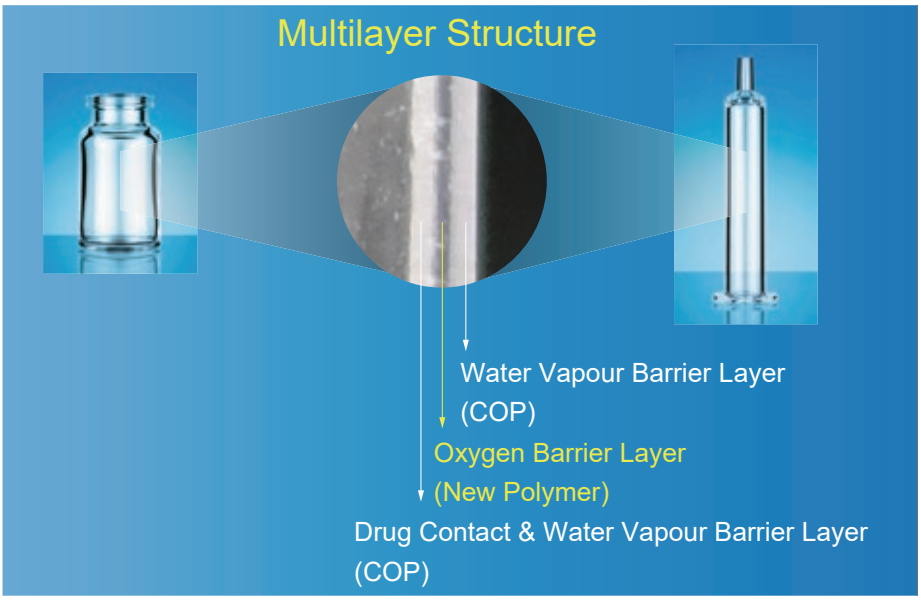

Figure 1: The multilayer structure of OXYCAPT.

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"The oxygen barrier of the OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial."

EXCELLENT OXYGEN BARRIER

There are two types of OXYCAPT™ multilayer plastic vial and syringe – OXYCAPT-A and OXYCAPT-P. OXYCAPT-A has achieved a glass-like oxygen barrier. According to some internal studies, OXYCAPT-A can keep a lower oxygen concentration in headspace than type 1 glass, thanks to its oxygen-absorbing function. Although there is no oxygen-absorbing function in OXYCAPT-P, it has also achieved an excellent oxygen barrier. For example, the oxygen barrier of the OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial (Figure 2). OXYCAPT-A is particularly suitable for oxygen-sensitive drugs and OXYCAPT-P is recommended for any drug.

OXYCAPT™ also has UV barrier properties. For example, although about 70% of UV light of 300 nm transmits through glass and COP, only 1.7% UV light transmits through OXYCAPT™ (Figure 3). This feature also contributes to the stability of biologics.

When it comes to its water vapour barrier, OXYCAPT™ cannot reach the performance of glass. However, it is similar to COP which has been used for injectable drugs for a long time, and easily meets the requirements of a water vapour barrier stipulated in the ICH guideline.

LOW LEVELS OF EXTRACTABLES

OXYCAPT™ generates extremely low levels of extractables. For example, in one study that measured 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 control, no impurities were detected in any of the OXYCAPT™ containers. A second study was conducted to measure inorganic extractables from

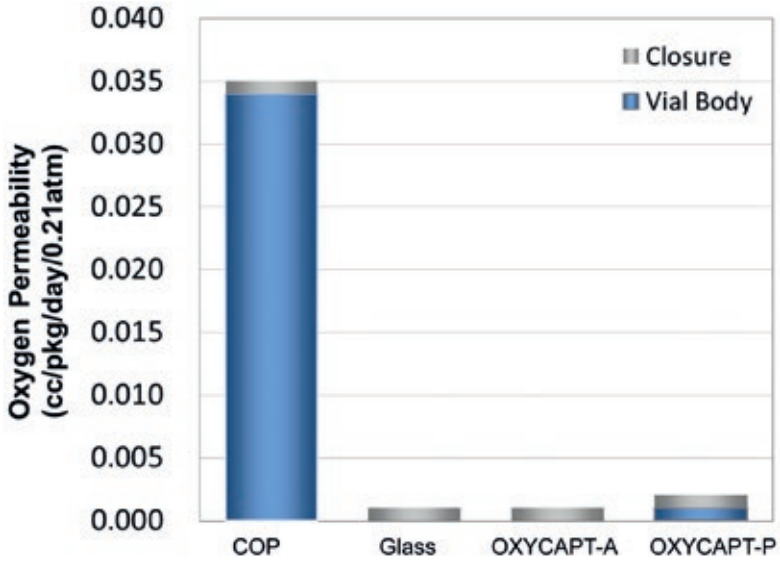

Figure 2: Oxygen permeability of the types of OXYCAPT.

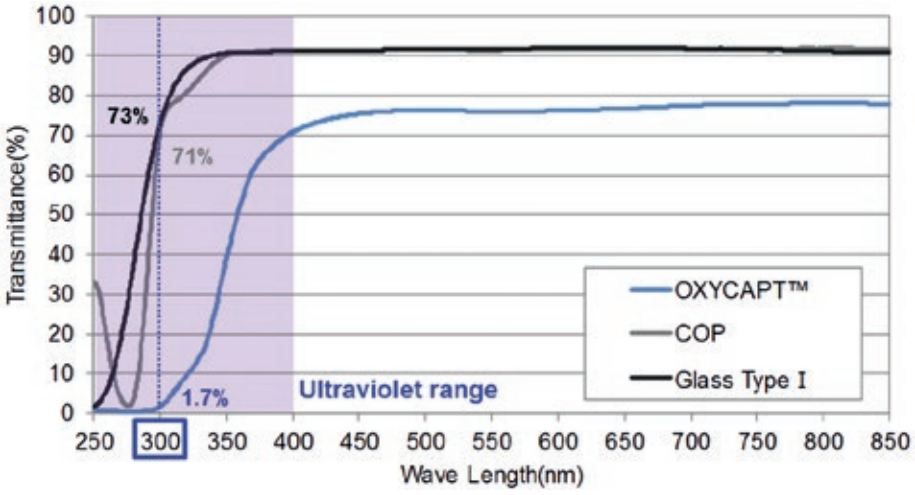

Figure 3: Ultraviolet light barrier of OXYCAPT™.

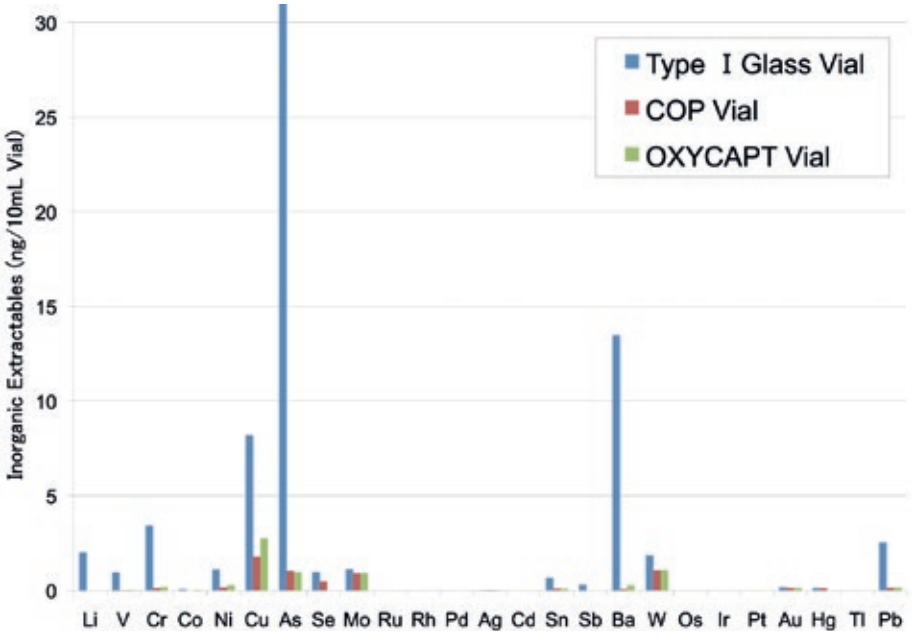

Figure 4: Graph of inorganic extractables.

OXYCAPT™. The level of extractables was similar to that from COP – which is well known as an extremely pure polymer – and less than that of type 1 glass (Figure 4).

The OXYCAPT™ syringe consists of tip-cap, barrel, PTFE-laminated stopper and plunger rod (Figure 5). Although the stoppers are coated with a very small amount of silicone oil, none is baked on the barrel. According to our internal studies using antibodies, we have found this feature noticeably reduces instances of protein aggregation compared with existing type 1 glass syringes.

The OXYCAPT™ vial and syringe are produced by co-injection moulding technology. Although this technology has been applied to beverage bottles for many years, MGC is the first company to succeed in developing multilayer plastic syringes. We have also developed inspection methods for the oxygen barrier layer. All the containers are 100% inspected by state-of-the-art machinery.

FREE SAMPLES FOR INITIAL TESTING

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 and tub formats (Figure 6). The nest and tub are primarily sterilised by gamma ray. There are 2 mL, 6 mL, 10 mL and 20 mL variants for vials, and 1 mL long and 2.25 mL variants for syringes (Table 1). We are willing to provide samples for initial testing free of charge.

> "We have recently decided to invest in a facility for the staked-needle syringe – and the necessary equipment is due to be installed this year."

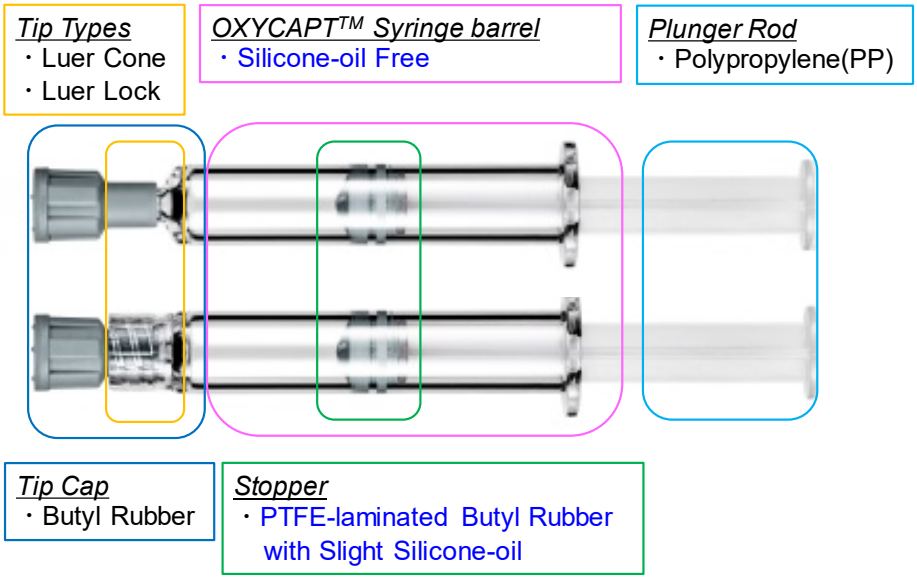

Figure 5: Components of the OXYCAPT syringe.

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

The target therapeutic application for OXYCAPT™ is biologics. As the ICH guideline "Stability of Biotechnological/ Biological Products Q5C" mentions, oxidation is one of the causes of protein instability. Some features of OXYCAPT™ – such as its high oxygen and UV barrier properties – contribute to the stability of biologics.

In addition, we believe OXYCAPT™ can be applied to epinephrine, as it is well known as an oxygen-sensitive drug. The breakage that can occur with glass syringes is not suitable for emergency drugs, so some suppliers have tried to develop new pen injectors made of plastic. Also, customers have started evaluating the OXYCAPT™ vial for their gene and cell therapy. Our ready-to-use vial sterilised by gamma is ideal for protein-based drugs.

Some customers have asked us to develop staked-needle multilayer plastic syringes, so we started tackling this development a few years ago. We have

Figure 6: The nest and tub.

Type	Volume	ISO	Parts	Option
Vial	2 mL	ISO 8362-1	Vial	Bulk or RTU
	6 mL	ISO 8362-1	Vial	Bulk or RTU
	10 mL	ISO 8362-1	Vial	Bulk or RTU
	20 mL	ISO 8362-1	Vial	Bulk or RTU
Syringe	1 mL Long	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU
	2.25 mL	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU

Table 1: Product portfolio.

Figure 7: Staked-needle syringe (under development).

Samples	Numbers of Breakage at 1st Testing (for whole parts)	Numbers of Breakage at 2nd Testing (for flange part)	Numbers of Breakage at 3rd Testing (For lure part)	Numbers of Syringes without Breakage through 3 Testing
OXYCAPT™	0/20	0/20	0/20	20/20
Glass	12/20	10/20 (From 1st testing: 5/8) (New: 5/12)	2/20 (From 1st testing: 1/3) (From 2nd testing: 1/7) (New: 0/10)	2/20

Table 2: Drop testing of syringe.

ABOUT THE AUTHORS

Shota Arakawa is a researcher in the advanced business development division of Mitsubishi Gas Chemical. He gained a Diploma in Science in 2007 and a Master Degree of Science in 2009 from Osaka University (Japan). Since April 2009 he has been in charge of macromolecular science, especially the synthesis of polymers and material development, for MGC. In 2012 he joined the development team for OXYCAPT.

Tomohiro Suzuki joined Mitsubishi Gas Chemical in 1998. He worked in the oxygen absorbers division until 2011, and was then transferred to the advanced business development division in 2012 to join the OXYCAPT development team. Since then, he has been in charge of the marketing of the OXYCAPT plastic vial and syringe.

recently decided to invest in a facility for the staked-needle syringe (Figure 7) – and the necessary equipment is due to be installed this year. The OXYCAPT™ syringe with a needle has some special features:

- tungsten-free
- glue/adhesive-free
- available in several gauges and needle lengths
- ultrasonic welding of syringe barrel, adapter and needle
- needle conforms to ISO 7864
- syringe conforms to ISO 7886-1.

BENEFITS FOR BIOLOGICS

We would also like to share the latest data from our drop testing of syringes. In a study based on ISO 11608-1:2014 (requirements and testing methods for needle-based injection systems), 20 gamma-sterilised OXYCAPT™ 1 mL long syringes and existing type 1 glass syringes were dropped from a height of one metre three times (horizontally once and vertically twice) on to a steel plate. Although 90% of glass syringes were broken, no breakage was observed among the OXYCAPT™ syringes (Table 2).

CONCLUSION

In conclusion, OXYCAPT™ has been developed to solve some of the problems facing the pharmaceutical industry in creating syringes and vials suitable for the delivery of biologics, including via wearable devices. In addition to the special features of COP, such as a high water-vapour barrier, high breakage resistance, very low extractables and low protein adsorption, OXYCAPT™ can also provide a high oxygen and UV barrier.

We believe OXYCAPT™ brings numerous considerable benefits to the rapidly growing field of biologics and regenerative medicines.

ABOUT THE COMPANY

Mitsubishi Gas Chemical (MGC) operates in a wide range of fields, from basic chemicals to fine chemicals and functional materials. MGC established its advanced business development division in 2012 as a centre to create new businesses, and developed the OXYCAPT™ plastic vial and syringe as an alternative to glass containers.

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2020/21 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
April 2020	Pulmonary & Nasal Drug Delivery	Mar 12, 2020
May 2020	Injectable Drug Delivery: Formulations & Devices	Apr 2, 2020
June 2020	Connecting Drug Delivery	May 7, 2020
July 2020	Novel Oral Delivery Systems	Jun 4, 2020
August 2020	Industrialising Drug Delivery	Jul 2, 2020
September 2020	Wearable Injectors	Aug 6, 2020
October 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
November 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
December 2020	Connecting Drug Delivery	Nov 5, 2020
January 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
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March 2021	Ophthalmic Drug Delivery	Feb 4, 2021

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PREFILLED SAFETY SYRINGE MARKET THRIVES AMID SELF-ADMINISTRATION TREND

In this article, George I'ons, Head of Product Strategy and Insights at Owen Mumford Pharmaceutical Services, looks at how the growing trend of patient self-administration is driving demand for prefilled safety syringes.

It is well understood that many populations are ageing – for example, by 2030, it is anticipated that there will be more than 21,000 centenarians in the UK, with one in five people aged 65 and over.[1] As life expectancy rises, the likelihood of time spent in poor health with multiple chronic health conditions also increases.

"Needlestick injuries still present a risk to users and their carers in both clinical and non-clinical settings."

At the same time, the gap between the number of clinically trained staff needed and those available is projected to reach almost 250,000 by 2030,[2] leaving the existing workforce significantly overstretched. Emerging from the acknowledgment that constraints placed on hospitals by staff shortages, stretched budgets and an ageing population could impact the healthcare system as a whole, the growing trend of home-based treatment as well as patient self-administration is also evidence of a transitioning healthcare landscape.

In the past few years, a wave of biological therapies for patients with chronic conditions has entered the market. These therapies are often the ones to provide the best outcomes for patients suffering from chronic conditions such as neurological, cardiovascular and autoimmune diseases. Their administration, typically via subcutaneous injection, makes them a perfect candidate for self-administration using prefilled syringes.

"Medical device manufacturers are key to shaping the future of products for self-administration of injections and should ensure designs have integrated robust needlestick-prevention features."

PATIENT QUALITY OF LIFE

Similarly, the frequency of injections required to treat these chronic conditions further increases their suitability for a home environment rather than obliging patients to visit a clinic for every single injection. Home-based treatment can greatly improve patient quality of life and provide support to patients who live far from a hospital or who are less able to travel.[3] Providing patients with the tools to self-administer their medication also hands them some power and responsibility to manage their own disease and is effective in helping to reduce the burden on hospitals.

Outsourcing low-risk medical procedures for chronic patients could alleviate some of the pressure on hospitals. However, needlestick injuries still present a risk to users and their carers in both clinical and non-clinical settings. In this sense, the shift of drug delivery towards home environments is a useful reminder that best practices around the safe usage of sharps, including needles, should not only be extended beyond hospital walls but also reinforced in the hospital setting.

Crucially, medical device manufacturers are key to shaping the future of products for self-administration of injections and should ensure designs have integrated robust needlestick-prevention features.

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The activation and deployment of any needle-shielding feature should factor in the capabilities of all patients and should ideally be an automatic part of the normal use of the device.

HIGH RATES OF INJURY

The implementation of the EU Directive 2010/52/EU more than six years ago for the prevention of sharps injuries has had a positive outcome – yet needlestick injuries continue to occur, including among trained medical staff. A new survey suggests that 94% of practising UK surgeons have experienced a needlestick injury or have witnessed a colleague experience one.[4] With such high rates of injury, even within a formal healthcare setting, some of the solution now rests with manufacturers to engineer devices that are not only better suited to self-administering patients but also reduce risks of needlesticks for healthcare practitioners.

Beyond hospital walls, it is estimated that – across all EU economies – the compliance level for safety-engineered injection devices falls from 70% to 60% when moving from clinical to non-traditional settings.[5] Needless to say, non-compliance is linked to a higher risk of needlestick injuries occurring and of patients, carers and residential non-users contracting more than 20 possible blood-borne infections. Often unaware of the risks presented by a potentially contaminated device, family lack of awareness makes them highly unlikely to report any exposure or seek treatment or advice – with an estimated 50% of sharps injuries going completely unreported.[6]

Unsurprisingly, this backdrop of increasing self-administration has driven a growing need for prefilled safety syringes (Figure 1). Integrating safer features into the design of drug delivery devices may reportedly reduce needlestick injuries and contaminations by up to 80%.[7] More concretely, while devices with hollow-bore needles or syringes which retain an exposed needle after use present a heightened risk, retracting and needle-shielding mechanisms are much safer. It therefore comes as no surprise that global spending on safety syringes reached US$772 million (£594 million) in 2018 and is expected to grow by a compound annual growth rate of 8.1%, reaching $1.137 billion by 2023.[8]

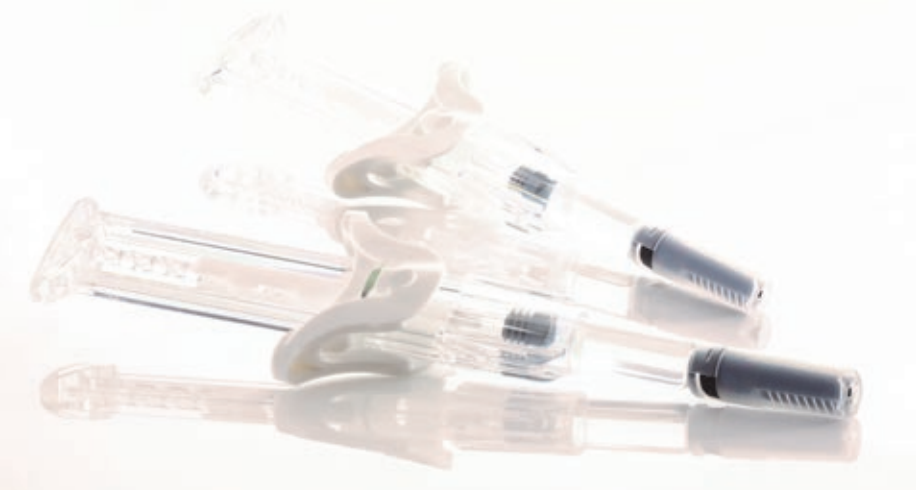

Figure 1: The growing need for prefilled safety syringes is driven by the increasing number of injectable products designed for self-administration.

LEVEL OF INDEPENDENCE

More than reducing injuries, prefilled safety syringes must be designed and engineered factoring in the dexterity – or lack thereof – of the patients they may treat. The growing requirement for human factors testing, as well as the need for devices to be intuitive and easy to use, require minimal force to activate and include passive safety mechanisms to reduce additional activation steps, are further influencing the market for prefilled safety syringes.

In conclusion, enabling a wide range of patients to administer their medication safely without professional assistance, safety prefilled syringes are key to unlocking a certain level of independence for patients, whilst also minimising the safety risks typically present during unsupervised administration.

ABOUT THE COMPANY

Owen Mumford is a healthcare company and device manufacturer that commercialises pioneering medical products for its own brand and custom device solutions for the world's major pharma and diagnostic companies. Owen Mumford's goal is to enhance access to diagnostics, encourage adherence to treatment and reduce healthcare costs.

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ABOUT THE AUTHOR

George I'ons is Head of Product Strategy and Insights, having worked at Owen Mumford since 2006. His current focus is on deciphering the rapidly changing pharma and biotech sectors in relation to their needs for combination products. In his previous roles in business development, he worked closely alongside the research and development team to develop devices for a variety of global pharma and diagnostic clients. Prior to Owen Mumford, Mr I'ons worked for Abbott in marketing roles in Germany, focusing on its diabetes business.

CHOOSING THE RIGHT LABEL MATERIAL FOR PREFILLED SYRINGES

In this article, Jos van Noort, Principal Scientist, Global Pharma Applications, Avery Dennison Materials, outlines some of the key factors that must be taken into consideration when selecting a label for prefillable syringes.

The preferred marking technology for prefilled syringes and autoinjector cartridges is self-adhesive labels, which offer the versatility that the pharmaceutical industry is looking for. As is the case when selecting a packaging solution, many influencing factors and tests need to be conducted in order to choose the right label material and to minimise the risk of a failed labelling solution. Typical label material is built from three layers: facestock, adhesive and release liner which is the label carrier (see Figure 1).

Four key application parameters must be taken into account when choosing a label material for an injectable device:

- Diameter of the primary packaging: the typical diameter of a prefilled syringe is between 7 and 20 mm (0.5 mL).
- Dispensing speed: the products are usually packed on packaging lines at labelling speeds up to 600 pcs / min.
- Temperature across the supply chain: medications are sensitive to temperature and some have to be kept in a cold environment (for example, 2-8°C, or below -20°C).
- Patient safety: syringes and injectors contain liquid medicine, so they must resist migration of any label components.

SMALL CONTAINER DIAMETERS

Prefilled syringes are typically small containers with diameters down to 7 mm. This means that they have higher curvature. Thus, labelling requires a label facestock that is conformable enough for application on a small-diameter syringe, but also stiff enough to facilitate high-speed labelling.

> "Labelling requires a label facestock that is conformable enough for application on a small-diameter syringe, but also stiff enough to facilitate high-speed labelling."

The choice of label adhesive is also critical, since it must have a high resistance to shearing away from the surface, so that lifting of label edges over time is avoided. In the pressure-sensitive materials industry this resistance is known as mandrel hold, and is specified by FINAT (European association for the self-adhesive label industry) test method 24 (FTM 24). In the label industry, general testing methods are established by FINAT. These methods measure label material performance, however, it is important to note that, whilst often useful, they are not always relevant in the pharmaceutical industry because of its very specific application requirements.

During the FTM 24 test, sample label is applied onto three-quarters of the circumference of the test rod (diameters 7 mm and 15 mm). Samples are then inspected after seven days and the edge

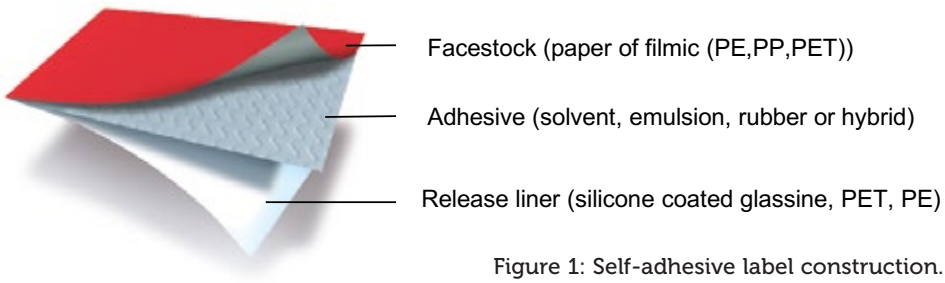

Figure 1: Self-adhesive label construction.

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lift is measured. To meet the needs of the pharmaceutical industry, it is recommended to additionally inspect the samples after 14 and 30 days.

The type of adhesive chosen should offer good adherence to the substrate and a well balanced internal strength. The adhesion to the substrate depends also on its surface energy – high-surface-energy substrates like metal or glass have strong molecular attraction, so the mandrel hold on this type of substrate tends to be better. On the other hand, low-surface-energy substrates like high-density polyethylene (HDPE) or polypropylene (PP) have weaker attractive forces meaning weaker mandrel hold. Figure 2 summarises adhesive performance according to type.

DISPENSING SPEED

Label materials intended for use on high-speed packaging lines (faster than 150 pcs/min) must be robust and have high initial tack. Loop tack test (FTM 9) is used to assess the adhesive initial tack (see Figures 3 and 4).

A release liner made from PET is advised, since PET has a significantly higher internal strength than paper or glassine liners to withstand the application speed. Thinner PET grades (>30 µm) are suitable for most applications.

Another important consideration is choosing an adhesive with high initial tack. Labels are released from the liner and onto the substrate at very high speeds, with an application time less than a quarter of a second. It is critical that the label material's adhesive has a high initial tack to facilitate good pick-up of the label from the liner to the syringe. However, ensuring a balance between high tack and high adhesion is also important to reduce the potential for flagging of the label over time (Figure 5). It is by balancing these adhesive characteristics in combination with the face material that a construction is made suitable for an application.

Additionally, when using UV detection systems to confirm the label presence, the label has to be luminescent. Label materials with luminescent topcoat are a good solution thanks to the stability and durability of the luminescence they provide.

Finally, because of the variety of dispensing machines and application mechanisms, labelling materials must be tested in real-world circumstances in order to confirm the outcome of laboratory testing.

		Acrylic Emulsion	Acrylic Solvent	Solvent Rubber
Initial tack/Adhesion	HDPE/LDPE	•	•	•••
	PP	•	•	•••
	Glass	••	•••	•••
	PET	••	•••	•••
Small Diameter* (Mandrel)	<15 mm	••	•••	•••
Sterilisation Resistance	Steam	••	•••	••
	ETO	••	•••	••
	Radiation	••	•••	••
Chemical Resistance		••	•••	•
Heat Resistance		•••	•••	••
Humidity Resistance		•	•••	•••
Clarity	Clear-on-Clear	•••	•••	•
High-speed Converting/ Dispensing		•••	•••	••

Good • Better •• Best •••

* Depend on face material and type of substrate (Glass, plastic)

Figure 2: Type of adhesive and performance matrix.

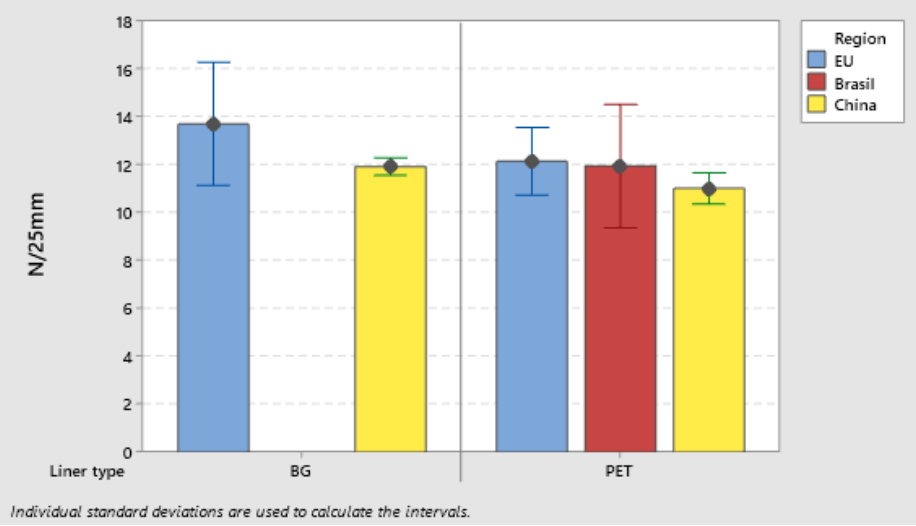

Figure 3: Loop tack adhesion on glass S692NP low-migration adhesive.

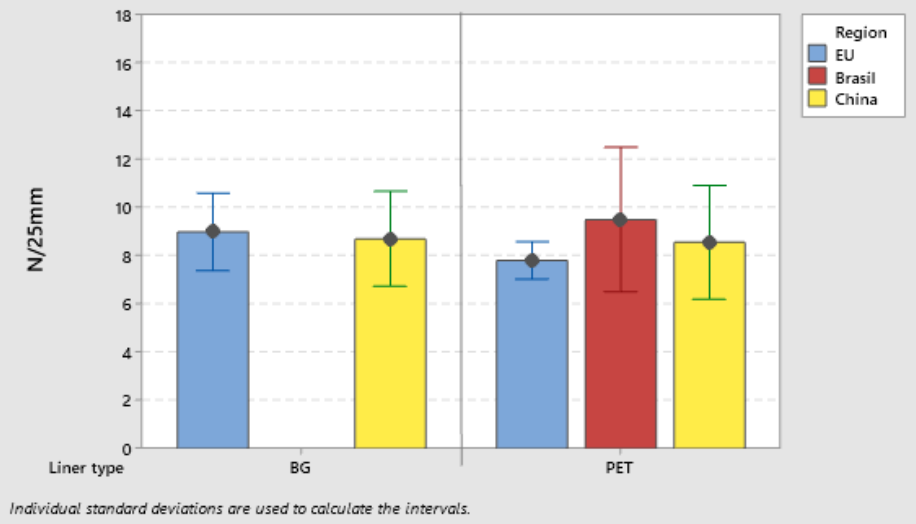

Figure 4: Loop tack adhesion on PP S692NP low-migration adhesive.

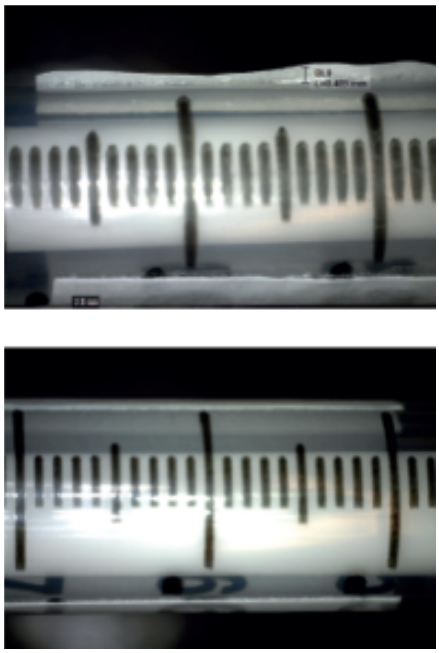

Figure 5: Example of flagging (top) compared with proper mandrel hold (bottom).

TEMPERATURE ACROSS THE SUPPLY CHAIN

As well as dispensing speed and container size, temperature and humidity must also be considered. The conditions experienced by a product across the supply chain influences label material selection and performance.

With more advanced medicines such as biologics, there is a more complex supply chain. Prefilled syringes can be exposed to extremely high temperatures and humidity during autoclave sterilisation, or to low temperatures when the finished product is stored or transported. This creates another challenge for label materials, which must stay on the substrate with unchanged performance and appearance.

Changing temperature also causes condensation on the surface of syringes and label substrate. Extended exposure to moisture might cause adhesive whitening and label creasing if the wrong label material is used. With these parameters in mind, it is crucial to distinguish between application temperature and service temperature when choosing the adhesive. Application temperature is the temperature when the label is applied, and service temperature is a range within which the adhesive will function once the label has been applied.

FTM 13 assesses the ability of a pressure-sensitive material to adhere under low temperature conditions. Labels are applied to various substrates (polyethylene terephthalate (PET), glass, polyethylene (PE), stainless steel) and stored under chill (4°C) and deep freeze (-25°C) conditions. After one hour, and at seven days, the removability of the labels is accessed. It is recommended to also test cyclic olefin copolymer (COC) and cyclo-olefin polymer (COP) substrates and extend the testing to 14 and 30 days. Additionally, high temperature resistance is tested in steam sterilisation at 121°C for 20 minutes.

PATIENT SAFETY

Surpassing all technical requirements is patient safety and brand protection. Prefilled syringes made of plastics like COC or COP can generate benefits such as convenience and possible cost improvements, when compared with traditional glass syringes. Plastic syringes containing liquid medicine can be exposed to contamination from label adhesives, inks, coatings and varnishes - any of which may migrate through the container if specified incorrectly.

To prevent potential contamination of the medicine inside containers, certified labelling materials must be used, alongside an adequate printing technique from the label material converter. Migration studies and testing of specific label materials can be conducted by independent testing institutes on request.

The migration potential of the label material should be assessed by its manufacturer, in co-operation with an independent testing institute. Dedicated pharmaceutical adhesives must have a complete set of certificates (such as migration and toxicology. among others).

Brand owners also need to consider consumer and brand protection against counterfeit products. These can enter their supply chain and ultimately reach the consumer. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) estimates that 15% of medicines worldwide may be fake. Although, protection from counterfeit medicines is a complex topic, which requires multiple prevention systems and solutions to protect the value chain, label materials can be a useful element. One solution is luminescent labelling, revealing a specific colour or pattern under UV light. Label materials with luminescent topcoating can have different colours, and these can be difficult to copy. They can also have a customised pattern with a brand logo or medicine name, which is visible only under UV light.

> "Although, protection from counterfeit medicines is a complex topic, which requires multiple prevention systems and solutions to protect the value chain, label materials can be a useful element."

CONCLUSION

We have highlighted four main factors to address when choosing a label material for prefilled syringes: diameter, dispensing, temperature, and patient safety. All four factors are important considerations when choosing a label material for a syringe. Of course, there can be other considerations specific to a product and/or value stream. These may include exposure to certain chemicals or sanitisers, the type of secondary packaging used, the type of printing technology, and the types of inks used.

In order to ensure that an optimal label solution is selected, it is also desirable to involve the label material manufacturer early on in the development of drug packaging. This allows the design and administration of a specific testing regime that aims to mimic the product's real-life application and service environment. The result is a reduced risk of selecting an inappropriate label solution, and a shorter trial time at lower cost.

ABOUT THE COMPANY

Avery Dennison's line of dedicated pharmaceutical labelling materials has been developed to meet the highest requirements of the sector, which presents many packaging and labelling challenges; these include security, container size, harsh environments, and stringent regulations. Avery Dennison's dedicated pharmaceutical portfolio comes with 12 months change notification, change management and compliance documentation. Furthermore, Avery Dennison has developed specific testing methods to mimic real-life pharma applications and service environments, to ensure that the right labelling solution is selected for a specific application. These tests are available to pharma brand owners together with the option of customised analytical tests in our central laboratory.

EU MDR: ANCILLARY DELIVERY DEVICES FACE EQUAL SCRUTINY TO STANDALONE MEDICAL DEVICES

In this article, Elizma Parry, Director, Global Clinical Practice at Maetrics, offers her expertise and practical guidance to businesses hoping to achieve a CE mark for a medical device. With new regulations being implemented this year, and little time to spare before the point of no return, pharmaceutical manufacturers must quickly embark on the first of a series of preparatory steps if they hope to achieve smooth and timely compliance.

Every medical device manufacturer placing products on the market in the EU knows the huge bearing the EU's Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR) are having on the EU regulatory environment. Less obvious, though, is the direct impact these regulatory changes may have on pharma companies and their products.

Although the new regulations mainly concern medical device manufacturers, pharma companies should not assume exemption from the tightening of clinical oversight sweeping across the EU. If they are manufacturing combination products or companion diagnostics, pharma businesses will need to get to grips with the exact requirements before the MDR and IVDR come into effect in May 2020 and May 2022, respectively.

In the EU, combination products are regulated as either medicinal products or medical devices, depending on which component has the ancillary function. Insulin injector pens and metered dose inhalers, for example, contain a medical device component which serves as the delivery system of the integral drug component – making its role ancillary to the drug. This kind of combination product is presently regulated as a medicinal product under the EU Medicinal Product Directive (MPD) 2001/83/EC, thereby focusing scrutiny mainly on the medicinal formulation of the product.

> "Not all products composed of both a medicinal and device element will constitute a combination product."

> "The MDR will leave no medical device unscrutinised, regardless of whether its function is central or ancillary to the product."

NO MEDICAL DEVICE UNSCRUTINISED

Addressing the regulatory gap that existed for combination products under the previous directives, the MDR will leave no medical device unscrutinised, regardless of whether its function is central or ancillary to the product. From May 2020 onwards, combination products will need to meet the requirements as set out in Article 117 of the MDR, which amends Annex I of the MPD.

This reshuffling emanates from the growing complexity of combination products and the need to regulate ancillary device components with the same scrutiny as standalone medical devices. Crucially, not all products composed of both a medicinal and device element will constitute a combination product – only those where the manufacturer intends for it to be used together to perform effectively.

As such, the MDR will particularly impact pharma companies manufacturing combination products with ancillary medical devices, for this will represent a larger adjustment than for those manufacturing products already regulated as medical devices. Pharma companies unaccustomed to this might lack the data required to submit a clinical evaluation report and may

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need to take on the costly and time-consuming task of gathering additional clinical data for the device component. Such businesses are advised to invest in resources first time round to facilitate the continuous updating of clinical data in the future.

STRUGGLE TO KEEP UP WITH DEMAND

Similarly, combination product manufacturers might be reaching out to a medical device designated notified body for the first time. With the EU presently being short on the notified bodies required to review technical documentation, it is probable those in operation will struggle to keep up with demand. Today, there are only nine designated notified bodies under the MDR, so delays in the approval process are very likely. With the MDR deadline less than six months away, manufacturers are strongly urged to submit their documentation as soon as possible to make the cut-off date.

Companion diagnostics will equally be affected by the changing regulatory landscape – falling under the remit of IVDR. Within a newly established IVDR risk-based classification, companion diagnostics will be classified under the second-highest risk category, Class C, and will therefore be subject to a high level of clinical oversight, particularly for pharma companies developing their own companion diagnostics. Given the co-development of the IVD device with its associated medicinal product, the IVD notified body will also need to liaise with a medicinal Competent Authority (CA).

> "Companion diagnostics will equally be affected by the changing regulatory landscape – falling under the remit of IVDR."

The IVDR world is also more seriously affected by the shortage of notified bodies, with only three designated organisations currently operating. Pharma companies are therefore not only queuing to receive certification from a notified body but also for these notified bodies to be designated for companion diagnostic conformity assessments under the IVDR. In this sense, manufacturers are advised to go a step further than simply submitting their documentation on time – they may actually want to approach organisations awaiting designation from their national CA for their specific product area beforehand. Doing so will help ensure businesses secure a place at the front of the queue.

ALLOW ADDITIONAL TIME

Under the MDR and IVDR, tighter regulation of combination products and companion diagnostics will be enforced, and pharma companies will have to abide by the same requirements as medical device manufacturers with respect to the device component. But they might lack the experience that medical device companies have in collating the necessary documentation and liaising with a notified body – and should therefore allow additional time to complete these stages.

Only businesses prepared to face the negative outcomes of a missed deadline – potential removal of their products from EU markets and devastating reputational losses – should disregard the crucial importance of preparing for compliance with the new requirements.

ABOUT THE COMPANY

Founded in 1984, Maetrics is a global life sciences consulting firm focused exclusively on regulatory, quality and compliance solutions for medical device, diagnostic, pharma and biotechnology companies.

ABOUT THE AUTHOR

Elizma Parry brings more than 25 years of experience to the Maetrics team and provides clients with expert counsel in the clinical practice environment. A highly qualified industry professional, she is a proven leader with a strong track record of clinical safety, regulatory and quality management experience.

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