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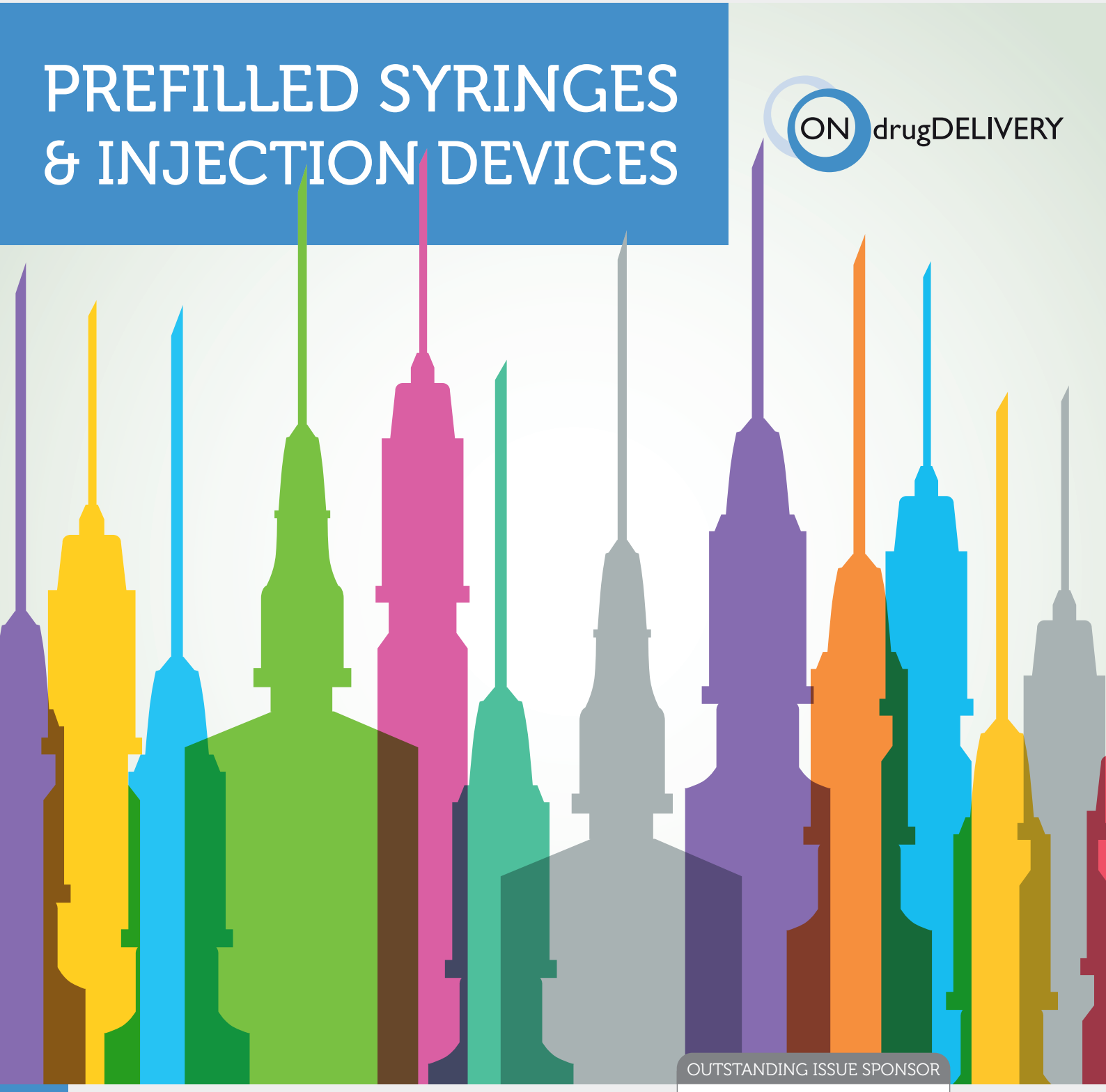

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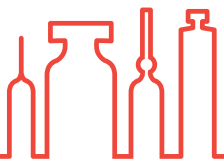

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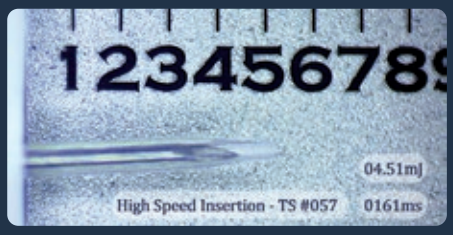

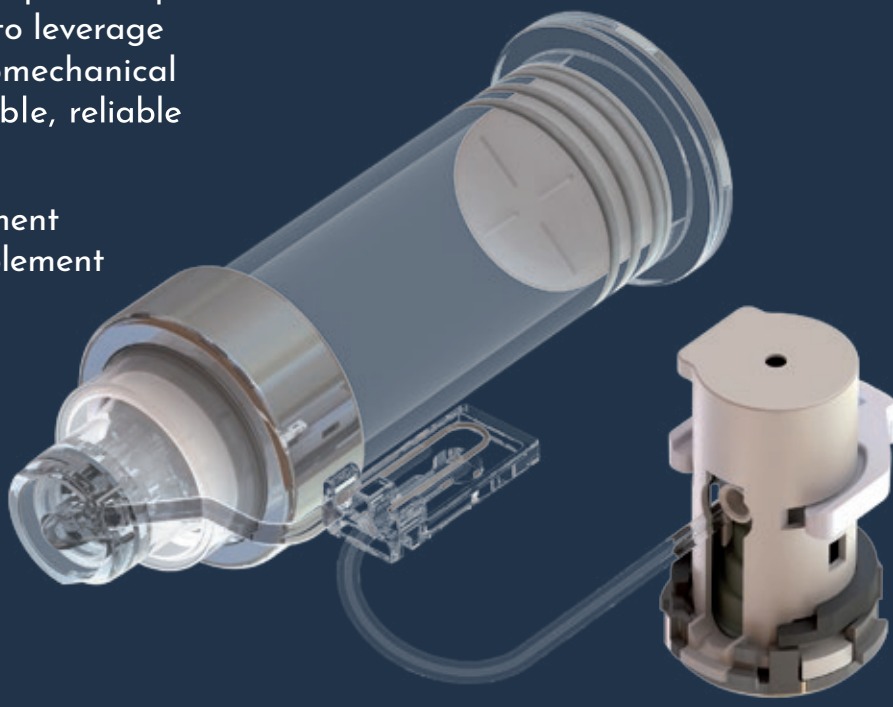

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HOW LONG CAN YOU HOLD THE DEVICE AGAINST THE SKIN? INSIGHTS FROM AN EMPIRICAL STUDY USING HAND-HELD AUTOINJECTORS

In this article, Andreas Schneider, PhD, Innovation and Business Development Director at Ypsomed, summarises recent empirical work investigating the ability of users of hand-held devices to complete longer injection times effectively. The study provides insights into the effects of injection duration on the force exerted by the user to hold the device against the injection site. It also highlights whether and how the characteristics of patient groups affect their ability to withstand longer injection duration, and considers the upper feasible limit of injection duration.

QUESTIONING THE FEASIBLE UPPER LIMIT OF INJECTION DURATION FOR AUTOINJECTORS

The drug delivery industry has long debated over the subcutaneous delivery of single high-dose volumes with handheld prefilled autoinjectors. Technological advances, combined with a better understanding of the pharmacokinetics and tolerability of single large-volume doses, have led to a reconsideration of the subcutaneous administration of 1 mL within 10 seconds as the upper feasible limit for autoinjectors.[1] In fact, the approval of two recent landmark products provides evidence that regulatory agencies support longer, high-volume injections to reduce injection frequency further, minimise patients' day-to-day lifestyle disruptions and improve therapy outcomes.

First, Teva Pharmaceutical Industries has received US FDA approval for a high-volume prefilled autoinjector device for its migraine-treatment drug AJOVY® (fremanezumab-vfrm). The two-step autoinjector, based on the YpsoMate 2.25 mL platform, enables the safe and effective administration of a single dose of 1.5 mL (225 mg). Figure 1 illustrates the single-use prefilled high-volume AJOVY® autoinjector.

> "Technological advances... have led to a reconsideration of the subcutaneous administration of 1 mL within 10 seconds as the upper feasible limit for autoinjectors."

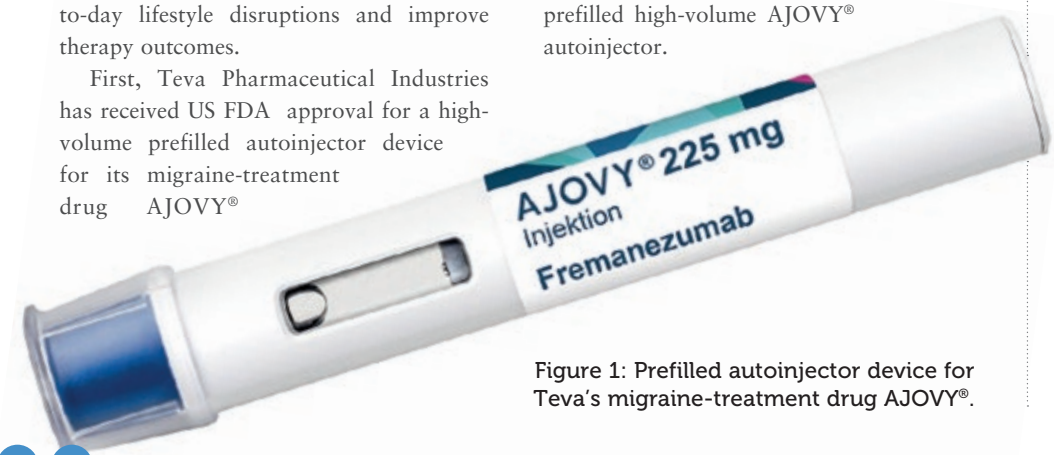

Figure 1: Prefilled autoinjector device for Teva's migraine-treatment drug AJOVY®.

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"It is of utmost importance to understand better how long patients are able to hold autoinjectors against the skin to successfully complete a self-injection."

Figure 2: The market-proven company: 2-step YpsoMate 2.25 autoinjector platform.

Second, the FDA also approved Regeneron and Sanofi's Dupixent® (dupilumab) prefilled autoinjector for all indications in patients aged 12 years and older. The device allows patients to self inject a single high-volume dose of 2.0 mL (300 mg).

However, studies have shown that large single doses translate into longer injection times to avoid higher perceived pain, subcutaneous pressure and injection site leakage. Interestingly, there is limited evidence of the feasibility of longer injections when using hand-held autoinjectors. There is much at stake. The safe and effective use of the device is a necessary condition for effective product approval and commercial uptake. Therefore, it is of utmost importance to understand better how long patients are able to hold autoinjectors against the skin to successfully complete a self-injection. Also, more insights are needed on how different user groups, such as elderly and dexterity-impaired individuals, cope with the longer injection duration.

A SENSOR-AUGMENTED APPROACH

The simulated-use study, based on single-site visits, included 32 adolescent, adult and elderly patients across chronic disease states, non-professional caregivers and healthcare professionals. All patients suffered from at least one chronic disease state that offers autoinjector-based treatment options. The participants performed three simulated injections at increasing pre-set injection times that ranged from approximately seven to 30 seconds.

The prefilled single-use YpsoMate 2.25 mL autoinjector was included in the study (Figure 2). Its push-on-skin release and audible and visual feedback provides high patient confidence and convenience during drug self-administration. Users first push the single-use autoinjector on skin to initiate the injection and then sustain a minimum force to hold the device against the skin to complete the injection.

The participants performed the injections in a custom-built foam cushion with embedded force sensors. While attached to the abdomen of the participants, the sensors continuously tracked the user's force-time curve for each simulated injection. Figure 3 shows the experimental set-up used for data collection.

Figure 4 illustrates a typical user's force-time curve obtained for each simulated injection. Data included the time at which the users applied the minimum, mean and maximum force during the injection. The data points were then used to quantitatively assess the impact of the injection duration on the user's ability to effectively perform injections.

RE-THINKING THE CURRENT UPPER FEASIBLE LIMIT OF INJECTION DURATION

The simulated-use study confirms that participants are able to use handheld autoinjectors to administer single high-volume injections, which last longer than 10 seconds, to deliver the actual medication. Increasing the injection duration to 30 seconds did not lead to any usage errors, usage difficulties or further deviations from the usage instructions. Usage errors occurred, if at all, due to lack of training and participants' familiarisation with the instructions for use. Patient characteristics, such as dexterity impairments, gender,

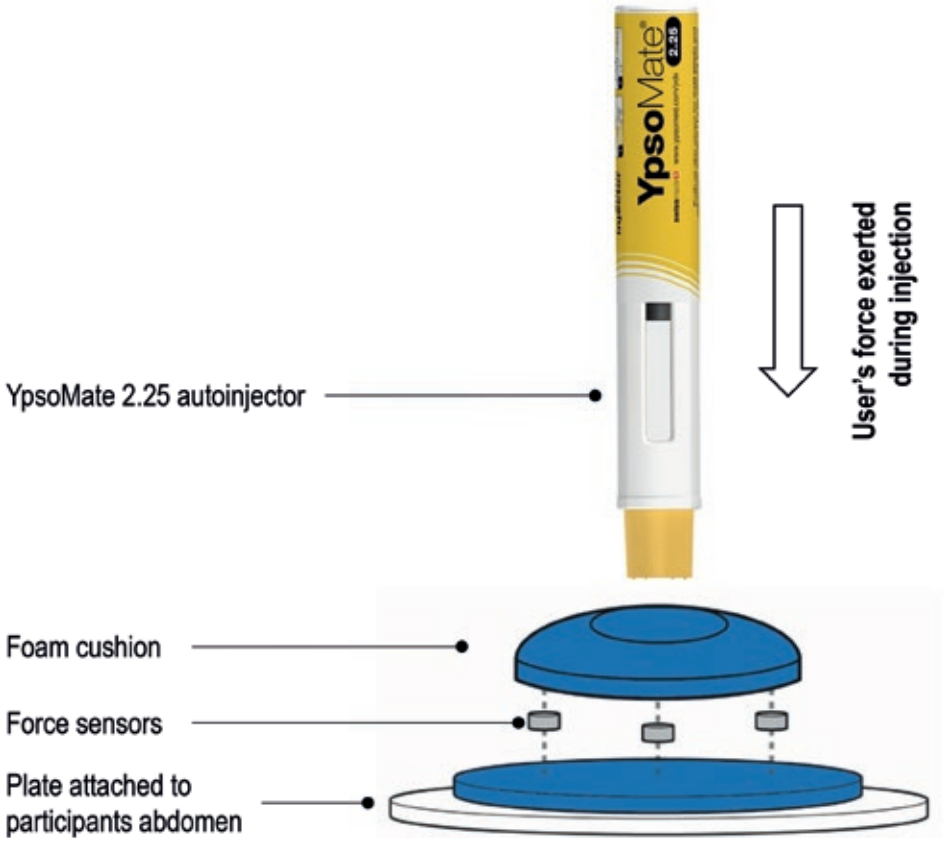


Figure 3: Experimental set-up to capture the user's force-time curve.

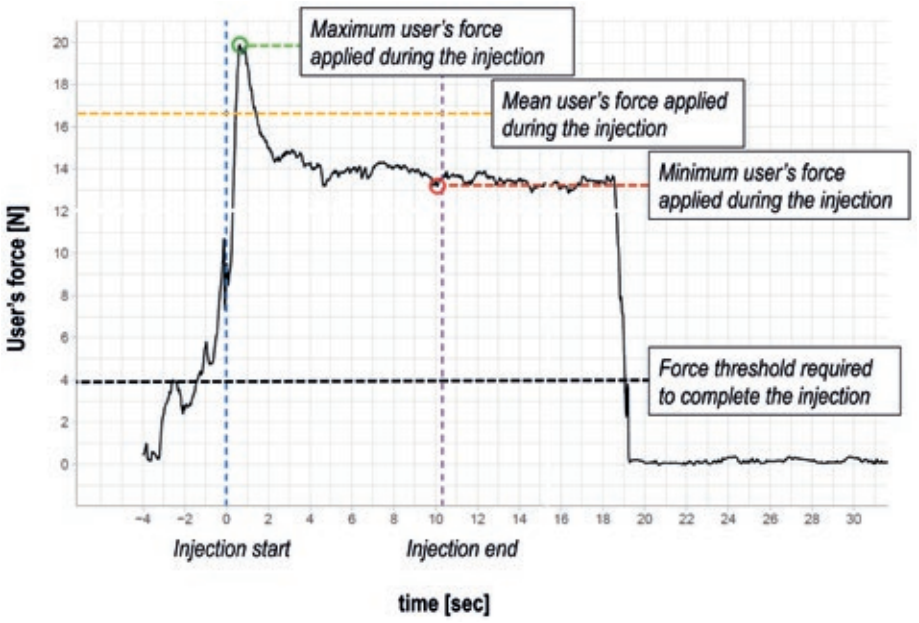


Figure 4: Illustration of a typical user's force-time curve.

injection experience and age-related conditions did not negatively impact the user's ability to effectively complete longer injection durations.

Contrary to our expectations, the study revealed that elderly patients actually exerted a higher mean force than adolescent patients when holding the device against the skin. Although prior studies have highlighted how grip strength decreases with age, the results did not confirm any age-related effects for the overall user population. In fact, older patients' awareness of impairments that may limit the effective performance of longer injections can lead to overcompensation and thus result in higher downward pressure on the autoinjector during the injection.

INJECTION DURATION OF 50 SECONDS WITH HAND-HELD AUTOINJECTORS?

These insights advance our understanding of how injection duration influences the user's ability to hold the device against the skin. First, the study revealed a significant, yet small, negative effect of the injection duration on the minimum and mean user's force exerted during the injection. Extending the injection duration by one additional second reduced the minimum and mean user's force exerted to hold the device against skin by 1.3% and 1.1%, respectively.

The force reduction for the one-second increase in injection duration has important implications for the design and development of new autoinjector devices. The results suggest, for example, that an average user may be able to complete injections effectively with a target injection duration of 50 seconds, using a handheld autoinjector that requires approximately 15 N to trigger the injection and a minimum force of 4 N to hold the device against the skin during the injection.

Interestingly, the market is already moving in this direction. For example, the full prescribing information of the AJOVY® prefilled autoinjector instructs the user to keep holding the device down against the skin for about 30 seconds. Although theoretically feasible, the suitability of even longer injection times must be carefully balanced with user preferences and alternative device designs, such as wearable patch injectors.

The study also revealed an unexpected twist. It showed that the negative effects of injection duration on users' forces was most pronounced in patient groups who exerted the least force to hold the device against the skin.* These patient groups, among them older female patients, are the most sensitive to the negative effect of the injection duration on the user's force, and thus show the lowest ability to withstand longer injection durations. Although dexterity, gender, age and injection experience have no overall impact on the ability to complete injections effectively, more nuanced effects at the patient group level need to be considered when designing future autoinjector devices. For example, the industry must be careful not to increase the injection duration for therapies to treat chronic disease states, such as osteoporosis, which specifically target older female patients.

SENSOR-AUGMENTED USABILITY STUDIES – A NEW STATE OF THE ART?

The study provides initial empirical evidence of the feasibility of longer injection durations using hand-held autoinjectors. Quantifying the effects of the injection duration on users' ability to hold the device against the skin during the injection demonstrates that extending the injection duration by one-second increments, on average, results in a reduction of the minimum user force of 1.3%. Additionally, these negative effects were most accentuated for patient groups, such as older female patients, who applied lower forces to keep the device pushed against the injection site.

Not only does the empirical research provide important insights into the feasibility of longer high-volume injection durations, but it also advances methodologically the study of patient behaviours during simulated-use studies. Researchers have only recently begun to introduce advanced sensor-augmented experimental methods to better characterise how participants engage with self-injection device technologies. As we continue to push the upper limit of injection duration with autoinjectors, we need to also keep pace with innovative methods to establish objective measures of how users self-administrate drugs – beyond the conventional endpoints of safe and effective use.

> "An average user may be able to complete injections effectively with a target injection duration of 50 seconds, using a handheld autoinjector that requires approximately 15 N to trigger the injection and a minimum force of 4 N to hold the device against the skin during the injection."

"The study results provide initial empirical evidence of the feasibility of longer injection durations using hand-held autoinjectors."

ABOUT THE STUDY

The empirical study summarised here was funded by Ypsomed and conducted in collaboration with Design Science (Philadelphia, PA, US). As a leading developer and manufacturer of self-injection systems for subcutaneous drug delivery, Ypsomed has established a scientific research and communications programme with the purpose of advancing new insights that are 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, such as the PDA Universe of Pre-Filled Syringes and Injection Devices.

ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms consist of 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 over 30 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the 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. The company leverages its 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 location. Ypsomed's FDA-registered manufacturing facilities are regularly inspected by pharma customers and regulatory agencies to supply devices for global markets including the US, Europe, Japan, China and India.

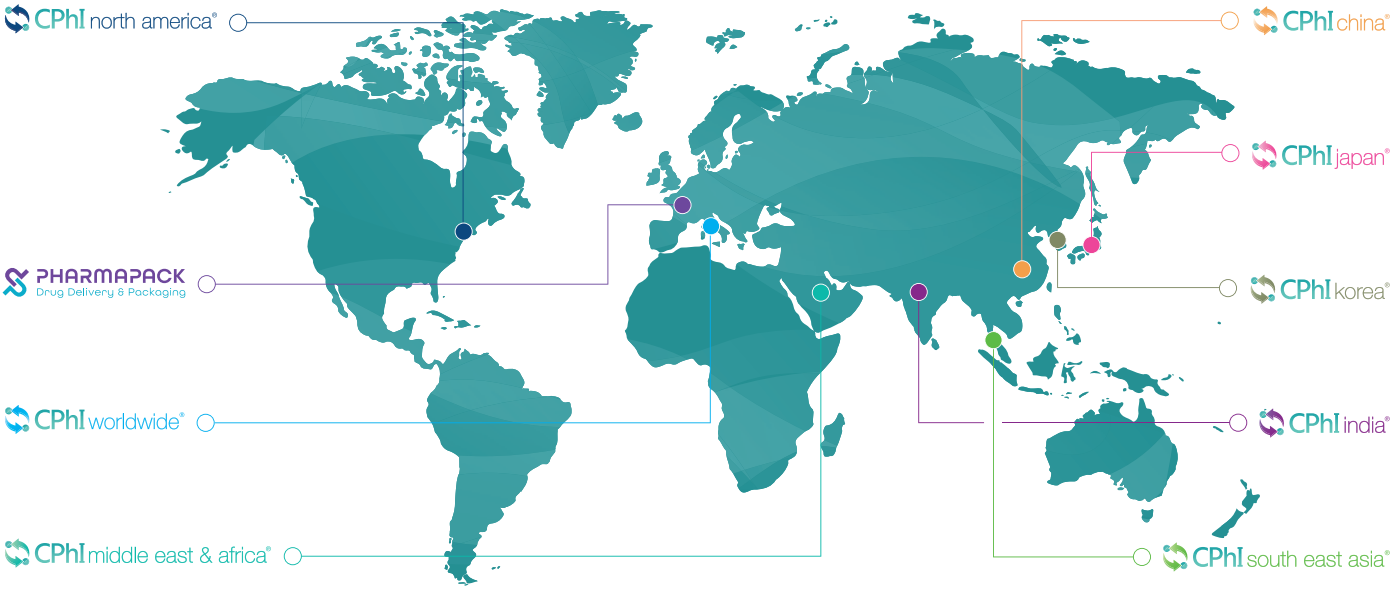
REFERENCE

1. *Schneider A et al, "Hold the device against the skin: the impact of injection duration on user's force for handheld autoinjectors". Expert Opin Drug Deliv, 2020, Vol 17(2), pp 225-236.*

**Linear regression models were built to assess the overall effect of injection duration on force applied to hold the device against the injection site. Quantile regression models were then used to show more nuanced effects of injection duration on the user's force. In particular, quantile regression revealed that the negative impact of injection duration on the user's force was most pronounced among participants who exerted the least force to hold the device against the skin, while it diminished for the higher quantiles.*

ABOUT THE AUTHOR

Andreas Schneider, PhD, is Innovation & Business Development Director at Ypsomed Delivery Systems. He leads a team that drives the definition and development of new drug delivery device platforms, such as next-generation pen and autoinjector devices, wearable patch injectors, connected systems and digital solutions. Dr Schneider has published various articles and given presentations in the areas of innovation management and drug delivery. He holds a PhD in innovation management and organisational sciences from ETH Zurich, Switzerland.



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PREPARING FOR MASS VACCINATION

In this article, Andy Fry, Founder, and Stephen Blatcher, PhD, Head of Early-Stage MedTech, both of Team Consulting, discuss the need for a mass vaccination device in response to the ongoing covid-19 pandemic. In particular, the authors discuss the benefits and challenges of turning to needle-free injection technology as a solution.

There are currently multiple covid-19 vaccine development programmes running across the world. Hopefully, some of these will shortly be approved for use and will have a major impact on the current pandemic. In parallel, significant investment is being made by governments and non-profit organisations to build adequate capacity for the delivery and administration of such vaccines at both the national and global scale.[1] With potentially hundreds of millions of doses to be administered annually, it is important to think carefully about the platform that will be used for covid-19 vaccine delivery.

"The low cost and ready availability of hypodermic syringes makes them immediately attractive, but the cost burden of needlestick injuries cannot be ignored. Needle-free injection eliminates this risk and, when designed appropriately, enables safe, targeted and reproducible dermal delivery."

The low cost and ready availability of hypodermic syringes makes them immediately attractive, but the cost burden of needlestick injuries cannot be ignored. Needle-free injection eliminates this risk and, when designed appropriately, enables safe, targeted and reproducible dermal delivery. Furthermore, needle-free delivery is independent of viscosity and hence independent of the flow characteristics of a vaccine. With so many candidate vaccines in development, there is potential to scale needle-free technologies in parallel with ongoing vaccine development programmes, safe in the knowledge that it has maximum potential to reliably deliver whichever vaccine(s) are proven to be effective.

CURRENT STATUS OF COVID-19 VACCINE DEVELOPMENTS

According to a report by The Lancet, there were already 10 SARS-CoV-2 vaccine candidates in clinical trials as of June 2020.[2] These include: mRNA vaccines such as the lipid nanoparticle-encapsulated vaccines mRNA-1273 (Moderna and the US NIH National Institute of Allergy and Infectious Diseases) and BNT162 (BioNTech and Pfizer); DNA vaccines such as INO-4800 (Inovio Pharmaceuticals), the delivery of which is enabled by a brief electrical pulse from the company's hand-held smart device, CELLECTRA, to open small pores in the cell reversibly to allow the plasmids to enter; an unnamed inactivated viral vaccine (Wuhan Institute of Biological Products and Sinopharm); protein subunits such as NVX-CoV2373 (Novavax), which uses Novavax's proprietary nanoparticle technology, Matrix-M; and an adenovirus vaccine, AZD1222 (under development by University of Oxford spinout Vaccitech, and AstraZeneca, with manufacturing support from Catalent's Cell & Gene Therapy division). Operation Warp Speed is underway and many more candidates are now in clinical trials.[3]

The Lancet report suggests that the average development time for a vaccine is 10 years, but the hope is that current life science tools can shorten the process to allow covid-19 vaccines to be delivered in 2020. It highlights that the typical success rate for vaccine development is only 6% and that even an 18-month development programme is considered very aggressive by infection experts. The report also warns that "global appetite for any successful vaccines, if and when they are ready, will bring its own difficulties. Developers are starting to scale up production even now, despite the risk that their favoured candidates will fall short. Distribution, delivery and administration need to be worked out."

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DELIVERY PLATFORMS FOR VACCINE ADMINISTRATION

Many people will have experienced annual influenza vaccinations being administered by intramuscular injection (generally used for adults) or by nasal delivery (generally used for children). These are the most common methods of vaccine administration and a review of covid-19 vaccine trials on ClinicalTrials.gov shows that, for a sample of 17 studies, the following administration methods were cited:

- Intramuscular injection (nine studies)
- Intradermal injection (two studies)
- Subcutaneous injection (two studies)
- Electroporation via the Cellectra 2000 (one study)
- IV infusions (one study)
- Not cited (two studies).

It is clear that parenteral delivery via hypodermic syringe remains the administration method of choice. Although the convenience and cost advantages of hypodermic syringes are undeniable, there is a strong case to be made that a better delivery platform exists to meet the unprecedented demand for rapid global mass vaccination against covid-19.

THE CASE FOR NEEDLE-FREE INJECTION

When appropriately configured, needle-free injection offers compelling advantages over hypodermic syringe delivery as a platform for mass vaccination. These advantages include:

- Dose sparing through intradermal efficiencies
- Reliable intradermal delivery
- Elimination of needlestick and re-use
- Insensitivity to vaccine flow characteristics
- Attractive healthcare economics.

The following sections cover each advantage listed in greater detail.

Dose Sparing Through Intradermal Efficiencies

Intradermal injection is a shallow injection of a substance into the dermis, which can be easily and reliably achieved with needle-free technology, as detailed in the next section. The dermis and epidermis of human skin are rich in antigen-presenting cells. As such, focusing the delivery of vaccines to these layers – rather than to muscle or subcutaneous tissue – should be more efficient, inducing protective immune responses with smaller amounts of vaccine antigen.

The potential benefit of dose efficiency through intradermal delivery has long been recognised,[4] with the WHO bulletin presciently stating that dose sparing might also "stretch" the availability of vaccines in cases where supply is limited by manufacturing capacity. This is probably most relevant for pandemic influenza vaccines where global production capacity limits access to a vaccine at the start of a pandemic. In 2009, the H1N1 vaccine was not available in most low-income countries until eight months after the WHO's declaration of the influenza pandemic.

Currently, no country in the world has access to a covid-19 vaccine and hence developing a delivery system that allows efficient vaccine dosing is a key early consideration.

Reliable Intradermal Delivery

The traditional procedure for intradermal delivery is needle-based injection via the Mantoux procedure, which involves injecting at an angle of administration of 5–15° (i.e. almost holding the syringe against the skin). With the bevel of the needle pointing upwards, the needle is inserted approximately 3 mm into the skin and the injection performed while watching for a small wheal or blister to appear. This procedure is most commonly used in BCG tuberculosis vaccinations.

The degree of needle control necessary in the Mantoux procedure requires careful delivery by the clinician and a high level of co-operation from the patient to ensure reliable intradermal delivery. In needle-free delivery, the substance being injected acts as the needle and hence, by controlling the dose volume and skin contact pressure, it is possible to achieve intradermal delivery easily and reliably.

One simple approach is the addition of a simple ring around the nozzle of a needle-free injector. This causes a dome of skin to reliably engage the nozzle of the injector, and also allows space for the skin to lift up into the characteristic blister or wheal that is generated by successful intradermal delivery. Figure 1 shows successful intradermal delivery achieved by a DosePro® (Zogenix, Emeryville, CA, US) needle-free device modified with a simple polycarbonate intradermal spacer component.

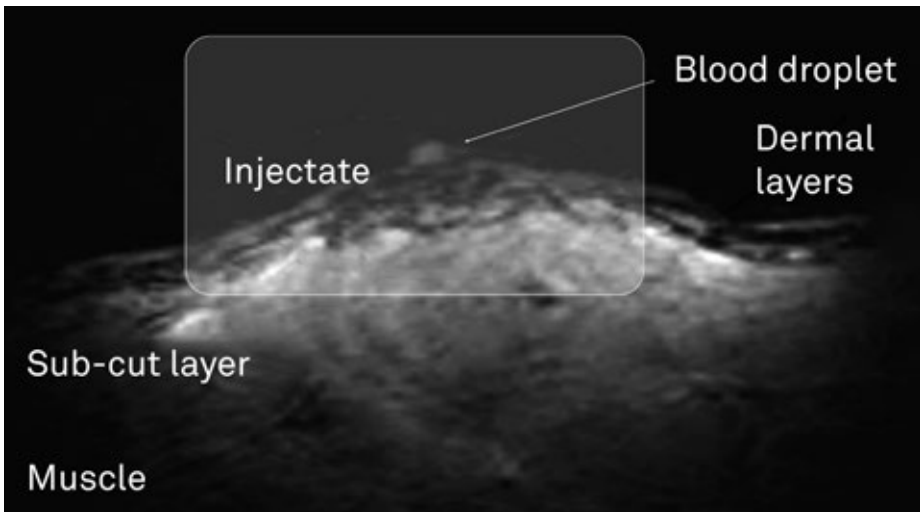


Figure 1: Successful intradermal delivery achieved by a DosePro needle-free device modified with a simple polycarbonate intradermal spacer component.

Elimination of Needlestick and Re-Use

A well-recognised advantage of needle-free delivery is the avoidance of needlestick injuries and the associated healthcare and societal costs that arise from them. Furthermore, disposable vaccine capsules provide single-use advantages, such as that any body fluids picked up from contact with a patient's intradermal blister will not be transferred to the next patient.

In a recent covid-19 webinar from PATH[5] (Seattle, WA, US) it was predicted that, in developing countries, the disruption in services from covid-19 isolation would knock progress in treating HIV, TB and malaria back by five years. Vaccination programmes for vulnerable groups will be a high priority in these countries. A needle-free injector with single-use, dose-efficient vaccine capsules offers the potential for safer, more reliable and lower-cost vaccination programmes in these vulnerable patient groups.

Insensitivity to Vaccine Flow Characteristics

A further advantage of needle-free injection is that the intradermal delivery performance is independent of the flow characteristics of the substance being delivered. As shown in Figure 2, for a conventional hypodermic syringe and needle, flow rate is characterised by the Hagen-Poiseuille equation, where:

- Q = flow rate
- D = needle bore
- L = needle length
- P = drive pressure
- μ = dynamic viscosity.

However, for a needle-free injector, as shown in Figure 3, delivery is through an orifice. Here, the flow is characterised by the Bernoulli equation, where:

- Q = flow rate
- D = orifice bore
- P = drive pressure
- ρ = density
- Cf = flow coefficient (0.95 for a practical round edged orifice).

The only fluid property which appears in the Hagen-Poiseille equation is μ, dynamic viscosity. The only fluid property which appears in the Bernoulli equation is ρ, density. For a conventional needle and syringe, it can be seen from the Hagen-Poiseuille equation that for any increase in viscosity, μ, an increase in pressure (i.e. an increase in the syringe plunger force) will be required to maintain the same flow rate.

However, when considering a needle-free injector, there is no viscosity term and, for the range of fluids of interest, the only property which affects the flow rate is density, ρ. Since most fluids of interest as injectables have approximately the same density, the pressure to deliver at a given flow rate, and hence the plunger force, will remain unchanged. This unique property makes it viable to scale the technology in parallel to ongoing vaccine development programmes, safe in the knowledge that it will tolerate different vaccine viscosities and hence should be capable of reliably delivering whichever vaccines are proven to be most effective.

Attractive Healthcare Economics

Needle-free injection relies upon a very high jet velocity; therefore, the pressure and operating force is much higher. Hence, all needle-free technologies rely upon a stored energy source, rather than unaided manual operation. Although this adds expense to the unit device cost (the unit cost of standard hypodermic syringes will always be cheaper), the potential benefits of reliable, safe, dose-efficient, needle-free delivery systems remain compelling from a healthcare economics perspective.

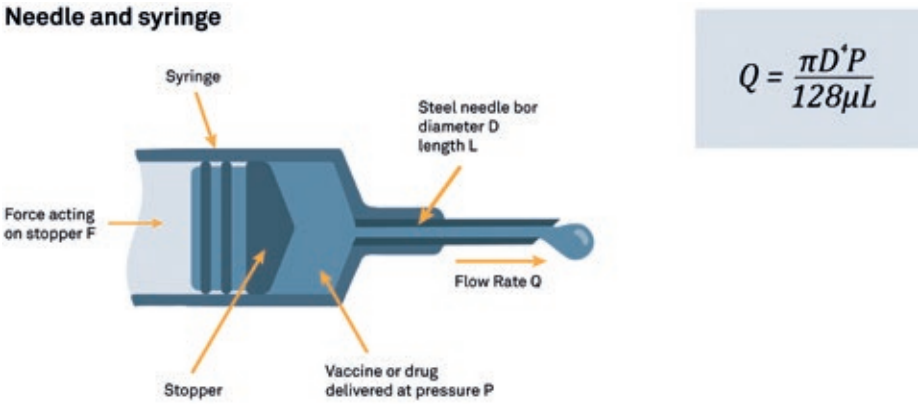


Figure 2: For a conventional hypodermic syringe and needle, flow rate is characterised by the Hagen-Poiseuille equation.

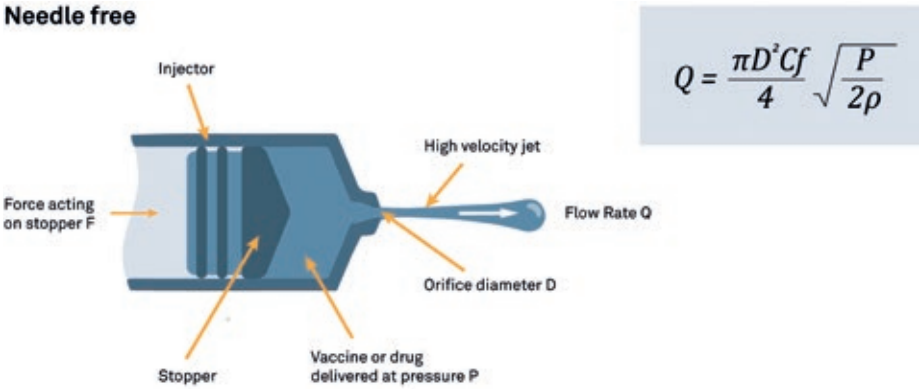


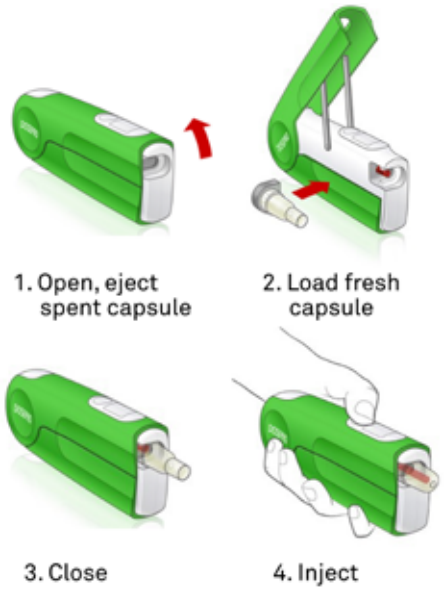
Figure 3: For a needle-free injector, delivery is through an orifice and the flow rate is characterised by the Bernoulli equation.

> "Based on work by Team Consulting, it is feasible to develop mass vaccination needle-free injectors where the cost of re-use is limited to a prefilled single-shot vaccine cartridge."

As highlighted previously, the ability to eliminate needlestick injuries is a significant economic benefit. The annual cost of treating needlestick injuries in hospital workers alone is as high as US$591 million (£458 million) in the US, $302 million (£234 million) in Japan and $900,000 (£698,000) in the UK.[6] These represent developed countries with the highest levels of training and resources available. covid-19 is a global pandemic, therefore the cost burden of needlestick injuries is likely to be far higher.

Based on work by Team Consulting, it is feasible to develop mass vaccination needle-free injectors where the cost of re-use is limited to a prefilled single-shot vaccine cartridge. One concept involves vaccines being dispensed from the low-volume single-shot, non-reusable capsule using a robust, high duty cycle, multi-use actuator device.

The Sumavel (sumatriptan) DosePro is a factory-filled, single-use needle-free injection product, which was approved in the US, UK and Germany for needle-free delivery of sumatriptan for migraine relief. Figure 4 shows a self-powered variant based on a system developed and proven in clinical trials in the early 2000s by Team Consulting – alongside a leading veterinary medicine company – for vaccination of farm animals. It is powered by a small reservoir of butane/propane fuel, similar in size to a cigarette lighter. The farm animal version was much like a power drill in size and appearance, but a scaled-down human-use version



- Light (0.5 Kg), compact device, minimal user effort (<15 N)
- Controlled, repeatable, silent needle-free injection
- Prefilled capsule, contents integrity protected throughout
- Safety interlocked mechanism ensures correct sequence
- On-board power for up to 3,000 injections

Figure 4: Mass vaccination device (with on-board fuel tank).

was built and tested. The images show the operational sequence of the system with cartridges (capsules) configured for subcutaneous injection.

An alternative approach is a mass vaccination system powered by pressurised nitrogen (Figure 5). The nitrogen-powered concept is simpler to use than the self-contained butane/propane fuelled device, but is dependent on the availability of a compressed nitrogen supply (typically a standard cylinder).

The self-contained nature of the butane/propane fuelled device – though requiring more user effort to prime the system – may be preferred in areas with limited infrastructure/logistics. The nitrogen-powered systems may be more widely accepted in developed countries.

CHALLENGES AND RISK

Clearly the decision to adopt needle-free technology is a significant one and not without risk. In addition to the development and scaling risks (applicable to any new medical technology) there is also the question of whether all vaccines will actually be suited to the efficiencies of intradermal delivery.

In terms of technical development and scaling, Team Consulting, in its 30+ years, has investigated needle-free platforms and seen encouraging clinical results, as well as approvals obtained. With sufficient investment it is very feasible to scale the technology to be ready to deliver novel vaccines at large scale. The key challenge will be the availability of large-scale filling systems and the supply of a custom vaccine cartridge. It is very likely that existing available filling systems will all be configured for filling "standard" prefillable syringes or vials. It will take at least 18 months and significant investment to set up the high-volume manufacturing and filling capacity for needle-free capsules, but this is still commensurate with the 18 months that vaccine experts consider it will likely take for a covid-19 vaccine to be developed.[2]

In terms of vaccine efficacy under intradermal administration, the WHO bulletin from 2011[4] states that "Live-attenuated vaccines have been successfully delivered intradermally and should be good candidates providing that appropriate formulations can be developed. Reduced doses of inactivated whole-virion vaccines have also shown satisfactory immunogenicity when delivered intradermally. Inactivated whole virion influenza vaccines might also be suitable because they have intrinsic immune-stimulating sequences, which might avoid the need for addition adjuvants". With timely investment, a low-volume needle-free system could be developed more quickly for researchers to use in vaccine trials, allowing vaccine efficacy under intradermal needle-free delivery to be demonstrated from the outset.

"It will take at least 18 months and significant investment to set up the high-volume manufacturing and filling capacity for needle-free capsules, but this is still commensurate with the 18 months that vaccine experts consider it will likely take for a covid-19 vaccine to be developed."

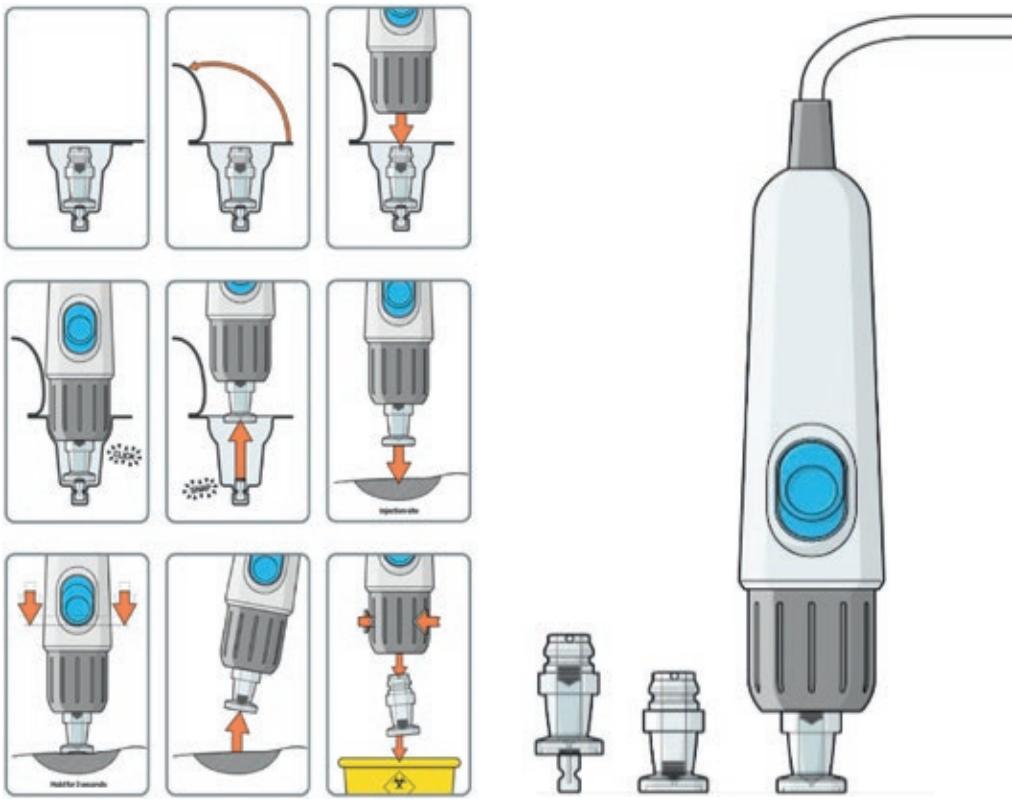


Figure 5: Compressed nitrogen powered vaccination system.

CONCLUSION

Governments, international agencies and technology companies are already investing significant sums of money into vaccine development programmes and associated delivery systems. With sufficient co-ordination across stakeholders, a reliable, needle-free, dose-efficient vaccine delivery system is a very viable concept that should be considered for mass vaccination of covid-19.

ABOUT THE COMPANY

Team Consulting is a medical device design and development consultancy based in Cambridge, UK. For 30 years Team has worked closely with its clients at leading pharmaceutical and device companies, applying its expertise in design, human factors, science and engineering to deliver successful devices from concept through to industrialisation and commercial launch. Everyone at Team is driven by the same desire, to make things better by working in collaboration with clients and each other.

REFERENCES

1. *Markarian J, "Industry Builds Fill/Finish Capacity for Pandemic Response". PharmTech, Jul 2020, Vol 13(8), pp 38–45.*
2. *Mullard A, "Covid-19 vaccine development pipeline gears up". The Lancet, Jun 2020, Vol 395(10239), pp 1751–1752.*
3. *Craven J, "Covid-19 vaccine tracker". Regulatory Focus, Sept 2020.*
4. *Hicklinj JK et al, "Intradermal delivery of vaccines: potential benefits and current challenges". Bulletin of the World Health Organization, 2011, Vol 98, pp 222–226.*
5. *"Continuing essential service delivery in a pandemic: HIV, tuberculosis, and malaria solutions in action". PATH Live Forum, May 2020.*
6. *Kunishima H, "Estimating the national cost burden of in-hospital needlestick injuries among healthcare workers in Japan". PLoS One, 2019, Vol 14(11), published online.*

ABOUT THE AUTHORS

Andy Fry has played a leading role in developing Team Consulting's drug delivery business, both in development of client and partner relationships and in technology development. He has helped both multinational and start-up companies identify and develop the right parenteral delivery system for their drugs.

Dr Stephen Blatcher joined Team Consulting's commercial team in 2019 to help expand the company's work in the MedTech space. With a particular focus on high-risk devices, his strategic business skills and background in engineering and biotechnology give him an aptitude for both managing technical projects and developing business opportunities.

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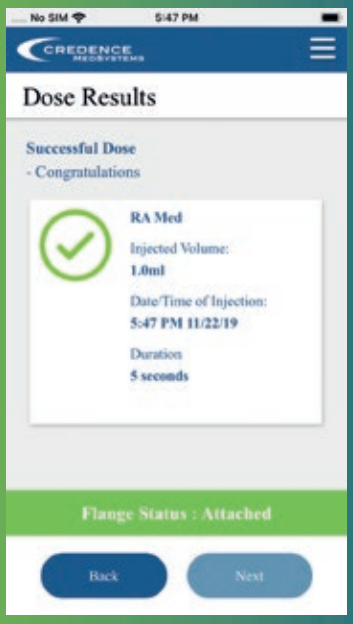

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THE NEW EMERGING NEEDS DRIVING AUTOINJECTOR DEVELOPMENT

In this article, Iain Simpson, PhD, Director, Front-End Innovation, Phillips-Medisize, discusses the emerging needs to be considered when bringing new autoinjector drug-device combinations to market.

Although the first autoinjectors entered the market in the 1980s – for the delivery of epinephrine in the treatment of anaphylaxis – 2006 marked the start of a wider use of these devices in the management of chronic diseases, with the approval of three single-use devices in the US: SureClick for Enbrel (etanercept) (Pfizer) and Aranesp (darbepoetin alfa) (Amgen), and the Humira Pen (adalimumab) (Abbvie). Since then, more than 20 autoinjector-drug combinations have entered the market in the US and Europe, with many more in development.

From a patient perspective, the motivation in introducing these devices was to enable safe and effective administration of medication outside the clinic, either by patients or their caregivers. From a commercial perspective, the approach offered pharmaceutical companies an opportunity for product differentiation in competitive markets such as the treatment of autoimmune diseases and the possibility of achieving higher drug sales from improved medication adherence due to the convenience of self-administration.

Early autoinjector launches were for delivered volumes up to 1 mL. However, research suggests a preference by patients for less frequent dosing, which then requires higher doses for the same therapeutic effect. Consequently, autoinjectors that can deliver up to 2.25 mL have been developed and are starting to enter the market.[1]

Reviewing the devices that have been launched onto the market – and the published data relating to their usability[2,3] and user preference[4] – it can be concluded that the dominant design for autoinjectors has become that of a disposable, spring-triggered device, with manual needle insertion and removal, shield triggered activation and passive needle protection. Several commercially available devices conform to this design and are tending to dominate the market. There appears limited scope to further improve the usability and safety of these devices.

Although other devices offer other potential benefits such as automated needle insertion and retraction to improve comfort, the ability to provide higher injection forces to reduce injection time, and trade-offs around cost, size and complexity need to be considered, suggesting these may only address niche applications. In addition, there are some reusable mechanical autoinjectors on the market, which have seen limited uptake apart from in the treatment of multiple sclerosis. Research has shown that some user groups see these devices as easy to use,[5] but require

> "Rather than considering drug-device combinations on a drug-by-drug basis, companies have started to look at platforms that can support multiple drugs."

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more user steps and resetting each time. Potential benefits around reduced cost per injection and the flexibility of being able to use the prefilled syringe (PFS) alone need to be balanced by inferior ease of use and device reliability. Likewise, there are some reusable electronic autoinjectors on the market but their uptake has been limited, presumably due to issues around size and complexity compared with disposable devices, as well as cost.

Rather than considering drug-device combinations on a drug-by-drug basis, companies have started to look at platforms that can support multiple drugs. Although both 1 mL and 2.25 mL PFSs can be delivered using spring-based devices, the latter usually requires a more powerful spring and stronger device body to contain the spring in its compressed state prior to injection. To support this platform approach, mathematical models have been developed[6] to evaluate the trade-offs between spring force, needle size, injection volume and delivery time – and user studies conducted across broad patient populations to confirm platform suitability to different patient groups.[7] But this does not negate the need to change components and, as a result, platforms for 1 mL and 2.25 mL injections have tended to be distinct to allow usability and delivery parameters to be optimised for each case. Consideration has also been given to ensuring differentiation between devices developed from the same platform for different drug products.[8]

AUTOINJECTORS – EMERGING NEEDS

We see several emerging needs that need to be considered when bringing new autoinjector drug-device combinations to market.

Addressing Medication Non-Adherence

Although medication non-adherence has long been recognised as a complex and serious issue in healthcare[9] and a cause of lost revenue for pharma companies,[10] frustratingly little progress has been made in addressing the issue. The introduction of autoinjectors for self-administration improves convenience and allows patients to take better control of their treatment schedule, which should favour adherence.[11] However, treatment at home might adversely impact the training and support patients can get from healthcare professionals (HCPs) in a clinical setting, which could have a negative impact on adherence.

Pharma companies try to address this issue through activities such as patient support programmes, which can be effective,[12] but these are expensive to implement – limiting their applicability in mainstream healthcare. Connected drug delivery devices offer the potential of capturing medication data automatically and using it to support patients directly in medication management or enabling others, such as HCPs, to provide timely, contextual support based on reliable and quantitative data.

Back in 2006, there was little expectation of the rapid increase in smartphone device use and hence little need to consider connectivity for drug delivery devices. Since the launch of the first iPhone in 2007, smartphone penetration has grown rapidly – with estimates suggesting >80% uptake in many countries[13] – and low-power connectivity arrived via Bluetooth Low Energy in 2009. The opportunity to integrate drug delivery devices into digital health systems is now a reality.

Connectivity can be added to existing disposable autoinjectors either by integrating electronics into the device or by developing an add-on module that can be attached to a device prior to injection and then reused with a further device for each injection. Although these avenues are being progressed, they both present some disadvantages. The former raises concerns around environmental sustainability as the integrated electronics will only be used once, and there may only be a short opportunity to access the data after an injection before the device is disposed of. Add-on devices introduce additional user steps to attach the device to a disposable autoinjector before an injection and to remove it afterwards. There are also technical complications around the ability of the add-on device to reliably detect an injection event. Neither of these approaches is therefore optimal in introducing connectivity.

Improving the Ability to Leverage Device Technology Across Multiple Drug Products

As described above, disposable autoinjectors are being developed as platform devices by device companies and their pharma partners. But the need to match spring force to different drug properties and PFS components introduces complexity. A more straightforward means of configuring a platform to new drugs would be desirable.

Environmental Sustainability

Back in 2006, environmental sustainability was not a major area of concern for the pharma industry. The benefits of introducing more self-administration of medication and a focus on ease of use for patients outweighed the negative impact of single-use devices compared with alternatives. And when considering sustainability, the pharma industry had more urgent areas of focus around drug manufacture, such as reducing the use of solvents or eliminating greenhouse gases such as the propellants used in some inhalers.

However, the situation is changing, and many pharma companies assess the impact of drug developments on sustainability. Although the addition of electronics adds to the environmental impact of a device, this can be reduced by recycling and more than offset by

Intelligent, reusable drive unit

- Powerful motor to drive controlled injection of liquid drugs (low and high viscosity)
- Full dose delivery in 10 seconds (adjustable)
- Simple sleeve triggered operation
- Intuitive visual/audible User Interface (GUI screen in Advanced version)
- Rechargeable with three-year service life
- Built-in Bluetooth low energy (BTLE) Connectivity

Single-use disposable cassette

- 1 mL and 2.25 mL prefilled syringes with rigid needle shield (RNS)
- Standard subcutaneous delivery
- Full needle safety before/after injection
- Over 50% less waste and storage space
- Large inspection window
- Optional radio frequency identification (RFID)

Figure 1: Overview of the Phillips-Medisize smart autoinjector.

Smart Autoinjector
Basic device

- Both 1 mL and 2.25 mL staked needle PFS
- Sleeve-triggered, two step
- Manual needle insertion/retraction
- Needle safe, sleeve interlock
- Audio-visual user feedback
- Low-to-high viscosity
- Standard 10-second injection (programmable)
- Emptying (full dose delivered)
- User with moderate-to-severe dexterity impairments
- S3 safety/risk classification
- BTLE connectivity
- Optional RFID cassette reading
- Rechargeable battery, two-three-year life

Smart Autoinjector
Advanced device

- Both 1 mL and 2.25 mL staked needle PFS
- Sleeve-triggered, two step
- Manual needle insertion/retraction
- Needle safe, sleeve interlock
- ***GUI screen and buttons for user guidance and control***
- Low-to-high viscosity
- ***Injection time set/adjusted by user (within predefined limits)***
- ***Potential for partial dosing***
- User with moderate-to-severe dexterity impairments
- S3 safety/risk classification
- BTLE connectivity
- Optional RFID cassette reading
- ***Rechargeable battery, three(+)-year life***

Figure 2: Basic and advanced models of the Philips-Medisize smart autoinjector.

the benefits it brings through improved adherence and a reduction in the need to travel for healthcare consultations or hospitalisation.[14]

A NEW CONNECTED SMART AUTOINJECTOR

With the above points strongly in mind, Phillips-Medisize has been developing a new smart autoinjector that is small, intuitive and easy to use for patients, provides a powerful and flexible platform for pharma companies, reduces the waste generated by disposable devices and is ready for the connected world. As shown in Figure 1, it consists of a single-use disposable cassette that contains the PFS and provides needle safety, and an electronic reusable drive unit that contains all the electronics and a display.

There are two models: basic and advanced (Figure 2). The key differences between then are around user guidance and flexibility of control. The advanced model has a graphical user interface (GUI) to provide more detailed user guidance and feedback, and the ability to incorporate in customer variants controls such as adjustment of speed of injection and the possibility for partial dosing from the PFS.

The current cassette design accommodates ISO standard 1 mL PFSs with small, cut and round flanges as well as the 2.25 mL PFS with small round flanges. A second cassette design can accommodate the other 2.25 mL flange formats, using a slightly larger drive unit. Delivery parameters for a particular drug, volume and syringe format can then be optimised by adjusting the motor control algorithms.

An initial user study (14 participants: six injection naïve and eight experienced autoinjector users) found similar scores for ease of use from experienced participants compared with their existing autoinjector (on a scale of 1-10, 10 being the highest ease of use, they scored 8.6 compared with 8.7 for their existing device). Six of the eight (6/8) experienced users preferred the smart artificial intelligence (AI) device over their existing device and 5/8 wanted a connected smartphone app that would support them with medication management with features such as diaries and reminders. All six naive users thought an app would be useful, with smart reminders and the calendar history view most of interest. All participants were conscious of sustainability and wanted to reduce waste. On a scale of 1-10 (10 being most environmentally sustainable) the average rating for the basic smart AI device was 6.2 compared with 2.0 for their current disposable device.

Market research conducted with most of the top 10 biopharmaceutical companies confirmed a high level of awareness around the need for improved sustainability and connectivity. The research also confirmed the desirability of a platform that could accommodate both 1 mL and 2.25 mL syringes. There was very favourable feedback on the smart AI concepts presented – and recognition that the motor-controlled delivery offers benefits around adaptability, the ability to optimise delivery for higher viscosities and patient comfort. Although there was generally a preference for the basic device, the benefits of a GUI

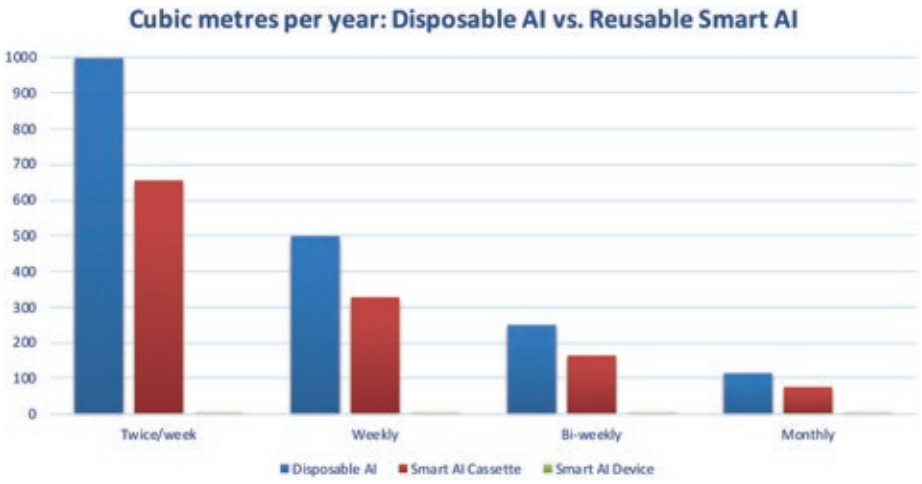

Figure 3: Waste generated by reusable smart AI devices compared with disposable autoinjectors (based on 150,000 patients per year and four years' device usage. Syringe and RNS not included for either device).

to support more complex use cases, such as a single dose involving multiple injections, was recognised.

Initial assessment of the environmental sustainability of smart autoinjectors compared with other autoinjectors has shown significant benefits when it comes to the impact of storage and shipping volume, and product waste on disposal. A full lifecycle assessment[15] – considering materials of construction, manufacture, distribution storage, use and disposal – is being developed. Figure 3 shows some early results on the wastage created by the smart autoinjector compared with disposable devices for a cohort of 150,000 patients over four years.

CONCLUSION

The current prevalence of single-use mechanical disposable devices has been built upon the need to address ease of use, convenience and safety of injection drug administration outside the clinic. Looking to the future, these needs will continue to be important in device development and selection. But they are becoming "hygiene factors" required by any self-injection device in the market and no longer differentiators that can create a source of competitive advantage for drug companies. Fortunately, new emerging needs create an opportunity to improve patient engagement in the management of disease in a more environmentally sustainable and cost-effective way that, in turn, creates new opportunities for competitive advantage for pharma companies willing to take on this challenge – as was the case back in the early 2000s when pioneering companies started to launch the current wave of disposable mechanical devices.

In conclusion, we believe that the requirements of new autoinjectors entering the market in the next 20 years will be based on four key aspects or "pillars":

1. Safety, convenience and ease of use, aligned with that already experienced with single-use disposable devices
2. The ability to configure device technology as a platform for use across multiple drugs and therapeutic areas with minimal redesign
3. Improved environmental sustainability
4. The use of connectivity to digitise medication events and provide additional off-device services that can improve patient engagement, monitoring and the gathering of more reliable real-word data around medication use.

In addressing the first of these pillars, it appears difficult to improve on existing disposable mechanical autoinjectors, although there are opportunities to make improvements in some areas – such as providing better feedback and reducing the force required to actuate the device and keep it in contact with the skin during injection. However, the development of reusable, electronic, connected devices offers distinct advantages when addressing the other three pillars. The main challenge in adopting this approach is then to ensure these new designs do not fall short in satisfying the first pillar.

Based on our experience in developing electronic autoinjectors over 10 or more years – and early market and user feedback on our new smart autoinjector platform – we are confident that we can address all four pillars and continue to play a leading role in supporting the self-injection market over the next 20 years.

ABOUT THE COMPANY

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

REFERENCES

1. *Schneider A et al, "Hold the device against the skin: the impact of injection duration on user's force for handheld autoinjectors". Expert Opin Drug Deliv, 2019, Vol 17(2), pp 225–236.*
2. *Weinhold T et al, "Improving the safety of disposable auto-injection devices: a systematic review of use errors". AAPS Open 4, 2018, article 7.*
3. *Schiff M et al, "Usability and Acceptability of the Abatacept Pre-Filled Autoinjector for the Subcutaneous Treatment of Rheumatoid Arthritis". Adv Ther, 2016, Vol 33(2), pp 199–213.*
4. *Tischer B, Mehl A, "Patients' and nurses' preferences for autoinjectors for rheumatoid arthritis: results of a European survey". Patient Prefer Adherence, 2018, Vol 12, pp1413–1424.*
5. *Wray S et al, "Ease of use of two autoinjectors in patients with multiple sclerosis treated with interferon beta-1a subcutaneously three times weekly: results of the randomized, crossover REDEFINE study". Expert Opin Drug Deliv, 2018, Vol 15(2), pp 127–135.*
6. *Wilkins J, Simpson I, "Mathematical modeling for faster autoinjector design". Drug Dev Deliv, 2012, Vol 12(6), pp 41–45.*
7. *Lange J, Richard P, Bradley N,*

"Usability of a new disposable autoinjector platform device: results of a formative study conducted with a broad user population". Med Devices (Auckl), 2015, Vol 8, pp 255–264.

8. *Schneider A, "How Users Distinguish Between Self-Injection Device Platforms". ONdrugDelivery Magazine, Issue 105 (Feb 2020), pp 24–28.*
9. *Sabate E, "Adherence to long-term therapies: Evidence for action". World Health Organization, 2003.*
10. *"Estimated Annual Pharmaceutical Revenue Loss Due to Medication Non-Adherence". Capgemini Consulting and HealthPrize Technologies, 2012.*
11. *Pouls BPH et al, "A pilot study examining patient preference and satisfaction for ava®, a reusable electronic injection device to administer certolizumab pegol". Expert Opin Drug Deliv, 2020, Vol 17(5), pp 705–711.*
12. *Rubin DT et al, "Impact of a Patient Support Program on Patient Adherence to Adalimumab and Direct Medical Costs in Crohn's Disease, Ulcerative Colitis, Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, and Ankylosing Spondylitis". J Manag Care Spec Pharm, 2017, Vol 23(8), pp 859–867.*
13. *"Global mobile consumer trends, 2nd edition". Deloitte, 2017.*
14. *"Digital Adherence Monitoring in Poorly Controlled Paediatric Asthma". Sustainable Healthcare Coalition, 2017.*
15. *Muralikrishna IV, Manickam V, "Environmental Management: Science and Engineering for Industry". 2017, pp 57–75.*

ABOUT THE AUTHOR

Iain Simpson, PhD, is a Director of Front-End Innovation at Phillips-Medisize. He is part of a global team of engineers, designers, researchers and business analysts developing industry leading solutions for drug delivery, digital medicine and Connected Health systems. Dr Simpson has more than 25 years of experience in multi-disciplinary technology and product development including business development, project management and technology assessment in US and European markets, the last 15 years of which has been gained in the life sciences sector both in consultancy and industry, and with an increasing emphasis on the use of devices and digital technologies to create product differentiation, improve patient engagement and better measure clinical outcomes in real world settings. He has a degree in physics, a PhD in experimental solid-state physics both from UCL (London, UK) and also an MBE in Technology Management from the Open University (UK). He has published several papers, chaired sessions and presented at international conferences on drug delivery, digital biomarkers, healthcare technology and technology licensing.

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DUOJECT MEDICAL SYSTEMS

THE IMPORTANCE OF A GREAT DEVELOPMENT EXPERIENCE TO ACHIEVE A GREAT MEDICAL DEVICE

In this article, William Fortina, Business Development Director at Duoject, considers the importance of the medical device development experience in the healthcare context and discusses the factors that make for a superior development process.

INTRODUCTION

In The Healthcare Context, What Would Be Considered A Great Medical Device?

If I had to describe a great medical device in one sentence, I would say: "A great medical device is one that results in proper ease of use and superior treatment adherence."

Of course, nothing is ever so straightforward. To develop a great medical device, there are multiple stakeholders to consider besides the actual patients. For example, you need to consider members within your organisation, and ask yourself questions such as:

- What are their individual and common objectives?
- What available resources do they have?
- What are their challenges, communication style, priorities, etc?

You should also take into account the type of healthcare system in place and reflect on several topics. For instance:

- What are the challenges related to patient care?
- How are treatments prescribed and administered?
- What qualifications are required for providing the treatment?

Other factors to contemplate may include drug handling, manufacturer's limitations, and how patients' family members may be assisting with the treatment.

There is also a whole ecosystem that influences what a great product should, or could, look like: regulations, supply chain constraints, environmental factors, sustainability, the competitive and patent landscape and more.

"What is a great medical device?" is therefore a complex question to answer. Most importantly, it is project specific. Considering this, the development process becomes crucial to ensure a successful end-

> "Before providing any project estimates, the development partner must first gain a solid understanding of your needs."

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Figure 1: In-depth interaction between the design company and client is crucial to understanding the project needs.

result. Therefore, we propose to discuss the question "What does a great medical device development process look like?"

DISCUSSION

Should you call on an external organisation to help you develop a new medical device, a few key aspects will ensure an outstanding development experience, resulting in a great product and commercial success. The following issues should be considered as you work with medical device development companies.

Your Medical Device Development Partner Starts By Developing A Thorough Understanding Of Your Project

Before providing any project estimates, the development partner must first gain a solid understanding of your needs. You may be eager to receive ballpark timelines and numbers from them for your own product feasibility assessment. Be wary, however, of any company that would provide numbers without fully understanding your requirements. Such figures would most likely not be close to reality, or may be divorced from your needs entirely.

Your chosen partner should sit with you to discuss the project. Their team members should thoroughly question you and your colleagues, and challenge your requirements and assumptions to ensure their accuracy. Only then will the partner truly understand your needs and be able to provide meaningful estimates for the work to be accomplished. Even if you can promptly supply a comprehensive project brief your partner should still come back to you for clarification nonetheless. If you cannot answer certain questions, remember that your best guess will always be better than theirs (Figure 1).

Once the project has started, your device partner's priority should be to investigate and fully identify the user and patient needs. This is accomplished through early human factors studies (HFS), involving a representative population of end-users. If this activity takes place, take it as a promising sign; while the opposite may also be true. If your partner raises aspects related to the user/patient experience that you had not previously considered, you can be extra confident your project is in good hands.

The Company Demonstrates Superior Communication Skills

Your job will be made easier if your partner shares an initial budget with you in a clear and comprehensible manner. At this stage, there are many unknowns for both companies. However, your experience will be more enjoyable if comprehensive budget and timeline estimates are communicated to you effectively. Your trust will continue to grow if your partner advises what limitations apply to their estimates; they should explicitly state the input and assumptions used to build the proposal. As the project moves forward, the validity of various assumptions will become clearer. Accordingly, a good partner will submit refined versions of those budgets for your review as the project evolves and the mandate becomes clearer.

In addition to providing a budget, your partner should also prepare a high-level project roadmap for you, highlighting the various foreseen project phases. If this roadmap is communicated skilfully, everyone you share it with within your organisation will be able to quickly understand the development path. Once again, a great partner will update, refine and share this roadmap with you on several occasions throughout the various development phases of your project.

A great device partner will shed light on market forces at play, which you may not have considered or been aware of. These forces can range from the intellectual property (IP) landscape to potential regulatory hurdles, and from production technologies to competing devices' strengths and shortcomings. This will enable you to better grasp limitations that apply to the project, or even alternate possibilities that exist, which you did not realise were available.

Finally, a good device company communicates regularly through a multitude of channels, as appropriate. For instance, good communication involves scheduling a direct conference call between your legal teams so they can quickly resolve legal

Figure 2: Sketches can be a simple yet effective communication tool.

formalities. Bad communication, however, may be e-mailing you daily and requiring you to forward the messages to your legal team when you should be focusing on the project. Good communication could be a simple acknowledgment your email was read and that an action will be taken, as required, with an indication of when your contact expects to get back to you with the elements you need. Bad communication is leaving you waiting and unsure of what is happening while your partner looks for answers about your various inquiries (Figure 2).

The Medical Device Design Firm Has A Well-Defined And Proven Development Process, Yet Demonstrates Flexibility

Good medical device design firms have a well-defined development process, sometimes showcased on their website. Each phase your partner completes should serve a purpose to ensure the final device they develop functions as intended. Do not hesitate to ask them about their development process, in order to better understand how they will develop your device.

On a side note, their development process should not be limited to designing a great device; it should also integrate design verification and validation activities, manufacturing, assembly and processing considerations. We have witnessed design companies create great designs, which unfortunately were impractical for industrialisation, sterilisation or drug product handling. Some design firms lack this industrial know-how during early development phases, leaving their clients with puzzling fabrication and supply chain challenges later on.

While most medical device design firms have created their proven development "recipes", be mindful that they may lack the agility required to adapt to changing circumstances. As is true for most companies, the bigger they get, the more rigid they become. It is worth noting that working with smaller design firms can offer more flexibility to address your needs and improve overall efficiency for your programme.

Your Selected Partner Can Manage Multiple Peripheral Aspects For You

Medical device design is tightly interconnected with the user and patient experience. Therefore, you will want to work with a company that has experience in designing HFS, and is able to manage them for you. As such, their first-hand findings gathered from HFS will be more readily integrated into your product's development. Your chosen partner should therefore demonstrate a successful track record regarding HFS (Figure 3).

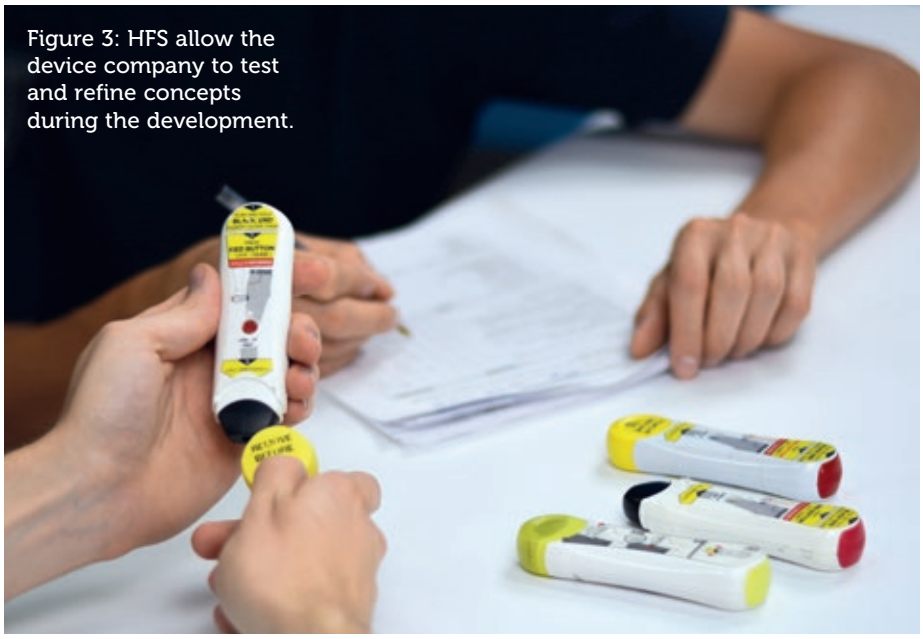

Figure 3: HFS allow the device company to test and refine concepts during the development.

> "Your partner should be able to work with you to identify the optimal regulatory path for your specific project and execute everything related to the device and drug-device combination."

Also, your partner should make your job easier by identifying and qualifying the most suitable Contract Development and Manufacturer Organisations (CDMOs), as required, for your programme (i.e. contract fillers, manufacturers, sterilisers, etc).

Finally, one of the most crucial aspects of your project – a great design firm will support you through regulatory filing. Your partner should be able to work with you to identify the optimal regulatory path for your specific project and execute everything related to the device and drug-device combination. They should generate the required product documentation and be by your side to answer questions before, during and after filing to regulatory

Figure 4: Rapid prototyping is a powerful tool to bring credibility and certainty to the project.

agencies, if required. The ideal partner should also demonstrate a track record of successful product filings, at least in the market you are aiming for, or have a clear strategy for applications in new markets. A design firm lacking this experience may not be the right partner for your medical device development.

A Partner Who Goes The Extra Mile

The last item on your checklist to a great development experience is an indication that your device design partner will go the extra mile for you. This should not be confused with simply working overtime to meet a tight deadline. Going the extra mile means a lot more than that. It is about offering better quality services:

- Have they ever invited you to attend a user testing session, offering insights into how people will use your device?
- Have they ever shared videos of such tests if you were not able to attend?
- Are they trying to help you solve your own internal challenges, for example, getting management buy-in, solving legal delays, IP hurdles, etc?
- Do they share extra deliverables to make the project more tangible within your organisation? It could be something as simple as including your logo on concept renderings, mailing you a mock-up prototype during the early development stages or sharing a product animation (Figure 4).
- Do they ask for your opinion and feedback to build upon and improve the quality of their services?

There are many ways to go the extra mile, and you will notice them when you catch yourself being positively surprised in some way by your partner.

If you want your device development experience to be just as this article described, we suggest seeking out three important traits when selecting your device development partner:

- A true **"Partner Mindset"** in order to understand your needs, make your job easier and demonstrate empathetic flexibility
- **Leadership** skills to guide your understanding of possibilities and limitations, provide guidance and manage all aspects of the project besides pure design
- **Creativity** to develop novel solutions and find innovative ways to increase your product value.

CONCLUSION

You want your products to be better than good, you want them to be great, and to impact patients' lives positively. A great medical device development experience will help you achieve this goal. The Duoject team strives to pursue all efforts to make the complete process a great experience for you. We accomplish this by constantly questioning ourselves and challenging our assumptions, by fostering honest and open communication with our clients and by going the extra mile whenever and however we can. If you have an unmet need for a medical device, let us work together on developing a great product for you and your patients.

ABOUT THE COMPANY

Duoject designs and develops advanced medical devices for the pharmaceutical industry. The company collaborates with its clients to create custom solutions aligned with their unique needs and goals. Duoject's technologies improve upon industry standards in safety, precision and ease of use, to optimise patients' adherence to treatments.

In addition to being a design and engineering partner for medical devices, Duoject provides a 360-degree service to support its client's missions at every step of the development process; including through regulatory affairs, manufacturing and project management support. Every project the company works on creates a strong IP background to ensure clients' commercial success for many years to come.

ABOUT THE AUTHOR

William Fortina is Business Development Director at Duoject Medical Systems, where he leads sales and marketing activities as well as strategic initiatives. He graduated from the University of New South Wales, Sydney, Australia, with a Master of Commerce before taking on sales roles in China, France, the US and Canada. Prior to joining Duoject in 2019, Mr Fortina worked for a leading drug delivery device manufacturer on projects involving ophthalmic, nasal, dermal and injectable delivery devices.

an Aptar pharma company

TRAINING DEVICES AND PATIENT EDUCATION PLAY A CRUCIAL ROLE IN THE SELF-INJECTION DRUG DELIVERY MARKET

In this article, Joe Reynolds, Senior Manager, Strategy and Patient Insights at Noble, discusses the role training devices and patient education play with regard to self-injection therapies.

BIOPHARMACEUTICALS: AN INDUSTRY MARKED BY GROWTH AND INNOVATION

The biopharmaceutical industry has experienced incredible exponential growth in recent decades. Annual revenues have increased from US$4.4 billion (£3.4 billion) in 1990 to $275 billion (£213 billion) in 2018 (a 6,250% increase) and now represent more than 25% of the total pharmaceutical market.[1]

> "The rising number of parenteral medications has prompted drug and packaging manufacturers to continue seeking more sophisticated delivery systems. By 2017, there were over 100 injectable drug products available in prefilled syringes and an ever-rising number of pipeline drugs targeted for delivery by this method."

A primary driver of this rapid expansion is the pioneering pursuit of biologics to treat the growing rate of chronic diseases.[2] Other factors fuelling the industry's robust economic growth are technological advancements, such as the use of smart data, machine learning and wireless connectivity, and the ongoing progress towards developing new products and services to better meet patients' needs and the challenges they confront in the daily use of their prescribed therapeutics.[3]

The Evolution of Injection Devices and Prefilled Syringes

Injectable drug delivery systems have come a long way from conventional syringes packaged with simple vials to include prefilled syringes, autoinjectors, pen injectors and needle-free systems. The origin of prefilled syringes dates back to the 1950s when they were introduced in a polio vaccination campaign.[4]

The rising number of parenteral medications has prompted drug and packaging manufacturers to continue seeking more sophisticated delivery systems. By 2017, there were over 100 injectable drug products available in prefilled syringes and an ever-rising number of pipeline drugs targeted for delivery by this method.[5]

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OPPORTUNITIES AND CHALLENGES FOR SELF-INJECTION DRUG DEVICES

The expanding development of biologic drugs to address chronic diseases, from diabetes and multiple sclerosis to Crohn's disease and rheumatoid arthritis, has resulted in an increasing cohort of patients who rely on self-injection devices to administer their medications at home. Supporting this trend are advances in the design of patient-centric devices, driven by usability and intuitiveness, which are transforming biologic drug delivery.[6] The involvement of training devices and patient education could be essential to the success of this transformation.

But with opportunity comes challenges; nearly half of health care professionals (HCPs) who prescribe self-injecting drug delivery devices do not train patients on how to self-inject correctly.[6*]

The covid-19 pandemic has helped to bring telemedicine into the mainstream as a safe and convenient alternative to traditional in-person medical care. Nearly 60% of respondents to a survey conducted in mid-March 2020 indicated that covid-19 made them more likely to consider using telehealth services in the future, yet over 40% expressed concerns about the ability to be properly diagnosed or treated in a virtual setting.[7] For those patients who lack hands-on access to an HCP, robust patient training and proper onboarding can further support them in adhering to their therapeutic treatments (Figure 1).

The Benefits of Training Devices Combined with Patient Education

Noble, an Aptar Pharma company, first saw the need for better self-injection training at the beginning of the 2010s. Since then, it has become a global leader in the development and delivery of medical device training solutions, patient onboarding strategies and multisensory products for patients and HCPs that aim to improve patient adherence and, ultimately, healthy outcomes.

> "The covid-19 pandemic has helped to bring telemedicine into the mainstream as a safe and convenient alternative to traditional in-person medical care."

Figure 1: For patients who lack hands-on access to an HCP, robust patient training and proper onboarding can further support them during this uptick in telemedicine appointments.

And yet, the need for ongoing patient training persists. While biologic and drug delivery advancements are giving more patients with chronic conditions greater access to therapeutic medications, some patients are non-adherent due to lack of training, improper use and recall erosion.

- 49% of HCPs do not train patients to correctly use their self-injection devices.[6*]
- 84% of patients do not use an autoinjector correctly.[8**]
- 90% of treatment information is forgotten in a week if patients do not practice at home, a phenomenon attributable to the "forgetting curve" theory that, without practice and repetition, retention and recall degrade over time.[9]

An Empirical Look at Patient Training

In 2018, Noble conducted a survey to understand better how patients learn, retain and recall information. This longitudinal study explored whether the use of injection training devices and other stimuli to help reinforce memory could, over a period of time, lead to decreased memory decay, fewer device errors and improvements in the onboarding experience for patients who self-inject.

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

During this first session, researchers replicated an optimal introductory in-office learning experience between an HCP and a patient. This session focused on introducing participants to the drug delivery device and then training them on how to use it with a demonstration device that did not include medication or a needle.

Afterwards, participants could practice on themselves with a training device, with researchers present. Participants were also given feedback and recommendations for improvement, as would occur during training with an HCP. After the 45-minute training session, they were sent home.

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

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

Participants were instructed to practise at home as little or as often as they preferred and were told to keep track of how many times they used their materials. Participants then did not hear from researchers for 14 days, allowing them to practise with the various materials as frequently or infrequently as they preferred. The purpose of this was to uncover the correlation between successful and unsuccessful self-injections and the participants' access to training materials.

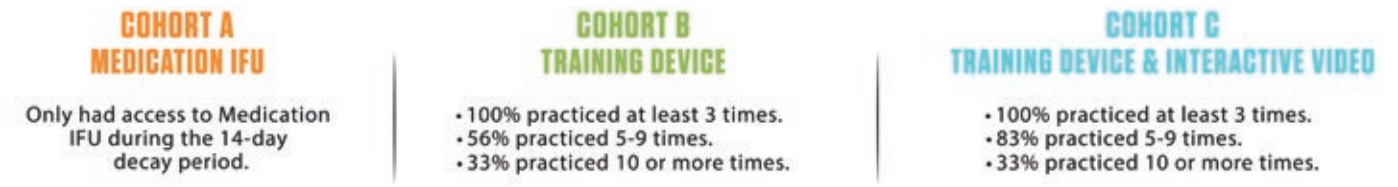

Figure 2: Research found participants with additional training resources were more engaged during the decay period.

The study confirmed that when patients are provided with materials to practise with at home, engagement in their therapy increases (Figure 2).

- 100% of participants practiced at least three times
- 70% of participants with demonstration devices (cohorts B and C), on average, practiced five-to-nine times
- 33% of subjects practiced 10 times or more
- 92% of participants indicated they prefer to receive a training device to take home and practice (Figure 3).

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

Figure 3: The majority of participants stated how important a training device would be to have in the home for practice.

Noble's Training Solutions Aim to Address the Needs of Today's Patients

Human behaviour and user experience are critical elements of a patient-centric training solution. Noble's training devices – including autoinjectors, prefilled syringes, on-body and respiratory devices – are calculated to mimic the feel, force and function of the actual drug delivery device so that patients can practise at home; potentially resulting in less error and increased device familiarity.

Noble also provides IFU for its training devices to help guide patients through proper administration prior to using the true drug delivery device. Specifically designed to complement the actual device, the training IFUs address human factors such as literacy-level messaging, multiple language options and simple step-by-step instructions.

Partnering with Biopharma to Advance Healthy Outcomes

To achieve the goal of fostering healthy outcomes for patients who self-administer their drug therapies, Noble partners with leading biopharmaceutical companies and original equipment manufacturers (OEMs) to develop and launch innovative training platforms and holistic solutions.

One such partnership is with BD. Noble's robust programme for the BD UltraSafe™ passive needle guard portfolio involves designing and manufacturing demonstration and onboarding devices, as well as supporting materials, with the aim of strengthening pharma's commercial launches and improving patient adherence.

The newest addition to Noble's line of demonstrators for the BD UltraSafe™ needle guard portfolio is the BD UltraSafe Plus™ 2.25 mL. Proprietary features of Noble demonstration devices include a resettable locking needle guard that simulates the safety systems with the ability to reset the device for multiple training sessions, and an encased faux needle designed to simulate the forces and feel of an injection.

From clinical trials through to post-launch, Noble's integrated approach includes human factors studies and patient experience mapping; launch strategy and pre-launch training summits; training device distribution and fulfillment; and patient and HCP engagement programmes. This combined comprehensive approach benefits not only the patient, but also Noble's partners, with improved speed to market, lower cost of entry and the ability to customise training devices to brand specifications.

CONCLUSION

Biopharma manufacturing is expected to continue evolving and adopting new and improved technologies, contributing to a global biotechnology market that is expected to surpass $775 billion (£601 billion) by 2024.[1] When it comes to the rising number of self-injection therapies, Noble recommends that patient training and education be part of the standard of care for biopharmaceutical companies and OEMs to help build more confident, healthy – and ultimately, adherent – patients who self-administer.

ABOUT THE COMPANY

Noble, an Aptar Pharma company, is 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,

> "Noble's training devices – including autoinjectors, prefilled syringes, on-body and respiratory devices – are calculated to mimic the feel, force and function of the actual drug delivery device so that patients can practise at home; potentially resulting in less error and increased device familiarity."

Demonstration Devices & Patient Onboarding Tools Aim to Improve Adherence

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prefilled syringes, and on-body, nasal and pulmonary devices in order to increase patient adherence and confidence and decrease usage errors.

**Data obtained via online survey of 1,166 physicians practicing in the US, of which 733 prescribed self-injection devices.*
***Study of 146 patients receiving allergy and immunology treatment, of which 102 patients were prescribed an epinephrine autoinjector.*

BD UltraSafe and BD UltraSafe Plus are registered trademarks of Becton, Dickinson and Company.

REFERENCES

1. *Rader R, Langer E, "Biopharma Market: An Inside Look". Pharma Manufacturing, November 15, 2018.*
2. *"Biotechnology Market will expand at 9.9% CAGR to hit $775 Billion by 2024". Press Release, Global Market Insights, January 23, 2019.*
3. *Event Web Page, "PDA Universe of Pre-Filled Syringes & Injection Devices Conference 2019". Accessed 2019.*
4. *Company Web Page, Becton Dickinson, October 2020.*
5. *"Prefilled Syringes Market (4th Edition), 2016–2026". Press Release, ReportBuyer, April 5, 2017.*
6. *Lang V, Nalan D, "Combination Product Patient Training: How are Patients Trained and Who Conducts the Training?". Am Soc Mech Eng, Frontiers in Biomedical Devices, 2018 Design of Medical Devices Conference.*
7. *"Survey Report: Americans' Perceptions of Telehealth in the Era of covid-19". Sykes. March 2020.*
8. *Potera C, "Misuse of Autoinjectors And Inhalers". Am J Nurs, 201, Vol 115(3), p17.*
9. *Kohn A, "Brain Science: The Forgetting Curve – the Dirty Secret of Corporate Training". Learning Solutions, March 13, 2014.*

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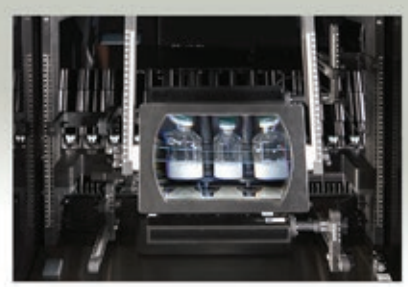
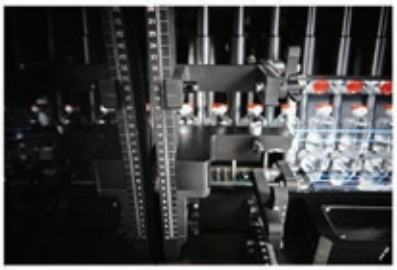
Joe Reynolds is the Senior Manager, Strategy & Patient Insights at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximise value for stakeholders. His experiences include commercial, managed care and product development initiatives with leading medical device, pharmaceutical and biopharmaceutical manufacturers. Mr Reynolds earned his BSc in Business Administration from the University of Central Florida, an MSc in Business from the University of South Florida, and a MSc in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.





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MEASURING AND MANAGING MEDICATION ADHERENCE FROM CLINICAL TRIALS TO ROUTINE CARE: THE INJAY MEMS AS® INITIATIVE

In this article, Arnaud Guillet, Business Development Director, Biocorp, and Bernard Vrijens, PhD, Scientific Lead, Aardex Group, discuss the issue of medication non-adherence in both clinical trials and commercialised drug products, and how Biocorp's Injay connected prefilled syringe solution combined with Aardex's MEMS Adherence Software provides a means to tackle this ongoing problem.

Low adherence to prescribed medication is a well-known issue to all healthcare stakeholders, its clinical and commercial impact having been quantified and heavily documented for many years now. The effects of this issue aren't limited to commercialised drugs and real-life conditions, they also massively affect clinical trials, which impacts the assessment of drug efficacy. When it comes to injectable molecules, and specifically to medication delivered by prefilled syringes (PFSs), patients face additional challenges compared with other types of drugs, such as difficulties with handling the device or needle phobia. These challenges exist right from the drug development stage and persist with increased intensity in routine care. This calls for a solution adapted to the specifics of the field.

> "Strong evidence suggests that up to 50% of trial participants, including those in Phase II, III and IV studies, across most therapeutic areas, do not adhere to the protocol-specified dosing regimens."

Based on this observation, Biocorp, a company that specialises in connected drug delivery devices, and Aardex, a leading player in the field of digital adherence management solutions for clinical trials, have decided to join forces and put together two of their key assets: Biocorp's Injay, a connected PFS solution, and Aardex's Medication Event Monitoring System Adherence Software (MEMS AS®). This combination offers a comprehensive solution to effectively measure and manage treatment adherence for PFS-based medication, both at clinical and commercial levels.

SOLVING THE PROBLEM OF NON-ADHERENCE DURING CLINIC TRIALS

The Consequences of Non-Adherence During Clinical Trials

Clinical trials are designed to evaluate the efficacy and safety of new medical treatments and are fundamental to the drug development process. However, when study participants do not take their medications as prescribed, it can result in underestimated drug efficacy and delay the approval of the investigational product. Strong evidence suggests that up to 50% of trial participants, including those in Phase II, III and IV studies, across most therapeutic areas, do not adhere to the protocol-specified dosing regimens.[1]

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This non-adherence affects medications across delivery routes and life-threatening diseases. The reasons for it are as numerous as they are complex. When it comes to injectables, patients face specific challenges, such as the aforementioned difficulty with handling the drug delivery device and needle phobia, but there can also be issues with complex treatment plans involving various injections spaced out over a period of time. This is particularly true with medication delivered via PFS, which is increasingly being used in clinical trials, especially those evaluating biologics.

While autoinjectors have been introduced to overcome many of the usability issues related to using PFS in routine care, this is not the case during clinical development. There is an urgent need, then, to help patients follow their self-injection regimens in future drug development programmes.

Measuring and Managing Adherence During Clinical Trials

Non-digital methods of monitoring medication adherence, such as pill counting or patient self-report diaries, can be biased, meaning they are not robust enough to be effective during clinical trials. More advanced digital monitoring methods provide a complete understanding of patient adherence behaviours and risk indicators that matter most for the success of a study.[2]

Electronic detection of treatment administration is a robust indicator of when a patient took a prescribed dose – in fact, it is 97% accurate when compared with blood concentrations. It is fair to say that this advanced method of digital monitoring provides the most accurate measure of medication adherence.[2]

Aardex's MEMS incorporates microcircuitry into pharmaceutical packages and devices of various designs. It detects when the medication is administered, then automatically timestamps and stores the dosing history data, before securely transmitting it to the cloud-based MEMS AS®, where it is appropriately analysed.

MEMS AS® is a secure, cloud-based platform that provides sophisticated analysis of medication-taking behaviours for powerful visualisation and focused feedback for the patient (Figure 1). This digital solution can be connected and integrated into third-party applications for risk stratification and patient empowerment. In recent years, MEMS AS® has grown its connected package device offering to a complete ecosystem of delivery systems covering all routes of drug administration, including injectables and inhalers.

Figure 1: MEMS AS® includes both a mobile app and a web portal.

Biocorp's connected PFS Injay (Figure 2) is now part of the MEMS AS® ecosystem and collects essential information such as injection completion, time and date, type of drug, batch number and expiration date. This data is transmitted wirelessly via near-field communication (NFC) through a simple tap of a button. This solution, when combined with MEM AS®, could be the most appropriate response to PFS-specific non-adherence issues during clinical trials.

MEMS AS® Mobile is an app dedicated to patients. It uses onboarding screens to ensure participants have the information they need about the clinical trial, such as dosing regimens, instructions and adherence information, as well as advice on developing strong adherence behaviours. Throughout a clinical trial, participants can access their scheduled appointments, reminders and medication history; can transfer their data to the central system; and can send additional adherence-related information by answering simple questions.

During clinical drug development, the MEMS AS® processes patient data from various compatible smart packages/devices. Using more than 70 proprietary and validated algorithms, it can present a comprehensive picture of patient adherence based on electronically compiled dosing history data. MEMS AS® facilitates connectivity with electronic data capture (EDC), interactive response technology (IRT) and third-party applications.

This advanced approach is a feasible, non-invasive, reliable and easily implemented method of quantifying medication adherence. Therefore, it is an effective way to monitor adherence, and mitigate the associated risks, during clinical trials.

Measuring and encouraging adherence is essential to the success of clinical trials and avoiding errors in the interpretation of patient risks and benefits. Every effort should, therefore, be made to incorporate digital monitoring measures into drug development.[3]

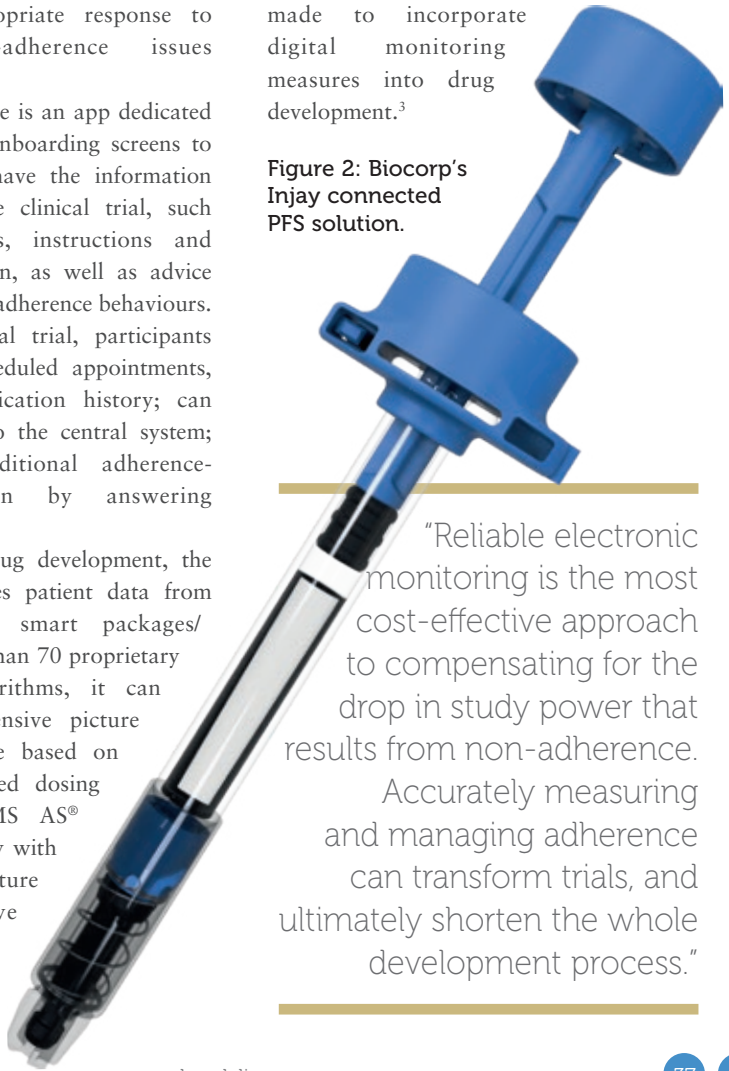

Figure 2: Biocorp's Injay connected PFS solution.

"Reliable electronic monitoring is the most cost-effective approach to compensating for the drop in study power that results from non-adherence. Accurately measuring and managing adherence can transform trials, and ultimately shorten the whole development process."

Optimising Adherence in Clinical Trials Yields Significant Benefits

Reliable electronic monitoring is the most cost-effective approach to compensating for the drop in study power that results from non-adherence. Accurately measuring and managing adherence can transform trials, and ultimately shorten the whole development process. Collecting this information during drug development informs evidence-based risk mitigation strategies and provides key patient behavioural data for a successful commercial strategy. This is demonstrated by MEMS AS®, which has been proven to improve medication adherence, data quality and integrity, and ensure high fidelity to the dosing regimen specified in the clinical trial protocols (Figure 3).

The partnership between Aardex and Biocorp offers a turnkey solution for pharma companies that are developing PFS injectable molecules and want to boost clinical trial efficacy and efficiency. What's more, this solution can be extended beyond the clinical phase, bringing significant benefits to commercialised daily practice.

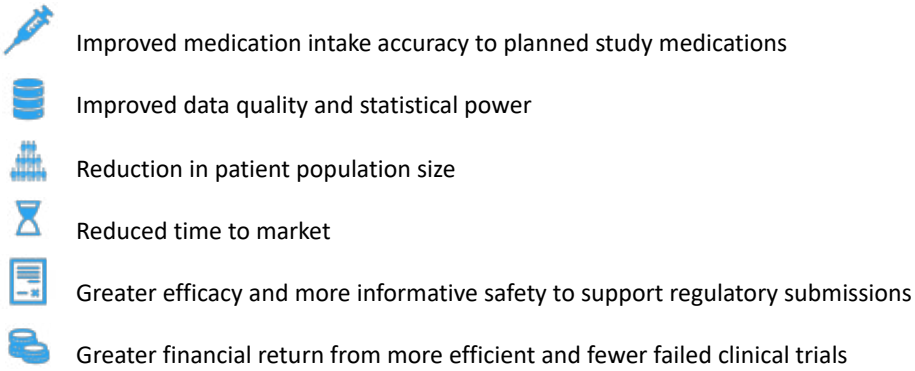

Figure 3: The clinical benefits of MEMS AS®. Source: FDA guidance on trials enrichment strategies and the ICH 9 (R1) addendum on estimands and sensitivity analysis in clinical trials.

USING THE INJAY MEMS AS® SOLUTION TO BOOST ADHERENCE FOR PFS-BASED COMMERCIALISED DRUGS: SPECIFIC USE CASE WITH RHEUMATOID ARTHRITIS TREATMENTS

In chronic diseases, adherence issues are even more prevalent than in clinical trials. People are usually left to manage their medication alone, without the benefit of a highly controlled environment and frequent support from healthcare professionals (HCPs). Some members of the industry have described this phenomenon as the "self management gap".[4] Traditional adherence rates for chronic diseases are around 50%[5] and this figure can significantly decrease over time, with a massive drop in medication refills after six months.[6] This calls for solutions to support and engage patients in the long run.

While these statistics hold true across delivery methods, injectable medicines present specific challenges. People need to learn how to use their injection devices properly, deal with the complexity of treatment protocols and maintain good technique over time. It's especially difficult for injectable treatments that are taken once a month or once a week, as the large gaps between injections often lead to patients forgetting good administration technique, or even forgetting to take their medication altogether.

This is typically the case in rheumatoid arthritis (RA). While some treatment options involve hospital administration, self-management is becoming the norm as various biologics are delivered via PFS as subcutaneous injections. Treatment protocols vary from a monthly or weekly injection for anti-TNF alpha products such as golimumab, certolizumab, adalimumab and etanercept, to daily administration, as with the anti-IL1 anankira or abatacept.

To ensure that their products are successful in real-life conditions, pharma companies commercialising biologics for RA need to design services that will boost treatment adherence and support effective delivery. To do so, they must leverage the available digital options and relevant tools.

USING THE MEMS AS® MOBILE APP AND INJAY TO SUPPORT ANTI-TNF TREATMENT MANAGEMENT

Using the example of an anti-TNF treatment, which is typically delivered by standard PFS every two weeks, we will illustrate how the Injay treatment delivery device combined with the MEMS AS® can support patients and HCPs, improve adherence and result in better clinical outcomes.

Treatment is delivered by the Injay-enabled PFS. This device is comprised of two components: a customised piston rod containing an NFC tag and a finger flange featuring an activator. Both Injay components have similar size and shape to regular PFS components. The Injay piston rod is installed by the pharma company on the assembly line after product filling, where the NFC tag is flashed with key product information. The Injay finger flange is assembled on the PFS after filling, and combines a backstop function. Injay does not add any new components to a traditional PFS package.

Patient onboarding is typically carried out in a hospital setting by a resident rheumatologist, who will offer the connected option, as well the opportunity to download the MEMS AS® Mobile app, and provide a prescription for the Injay-enabled PFS. A rheumatology HCP then would help the patient to install the app and teach them how to use the syringe.

Every two weeks, the MEMS AS® Mobile app will use push notifications to remind people to take their medicine. They will be prompted to open the app, where they will find a simplified treatment delivery guide, information about their treatment, including potential side effects, and motivational features. Guidance is critical to guarantee proper use of a PFS, yet recent studies have shown that many people struggle to follow all of the required steps outlined in instructions for use (IFU) documents.[7] Offering simplified, user-friendly guidance on the app is an effective way to address this issue.

Patients then use the Injay-enabled PFS and, when the piston rod reaches the stopping point, the system will detect a complete injection. They will then be able to timestamp their injection and transfer the product information stored on Injay's NFC tag, simply by placing the Injay device near their smartphone and enabling the app. The information is then stored in MEMS AS® Mobile app and becomes available in real time on the MEMS AS® web portal.

This extra step of transferring data to the smartphone could be considered a hurdle, but it is one that can be overcome by making sure the app is useful to the patient beyond data collection. In this configuration, the app is not merely a recording tool, it's a comprehensive way to engage patients, by providing reminders, injection guidance information and treatment information.

The MEMS AS® Mobile app can also be used to report side effects and monitor other patient factors.

All the information recorded by MEMS AS® is available to the referring physician in real time through the MEMS AS® web portal, which provides a detailed view of injection history, adherence rates and behaviour, potential issues reported and more. It can also be used as a means of communicating directly with patients, re-ordering prescriptions and even managing appointments.

To overworked HCPs, using connected solutions to monitor a pool of patients may be perceived as an additional burden. But this tool can actually help to optimise tasks by providing relevant analytics to identify at-risk patients, prioritise interventions within a multidisciplinary framework and adjust treatment plans. It also helps the care team to interact with patients remotely.

Finally, this approach has the potential to become an additional revenue stream. In many markets, reimbursement schemes are evolving to cover patient monitoring through connected solutions. For instance, in the US, Medicare and Medicaid released a new framework in November 2019 which extended access to reimbursement for certain acts (remote physiologic monitoring, chronic care management) and created new categories eligible for reimbursement (principal care management). These new reimbursement plans open new doors to engage HCPs, as well as compensate them for their time and service. Aardex and Biocorp are looking into these new schemes intensively, and designing the quality measures needed to make their common solution eligible for these reimbursements.

Beyond HCPs and monitoring reimbursements, this new, connected solution is an opportunity for pharma companies to enter into outcome-based contracts with public and private payers. Medication non-adherence is a significant cost burden on healthcare systems and individuals worldwide. There is a clear benefit to payers to look into solutions that target this specific issue and propose outcome-based deals. Interestingly, one of the most famous outcome-based contracts in the field of chronic disease management was signed in 2018 between Harvard Pilgrim and Amgen for Repatha® (evolocumab), a molecule targeting familial hypercholesterolemia, which is administered via PFS. Better adherence measurement and management could surely help towards achieving better outcomes in this specific case.

CONCLUSION

In clinical trials and clinical practice alike, patients not taking their medicine as prescribed presents huge health and economic challenges, impacting pharma companies and healthcare systems alike.

The collaboration between Biocorp and Aardex provides a unique opportunity to monitor patient adherence to PFS in clinical trials and medical practice, while driving up engagement. Injay is easy to use, and its MEMS AS® companion app provides patient support through education, notifications and behavioural advice. The solution provides HCPs will all the information they need to remotely monitor a patient's disease, and study teams with all the data they need to make risk-mitigation plans during clinical trials. And with outcome-based financial compensation moving into the mainstream, it's never been more important to take every opportunity to boost patients' wellbeing.

ABOUT THE COMPANIES

Biocorp is recognised for its expertise in the development and manufacture of medical devices and delivery systems. Today, Biocorp has acquired a leading position in the connected medical device market thanks to its Mallya technology. This intelligent sensor for insulin injection pens allows reliable monitoring of injected doses and thus offers better compliance in the treatment of diabetes. Available for sale from 2020, Mallya spearheads Biocorp's product portfolio of innovative connected solutions.

Aardex Group is a provider of digital solutions to measure and manage medication adherence. Located in Belgium, Switzerland and the US, Aardex develops and markets digital solutions for adherence-enhancing strategies in clinical trials, research settings and professional healthcare systems. Aardex is the central actor of a complete ecosystem that combines its MEMS AS® with a wide range of smart packages and devices that measure patient adherence across all routes of drug administration. The company's vision is to continuously innovate in data-driven

> "Medication non-adherence is a significant cost burden on healthcare systems and individuals worldwide. There is a clear benefit to payers to look into solutions that target this specific issue and propose outcome-based deals."

medication adherence solutions to enhance digital therapeutics and patient empowerment. Aardex is ISO certified, compliant with HIPAA, FDA 21 CFR Part 11 and GDPR, and is regularly audited by pharmaceutical companies.

REFERENCES

1. *Blaschke TF et al, "Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories". Annu Rev Pharmacol Toxicol, 2012, Vol 52, pp 275–301.*
2. *Vrijens B, Urquhart J, "Methods for measuring, enhancing, and accounting for medication adherence in clinical trials". Clin Pharmacol Ther, 2014, Vol 95(6), pp 617–626.*
3. *Breckenridge A et al, "Poor medication adherence in clinical trials: consequences and solutions". Nat Rev Drug Discov, 2017, Vol 16(3), pp 149–150.*
4. *Williams C, Rafiei R, Howald R, "Digital Health Reformulation: from Hope to Hype to Health". ONdrugDelivery Magazine, Issue 108 (June 2020), pp 51–56.*
5. *Kleinsinger F, "The unmet challenge of medication nonadherence". Perm J, 2018, Vol 22(3), pp 83–85.*
6. *"Patient adherence: the next frontier in patient care. Vision and reality, 9th Edition". Research report, Capgemini, 2011.*
7. *Baker C, "Improving Patient Onboarding with Advancements in Medical Device Training". Drug Discovery & Development, Feb 2015.*

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Bernard Vrijens is the Scientific Lead at Advanced Analytical Research on Drug Exposure (Aardex Group). He is also Invited Professor of Biostatistics at Liege University (Belgium). Dr Vrijens holds a PhD from the Department of Applied Mathematics and Informatics at Ghent University (Belgium), is the co-author of seven book chapters and over 100 peer-reviewed scientific papers, and named as inventor on six patents. Dr Vrijens is a founding member of the International Society for Medication Adherence (ESPACOMP), and an active member of several EU- and US-funded collaborative projects around the theme of adherence to medications.


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HOW DIGITAL TECHNOLOGY CAN TRANSFORM CLINICAL TRIALS

In this article, Sheila Trgovac, Vice-President Strategic Development, and Rebecca Ford, Director Program Management, both of Ximedica, suggest that now is the time for innovation in clinical trials – using a patient-centric approach whilst leveraging digital solutions to create a digital clinical trial ecosystem.

The healthcare industry continues its rapid growth year over year, with pharmaceutical development leading the pack. In this highly regulated industry, the regulatory agencies put patient safety ahead of all else – requiring rigorous, highly controlled clinical trials as part of the development process.

Clinical trials are incredibly costly and time-consuming endeavours. The average cost to conduct a Phase III trial is estimated at US$20 million (£15.5 million), with a median of $41,117 (£31,876) per patient and $3,562 (£2,761) per patient visit. These expenses have reportedly risen by 100% in the last 11 years.[1] A significant contributing factor in these remarkable costs – and why clinical trials often falter – comes down to reliable patient engagement. Today, less than 5% of the US population participates in clinical research,[2] with 86% of trials not meeting their enrolment timelines due to issues with recruitment.[3] Patient dropout is also a common problem, with 85% of all clinical trials failing to retain enough subjects to successfully complete a study.[4] These statistics are not surprising, as ~80% of potential participants are living more than two hours away from the nearest clinical trial site.[2]

With a push to lower the commercial price tags of new drugs – and find ways to get them to market sooner – pharmaceutical companies and regulatory bodies are increasingly more open to new clinical trial methodologies and tools, including self-administration at-home dosing, more patient-centric study designs, remote data collection and telehealth touchpoints. Innovative technologies – such as inexpensive sensors, embedded wearables, GPS, more ubiquitous WiFi connections and cloud-based data integration – are enabling easy, real-time, automated data capture.

In parallel, during the current covid-19 pandemic, the pharmaceutical industry is further forced to shift away from traditional clinical trial modalities with a bricks-and-mortar approach – where patients must go to a clinical site for dosing and follow-up – to a more patient-centric approach where the trial comes to the patients in the form of digital enablement. In a period of just a few months, 1,100 clinical trials were disrupted due to lockdown mandates, limited access to clinical sites and people's shift in priorities and comfort levels.[5]

The US FDA encouraged new strategies when it issued new guidelines in March 2020 for clinical studies that included "evaluating alternative methods for assessments, like phone contacts or virtual visits, and offering additional safety monitoring for those trial participants who may no longer have access to the investigational product or the investigational site".

> "Ensuring patient adherence to clinical protocols in an at-home setting is not a trivial problem to solve."

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CLINICAL TRIAL OPPORTUNITIES

Now is the time for innovations in clinical trials to provide a patient-centric approach to driving patient engagement and capturing remote and accurate clinical data (including primary endpoints and patient-reported outcomes) and to drive down clinical trial costs. Imagine a clinical trial that is routed in design around patient comfort yet enables the data capture needed to successfully ensure the safety and efficacy of a novel drug substance. Ximedica is uniquely suited to create and execute such a solution by leveraging technology and data analytics to remotely engage and monitor patients.

Additional benefits are generated when aggregated volumes reach a certain threshold (from multiple products or the entrance of a larger player). A product development firm can leverage the increased volume to diversify the supply chain to different contract manufacturing organisations around the world closer to the respective sales market regions (of company A). In case of future pandemics, tariffs or other impacts on the supply chain, the mid-size manufacturer (company A) is protected from one region's hotspot effect.

DRIVING ADHERENCE

Ensuring patient adherence to clinical protocols in an at-home setting is not a trivial problem to solve. Ultimately, patient adherence to the clinical protocols – including dosing and follow-ups – drives the data collection needed to successfully meet the safety and efficacy parameters laid out for successfully taking the new drug to market. Developing product systems combining thoughtfully designed hardware with digital solutions can get us to a place of adherence. Considering both designing for the user and the use environment enables patients to stay on track with minimal disruption to their daily lives.

Simple considerations as to when and where the patient is administering the drug provide significant insight into the needs for clinical trial. For example, should the system fit next to the patient bed or on a side table? Do the patient monitoring solutions need to be worn all day? Does the drug product require specific storage conditions? How often is the drug administered – daily, weekly, monthly? In the case of a longer latency between dosing or clinical follow-ups, using adaptive artificial intelligence (AI) can drive adherence through simple reminders to an app on your phone or an alarm linked to the data capture or packaging components of the drug delivery device. All of these considerations allow for more thoughtful solutions that ultimately aid, and potentially motivate, the patient to stay on track with the clinical trial.

> "With covid-19 accelerating the need for virtual visits through telehealth, the platform foundations have been laid to give patients access to healthcare professionals whilst in the comfort of their own home."

Another consideration when it comes to keeping patients engaged whilst leveraging the current digitally driven times involves the deployment of multi-channel communication to provide a community of support – giving patients a platform to connect to a digital community for support from professionals and peers, whilst also engaging them in electronically capturing their daily quality of life.

With covid-19 accelerating the need for virtual visits through telehealth, the platform foundations have been laid to give patients access to healthcare professionals whilst in the comfort of their own home. This access removes the need for patients to travel to the clinical trial site for routine follow-up visits. Furthermore, telehealth – in combination with electronic health records – allows patients to stay closer to home even when there is a need for blood draws and/or vital checks which could be done through a local lab.

ENSURING ACCURATE DATA CAPTURE IN A REMOTE SETTING

During a clinical trial, data is key. Whether it is capturing something as simple as how the patient is feeling, to basic vitals (for example, weight or temperature), to dosing, to critical endpoints – all the data needs to be captured, correlated and analysed through the clinical trial process to produce a safe and effective drug. In traditional clinical trial settings, patients would go to a clinical trial site to be dosed, for routine follow-ups and to check vitals. At each touchpoint, data would be captured in a very specific manner by a clinical investigator who had been trained to the clinical protocol. Based on the controls this puts in place, the data is presumed to be accurate.

> "Through innovative digital technologies, system solutions can be created and integrated to support the full clinical trial ecosystem."

When considering performing clinical trials in a remote setting, the control over data capture shifts from the clinical investigator to the patient. But even in the hands of the patient, it is imperative to capture both quantitative data points – like when the patient took their medication, how much of the medication was given and vital measurements – and qualitative data points, such as how the patient is feeling from day to day. Through innovative digital technologies, system solutions can be created and integrated to support the full clinical trial ecosystem.

For example, injection pens can be made with sensors for monitoring dose tracking, adherence to the dosing schedule and, in some cases, even progression of the disease state. By enabling the injection pen with the addition of wearable sensors, remote monitoring and electronic patient diaries, you begin to touch on system solutions that can capture the needed data remotely. These passive-data-capture digital solutions can not only capture the same data that would be captured in the clinic but can provide some significant benefits, with a larger quantity of data captured in less time.

According to a Harvard Business School study, if a participant visits a study site a few times a month, the sponsor can collect ~50 hours of data on the participant. Yet the passive collection of patient data in their own home can generate nearly 4,000 hours of data – representing a 75-fold increase. In many respects the data is also more authentic and reliable than that collected in a clinical lab environment. One recent study found that 64% of researchers have used digital health tools in their clinical trials, and 97% plan to use these tools in the next five years.[6]

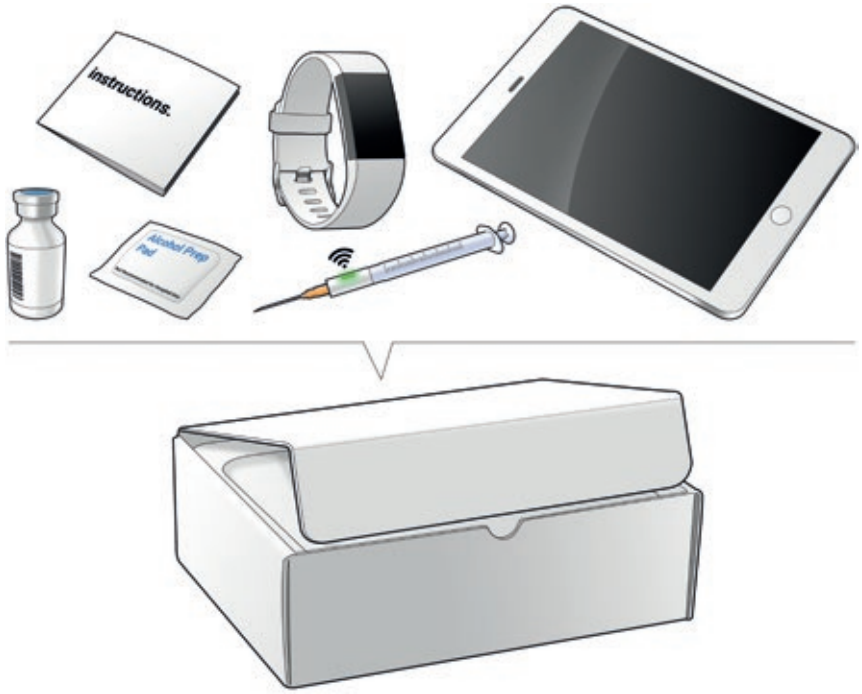

Figure 1: Aspirational illustration of a home setting solution.

EXECUTING A PATIENT-CENTERED SOLUTION

The challenge many clinical trial teams face is taking that first step of accurately defining the needs of the clinical trial and translating them into a system solution customised for that specific trial. Leveraging its core expertise in human-centred design and development, Ximedica is well situated to optimally translate the clinical trial experience to the home setting. Figure 1 shows an aspirational illustration of what that home solution could include.

To help demonstrate this, Ximedica has broken this problem down into some discrete areas for exploration and concept generation – patient engagement, dosage delivery, data tracking and follow-up, as shown in Figure 2. With each of these areas, there is regulatory consideration as to how it is applied to the solutions for use in a clinical trial and how that may translate into – or conflict with – commercial intent.

Putting commercial intent aside for the sake of exploring innovative options, Ximedica's team of engineers has come up with initial solution sets for the previously named categories, including connected/IoT (Internet of Things) smart caps; gamification or progress tracking for continued engagement; involvement of clinician or AI for accountability; in-home-enabled health or progress tracking; dose reminders; passive or minimal extra use steps for dose tracking; and patient interaction or engagement for symptom tracking. In Figures 3, 4 and 5 are some illustrations of what could become part of an overall patient-centric, trial-specific, remote system for clinical trials.

While this exercise was aspirational in nature and not limited to one specific clinical trial, the output informs us that the custom solution sets are limitless. With the right strategy and development team in place, a trial-specific solution can be developed to meet the needs of remote clinical trial execution.

DRIVING DOWN CLINICAL TRIAL COSTS

By driving patient engagement through enabling digital system solutions to capture patient data in a remote setting, we are aiding patient retention – which decreases the need for additional recruitment. Additionally, connected digital solutions remove the need for on-site patient visits – driving down the per-patient cost. If we are able to decrease the per-patient cost and simultaneously ensure higher patient retention, digital solutions in clinical trials are sure to support the movement to get drugs to market at a lower cost and in less time.

CONCLUSION

Leaders in biopharma clinical development are experiencing increasingly difficult challenges in screening, retaining and

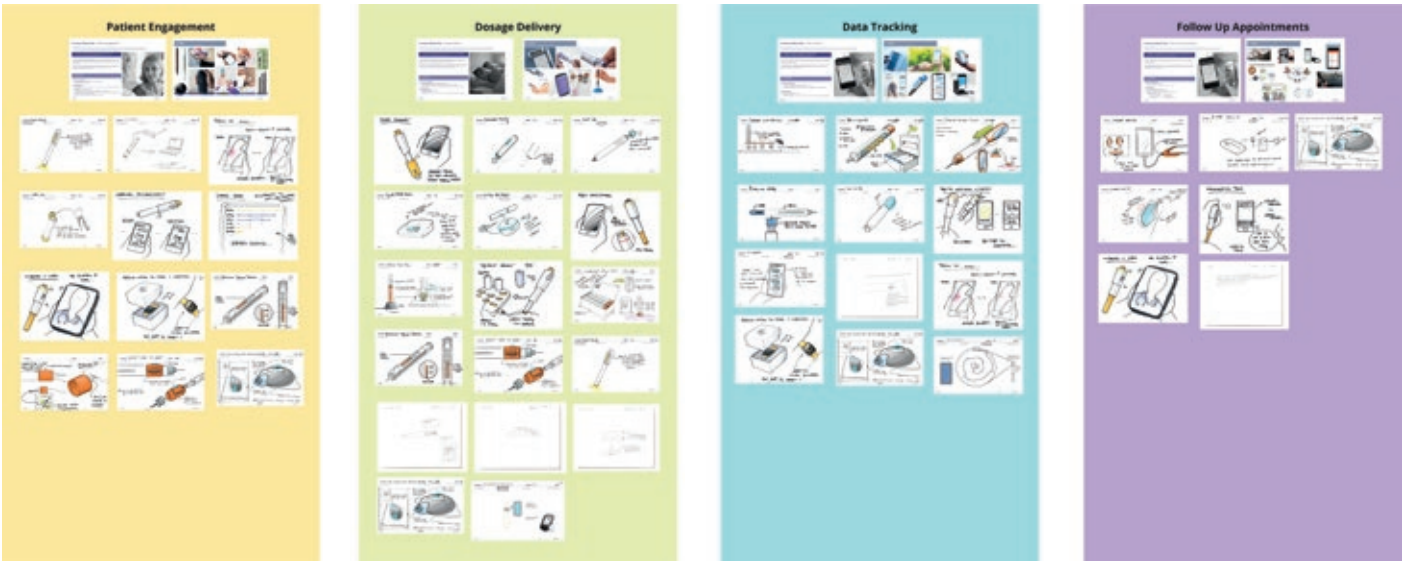

Figure 2: Clinical trial engagement concept generation storyboard.

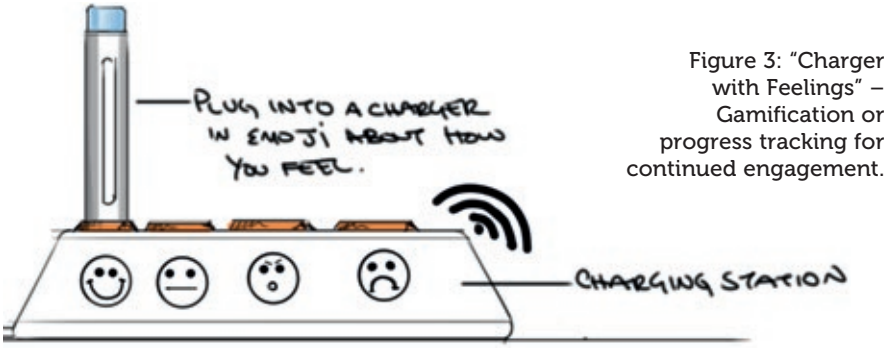

Figure 3: "Charger with Feelings" – Gamification or progress tracking for continued engagement.

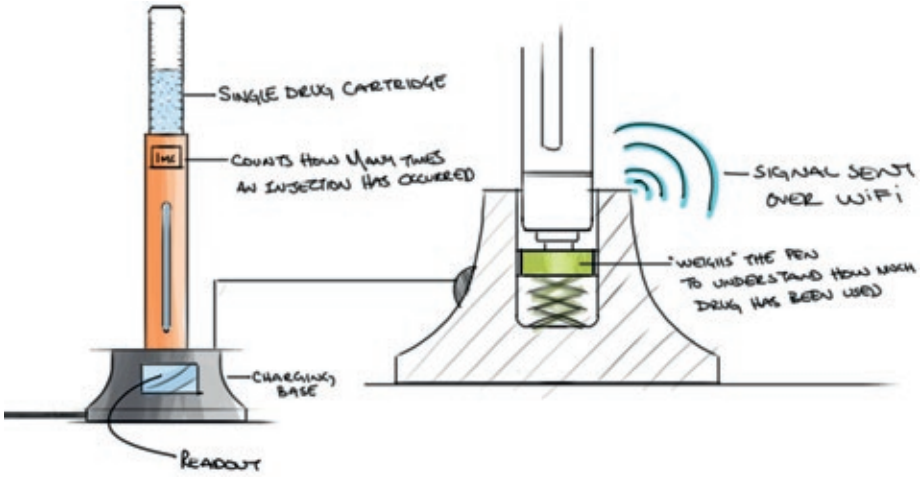

Figure 4: "Weigh the Pen" – Passive or minimal extra use step dose tracking.

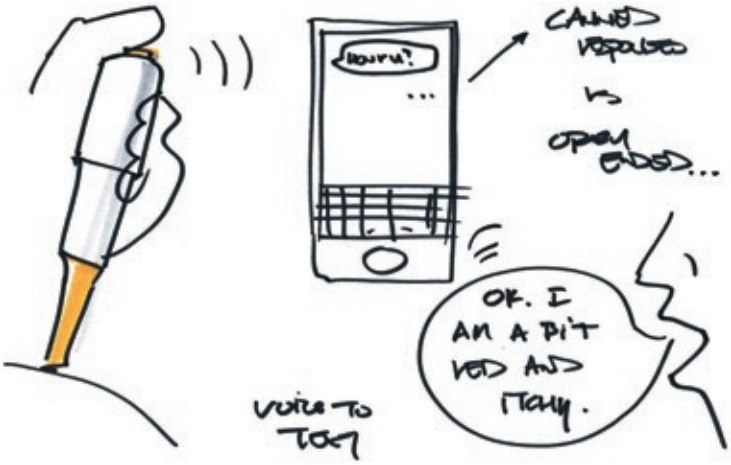

Figure 5: "Voice to Text" – Patient interaction or engagement for symptom tracking.

monitoring patients. Now is the time for innovation in clinical trials by seeking a patient-centric approach whilst leveraging the vast array of digital solutions to create a digital clinical trial ecosystem. Ximedica is uniquely poised to deploy game-changing technologies in the clinical trial process and welcomes the opportunity to collaborate and drive improved patient engagement and optimised clinical trial metrics.

ABOUT THE COMPANY

Ximedica is a full-service ISO 13485-certified and FDA-registered product development firm. It is a trusted advisor to many of the healthcare industry's top innovators, developing medical products that transform the lives of patients, caregivers and clinicians every day. From concept to commercialisation, Ximedica guides clients through every stage of the development process to bring innovative products to market faster, more consistently and more efficiently than ever before.

REFERENCES

1. *Rathore A, "Getting A Handle On Clinical Trial Costs". Clinical Leader, April 25, 2019.*
2. *Coravos A, "Decentralized clinical trials". Elektra Labs, November 12, 2018.*
3. *"The future of clinical trials". Research Report, Accenture, September 19, 2019.*
4. *Morgan C, "Are Site-Less Trials the Future of Clinical Research?". Drug Discovery & Development, September 25, 2017.*
5. *"Update on clinical trials disrupted due to covid-19". GlobalData Healthcare, May 14, 2020.*
6. *Coravos A, "Clinical trials are in need of a digital makeover. Web Page, Harvard Business School's Digital Initiative, January 23, 2018. (Accessed October 2020)*

ABOUT THE AUTHORS

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 innovative 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. Throughout her career, Ms Trgovac's experience in full phase development has resulted in successful commercial launches of impactful products.

Rebecca Ford has over 10 years of experience in engineering, new product design, development and project management across the medical device and pharmaceutical industries. She has a proven track record of leading cross-functional medical device development teams from concept through to release. Ms Ford joined Ximedica with experience in a variety of fields within the medical device market, including spinal instruments and implants, cell therapy, biologics and wound management. She has been successful in developing products in both large medical device company environments, such as Smith & Nephew, as well as start-up environments.

ENHANCING PROTEIN PRESERVATION DURING BIOLOGICAL DRUG PREPARATION AND DELIVERY

In this article, Adrien Bouillet, R&D Mechanical & Plastics Manager, EVEON, Loïc Girois, PhD Student, Laboratoire des Matériaux et du Génie Physique (LMGP), and Marianne Weidenhaupt, PhD, Associate Professor, LMGP, discuss the results of work carried out in joint efforts by EVEON and LMGP in the field of protein adsorption and aggregation, and how the results of this work have led to improvements in the design of EVEON's proprietary micropump.

Therapeutic proteins are injectable biological drugs with a high specificity, which are used for the treatment of many diseases, including diabetes, autoimmune diseases and cancer. They are regularly marketed as lyophilised powders that need to be reconstituted, either manually or automatically, prior to injection.

It is well established that exposure to certain material and air interfaces, to which proteins adsorb, can have a strong impact on their stability.[1] While adsorbing at interfaces, proteins change their conformation, which can lead to the formation of protein aggregates. This can entail a loss of function or lead to the development of immunogenic responses and, consequently, adverse reactions in patients. Moreover, these aggregates can also obstruct the fluid flow in reconstitution and injection devices, having a negative impact on their performance. Improving the stability of these drugs is generally achieved by formulation excipients, such as surfactants, but can also be maximised by a precise design of device components and fluidic protocols.

In order to enhance protein preservation during drug preparation and delivery, EVEON and LMGP have worked together through the LabCom programme to improve EVEON's technology platform. Three different versions of EVEON's proprietary micropump were studied for their mechanical performance, analysing the stability of an unformulated drug solution during pump cycles at different speeds (20, 50 and 80 rotations per minute).

> "It is well established that exposure to certain material and air interfaces, to which proteins adsorb, can have a strong impact on their stability."

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The drug chosen was an unformulated human insulin solution at 0.7 mg/mL in a 25 mM tris buffer of pH 7.4 with 125 mM NaCl. Unformulated insulin is well known for its high tendency to adsorb and aggregate at interfaces,[2] and can therefore be considered a suitable test case for a worst-case scenario with respect to drug aggregation. The unformulated protein solution was transferred through the pumps over 500 suction/discharge cycles. The operation specifications define 300 pumping cycles as a target limit. Typically, the torque values increase with pump cycles at all speeds.

Figure 1 shows the correlation between torque increase and speed for EVEON's original micropump and comparative results for the three pumps are shown at 80 rotations per minute in Figure 2. The micropump evolution (siliconised) showed the lowest and most stable torque values.

Insulin stability was monitored by Thioflavin T fluorescence (480 nm), a conformation-sensitive dye indicative of amyloid aggregates. The appearance of Thioflavin T-positive insulin aggregates in unformulated solutions was recorded for all pumps. The extent of fluorescence depended on insulin concentration, pumping speed and the number of cycles through the pumps. A thorough comparative analysis was completed on the micropump evolution (silicone free) and the micropump evolution (siliconised), the two pumps that showed the lowest torque values. At 80 rotations per minute and 500 cycles, aggregating was detected in one out of nine experimental runs for the micropump evolution (siliconised), whereas it was detected in four out of nine for the micropump evolution silicone free (Figures 3 and 4).

These results show that reduced torque values correlate positively with a lower aggregation potential when tested with unformulated insulin solutions in the pumps. All EVEON's micropumps showed no Thioflavin T-positive insulin aggregates when tested with formulated insulin solutions. The results led to a better understanding of the original version of the micropump, which allowed for a drastic reduction of the aggregation potential with the design of the new micropump evolution and its siliconised version.

In conclusion, the results confirmed that the new micropump evolution, even in its silicone-free version, may be considered

"The results led to a better understanding of the original version of the micropump, which allowed for a drastic reduction of the aggregation potential with the design of the new micropump evolution and its siliconised version."

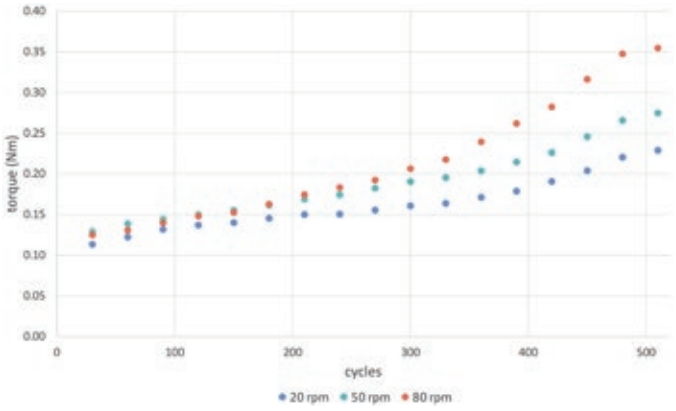

Figure 1: Torque as a function of number of cycles at three different speeds for EVEON's original micropump.

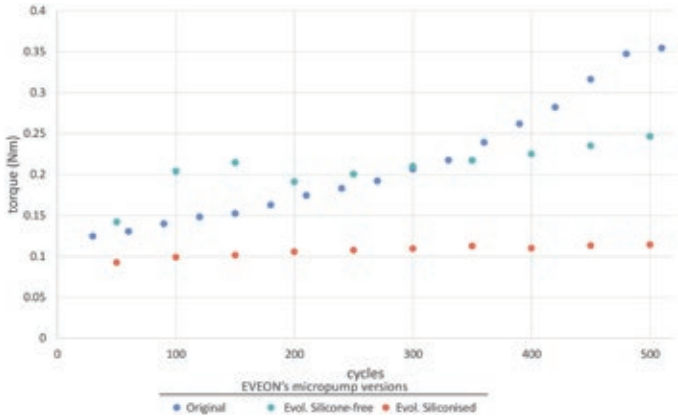

Figure 2: Torque as a function of number of cycles at 80 rotations per minute for three different versions of EVEON's proprietary micropump: original, evolution (silicone-free) and evolution (siliconised).

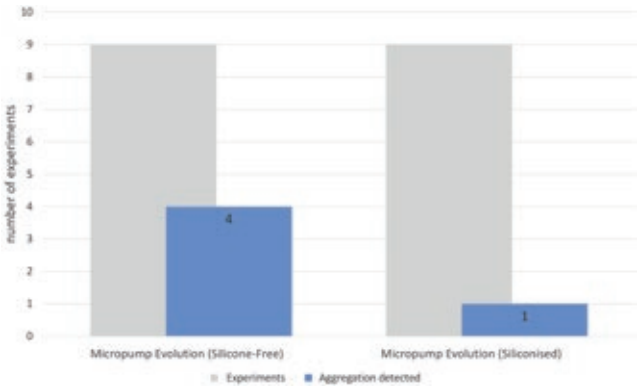

Figure 3: Insulin aggregation after 500 cycles at 80 rotations per minute for the two evolution versions of the pump. The number of experiments with Thioflavin T-positive insulin aggregation is shown with blue bars, and the total number of experiments (nine) is shown with grey bars.

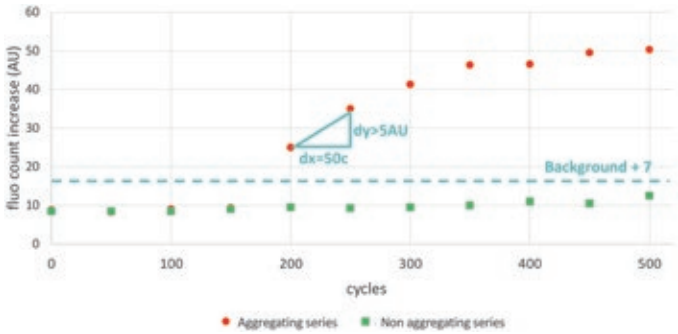

Figure 4: An experiment is considered ThioflavinT-positive when the fluorescence increment after 50 pump cycles is greater than five, and the fluorescence signal at 500 cycles is greater than seven times the baseline fluorescence.

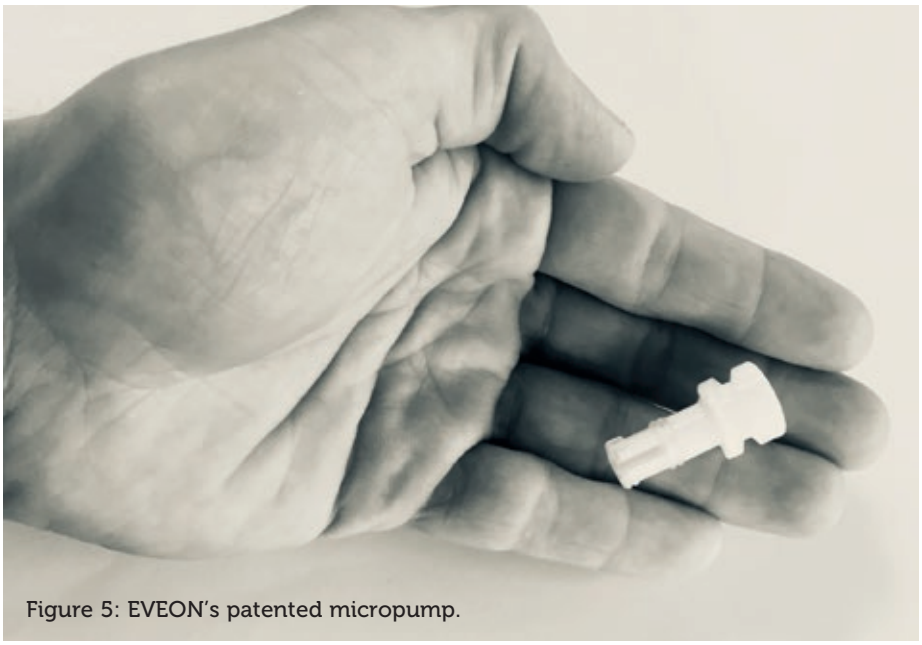

Figure 5: EVEON's patented micropump.

a preferable solution when looking to mitigate the risk of protein aggregates in biopharmaceuticals during drug preparation and delivery.

EVEON's proprietary micropump (Figure 5) is a modular platform design that may offer a reliable solution to pharmaceutical and biotech companies aiming to develop an automated drug preparation device for at-home patient care.

ABOUT THE ORGANISATIONS

EVEON is an ISO 13485 certified company that designs and produces automatic, secure and connected medical devices for the preparation and delivery of therapeutic treatments to improve patient quality of life. EVEON places the needs of patients and healthcare practitioners at the heart of its developments, designing simple and intuitive devices to improve therapeutic performance, compliance and homecare conditions. Its expertise has just been recognised by Forbes magazine, which ranks EVEON as the third most inventive company in France in the medical technologies category. As an end-to-end innovation partner, from concept to CE marking, with strong know-how and capabilities in fluidics, mechanics and electronics, EVEON is recognised as a key partner for innovative companies offering a global service from feasibility to manufacturing.

Laboratoire des Matériaux et du Génie Physique (LMGP) is a joint research unit of the Grenoble Institute of Technology and the French National Centre for Scientific Research (le centre national de la recherche scientifique, CNRS), developing research in materials for science and materials for biomedical engineering. It is active in the fields of functional thin films, surface nano-engineering and interactions between materials and biological matter. In the latter field, LMGP has long-standing expertise in the analysis of therapeutic protein stability at interfaces using biophysical surface-sensitive techniques and biochemical assays. LGMP and EVEON operate a common laboratory supported by the IDEX funding programme, with the aim of optimising the stability of therapeutic proteins in their automated preparation and injection devices. This academic-industrial alliance allows for the improvement of EVEON's products, while simultaneously gaining fundamental knowledge about protein stability at interfaces.

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REFERENCES

1. *Pinholt C et al, "The importance of interfaces in protein drug delivery-why is protein adsorption of interest in pharmaceutical formulations?". Expert Opin Drug Deliv, 2011, Vol 8(7), pp 949–964.*
2. *Sluzky V et al, "Kinetics of insulin aggregation in aqueous solutions upon agitation in the presence of hydrophobic surfaces". Proc Natl Acad Sci USA, 1991, Vol 88(21), pp 9377–9381.*

ABOUT THE AUTHORS

Adrien Bouillet holds a Masters degree in Mechanical Engineering and Integrated Design. He went abroad for the first years of his career, and worked as a Mechanical Design Engineer in Scotland, New-Zealand and Australia; upon moving back to France, Mr Bouillet joined EVEON in 2015. After five years, he took on the position of R&D Mechanical & Plastics Manager, leading a team of four Mechanical Design Engineers, two Plastics Engineers and one Mechanical CAD Technician. Placed at the heart of EVEON's development, the R&D Mechanical & Plastics team works very closely with both the Digital and Fluidics teams, to design ergonomic, smart and reliable products.

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Stevanato Group

LEVERAGING INTEGRATION AT EACH PHASE OF A DRUG DELIVERY SYSTEM PROJECT

In this article, Steven Kaufman, Vice-President Drug Delivery Systems, and Adam Stops, PhD, Drug Delivery System Product Manager, both of Stevanato Group, describe how an integrated offering can help customers at each phase of a drug delivery system project.

For more than 70 years, Stevanato Group has been renowned as a leading provider of primary packaging, producing cartridges, syringes and vials to the highest technological standards. The SG Fina, SG Nexa and SG Alba product lines are part of a wide range of glass solutions that embody Stevanato Group's long history of quality and reliability.

Today, as a full-service partner, Stevanato Group provides a suite of products, technologies and services for pharmaceutical companies. Customers can source their glass primary packaging, assess their formulation stability through analytical testing services, select one of the many proprietary drug delivery devices or even develop a new breakthrough device, and have their combination product manufactured to the highest standard using state-of-the-art injection moulding and automated assembly equipment with integrated inspection technologies. As a result of this comprehensive offering, Stevanato Group has established itself as a partner of choice within the industry.

A crucial aspect of Stevanato Group's business model is that customers can access these products, technologies and services independently. This flexibility enables clients who may be partnering with multiple suppliers to engage with Stevanato Group for any phase of their project and benefit from the resources, expertise and knowledge that the group offers within that discipline (Table 1).

However, as more and more primary containers are integrated into drug delivery devices, Stevanato Group's wide range of capabilities provides an advantage for building end-to-end solutions for pen injector, autoinjector, wearable and inhaler projects. By forging deeper partnerships with customers, the full depth and breadth

GLASS PRIMARY PACKAGING	ANALYTICAL SERVICES	CONTRACT MANUFACTURING	ASSEMBLY EQUIPMENT
SG ALBA®	CONTAINER SELECTION	DESIGN & DEVELOPMENT	SUB-ASSEMBLY
SG NEXA®	CONTAINER COMPATIBILITY	PRECISION INJECTION MOULDING	FINAL ASSEMBLY
SG FINA®	DRUG DEVICE OPTIMISATION	ASSEMBLY	PACKAGING & SERIALISATION
		REGULATORY AFFAIRS	
		IP	

Table 1: Customers can access a suite of products, technologies, services and capabilities independently or as a full package, for an integrated, end-to-end solution.

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of Stevanato Group's knowledge, experience and competencies can bring benefits to a project at multiple levels.

BENEFITS OF AN INTEGRATED APPROACH

Having evolved from a producer of pharmaceutical glass to a full solution provider, Stevanato Group understands how a pharmaceutical product, container, closure and drug delivery device interact with each other and work together to form a cohesive system. With this unique perspective, Stevanato Group has the ability to solve problems holistically. The primary container, the design of the drug delivery device and the manufacturing processes can all be optimised in a coherent approach with a common goal of producing a market-leading product.

For example, if a customer requested a design of an autoinjector with a unique technical requirement around dose accuracy, or if they wanted to increase overall cost efficiencies, Stevanato Group could approach this from several different angles:

- Primary container – is it possible to customise the container or adapt production techniques to better suit the new requirements?
- Device design – is it possible to refine the design of certain components?
- Plastic manufacturing – is it possible to tighten moulding tolerances, assembly processes and quality controls?
- Final assembly equipment – which are the critical assembly steps that need to be monitored to ensure device functionality?

As a single entity with control over multiple aspects of a project, Stevanato Group says it can take advantage of technical and commercial synergies. For example, a designer of a drug delivery device will spend a considerable amount of effort on a detailed tolerance analysis to ensure all the plastic components are well toleranced. However, for the most important component – the primary container – there is often a lack of information on process capability and reliability (Cpk and Ppk) because either the information is proprietary and/or the information required is new and unique to the device design. In both cases, the designer is in a compromised position and has to make estimates. This leads to inefficiencies in both device design and project timelines and, in worst case scenarios, can even compromise the robustness of the final product.

> "The primary container, the design of the drug delivery device and the manufacturing processes can all be optimised in a coherent approach with a common goal of producing a market-leading product."

At Stevanato Group, the device designer has access to all the necessary information, including the process performance and capabilities of the glass production line, and can work directly with the glass containers manufacturing team to develop solutions. This also applies to the manufacturing of the device itself: the designer works closely with manufacturing colleagues in Germany and the US who have market-leading expertise in injection moulding, as well as colleagues in Denmark who are world-renowned in automated assembly equipment suppliers. Communication between internal lines of business is transparent and information sharing is fluid. This powerful combination opens the door to smoother projects, more reliable products and improved customer relations.

To further illustrate some of the benefits of this holistic approach, what follows is a description of a typical project flow, according to Stevanato Group's development process. This approach facilitates communication between different departments and functions, so that knowledge, experience and synergies can be maximised for the benefit of customers, their projects and the resulting end products.

DEFINITION PHASE

Regardless of whether a pharmaceutical client seeks to customise a platform product, such as the SG Alina disposable pen injector, or develop an entirely new device concept on demand, the first step is the definition phase. This phase is where ideas, concepts and notions of what a product might be start to take shape. An interdisciplinary team will perform background research, early explorations and experiments which either compare platform device characteristics to customisation requests or – for a new concept – help define gaps in the market, technology capabilities and user needs, which often represent the key drivers for a particular project. This phase may include business case analysis, early technology explorations or other screening exercises.

> "A first draft of the product specifications and definition provides direction of what the product will do, how it will do it and what it could look like – setting the stage for the product performance focused development to come."

The goal before progressing to the next phase is to justify and define the project via preliminary technology risk assessment, intellectual property assessment, manufacturing assessments, and market and business assessments. Although many aspects are preliminary, these foundational activities are essential for providing the team with direction and framing the areas of work for the project.

Even in this early phase, the value of the Stevanato Group's integrated approach can start to be seen. From extensive knowledge in regulatory affairs, to supply chain and manufacturing know-how, to wide product line offerings and industry expertise, the Stevanato Group team can include experts from a wide range of functional areas. This team can help shape the project and identify future risks to be monitored and develop ways for them to be mitigated. At the culmination of this phase, a first draft of the product specifications and definition provides direction of what the product will do, how it will do it and what it could look like – setting the stage for the product performance focused development to come.

CONCEPT AND FEASIBILITY PHASE

The concept and feasibility phase is where the product really begins to take shape. Whilst the exact activities will vary depending on whether the project involves feasibility of a customisation request or concept generation for a new technology,

early shape models, human factors explorations and studies may be performed to start exploring the external design, while laboratory and breadboard prototypes may be built to develop the functional design. Early drafts are created, and early prototypes or models may help visualise the product concepts.

Thanks to Stevanato Group's integrated approach and long-term experience in glass container design and manufacturing, the core project team works in harmony with the internal glass primary container and laboratory teams to leverage the group's broad capabilities. This includes a comprehensive range of technical and analytical services available through its SG Lab (Italy) and its Technology Excellence Center (US TEC) in Boston (MA, US) – supported by a network of collaborations and partnerships with prestigious universities, research institutes and scientific organisations.

With a comprehensive understanding of the science behind glass primary packaging, Stevanato Group has the scientific and technological expertise to support pharma companies from early-stage formulations to device integration. As a direct result of these capabilities, Stevanato Group has devised a line of cartridges specifically for autoinjector, pen injector and wearable programmes. SG Nexa syringes are specifically designed to meet the dimensional requirements of device programmes and provide excellent mechanical resistance.

Highly qualified and experienced specialists can guide clients through the container selection process and optimisation options, while design engineers concurrently provide feedback on how the different container options may impact the device concepts and functionality. SG Lab and TEC provide testing and analytical expertise to support risk mitigation and development efforts. The input from the manufacturing team will be incorporated to ensure a viable scale-up plan.

While the full details continue to be developed in the next phase and changes can continue to be made, this phase ends when the customer agrees on the product concept, feasibility, prototypes and other information needed to deliver the product.

DEVELOPMENT PHASE

Once the selected concept and feasibility have been approved, the team dives into all the project details in depth. The development phase incorporates all the engineering, testing, analysis, refinement, iterations and modifications necessary to ready the product for production implementation.

Common activities during this phase can include laboratory functional testing, early stability studies, usability and formative human factors studies, measurement system development and small prototype production. The design is now fully analysed and detailed to ensure expected function, usability, manufacturability, cost and safety profiles. As product prototypes are evaluated to verify intended functionality and user feedback is incorporated, the designers can close in on final product performance requirements and specifications.

The engineering teams at Stevanato Group have access to a wealth of proven manufacturing and product knowledge and experience to ensure products can be produced and assembled efficiently and reliably at volume. This feedback can inform final design choices and features so that the design and manufacturing approach are iterated together; ensuring smooth technology transfer and manufacturing scale-up in the next phase.

By the end of the development phase, the design is considered frozen. All the product specifications have been finalised, the product is fully defined and the design has undergone engineering verification and formative user studies. Manufacturing plans are written and ready for implementation. Any IP submissions are finalised and the regulatory strategy is locked in.

DESIGN QUALIFICATION AND CLINICAL BATCH PRODUCTION

The next phase of the development is design qualification through verification testing and user validation studies. To enable this, manufacturing processes equivalent to the final production methods are initiated. Typically, these manufacturing methods will use single-cavity tooling and semi-automated assembly methods, depending on the project and the customer requirements. Stevanato Group uses moulds (Figure 1) produced to the highest quality and precision, which are then validated for part-to-part consistency using in-house metrology expertise.

In-house engineering teams also design each element of the assembly line, including part feeding, assembly, labelling and packaging, to ensure the chosen design at this phase can be scaled up to commercial volumes in the future. It is imperative that the choices made at this phase, for both injection moulding and assembly, are made with a view to commercial manufacturing processes. These manufacturing processes are qualified through installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) protocols, based on a set of robust and efficient protocols, built from a long history of manufacturing.

By leveraging Stevanato Group's integrated capabilities and holistic approach, issues that might arise are immediately investigated and resolved by a team of experts from all functional areas under one

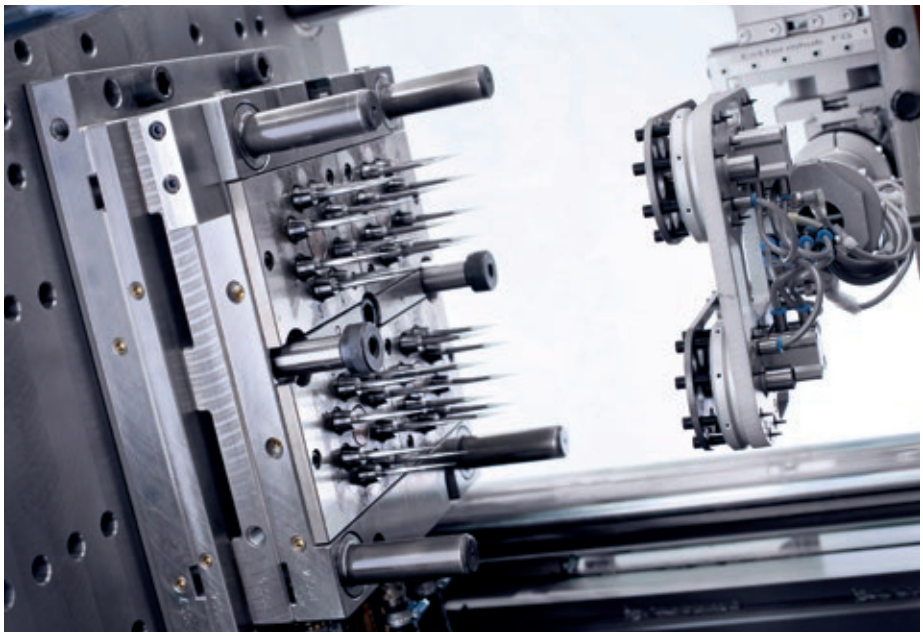

Figure 1: Stevanato Group boasts in-house expertise in tool design and maintenance, providing high-quality and precision moulds.

roof. This is extremely valuable, especially at a time when the pressure to succeed is high.

Following the validation of the manufacturing line, the device is then fully verified through design verification testing following international standard protocols and using in-house testing capabilities. Stevanato Group has invested heavily in device testing capabilities, in both its headquarters in Piombino Dese (Italy) and its primary device manufacturing site in Bad Oeynhausen (Germany).

Upon successful completion of design verification, the device is validated through user studies, including summative human factors studies, depending on the customer requirements – Stevanato Group can perform these activities on behalf of customers or support them during these phases. Subsequently, clinical batches are produced, typically in the range of 10,000 to 100,000 samples, to enable the customer to either perform clinical trial studies or stability testing, depending on the needs of the customer.

SCALE-UP AND INDUSTRIALISATION PHASE

Upon completion of the design qualification and clinical batch production, the focus is on scaling up production for commercial quantities. Commercial tooling and fixtures are commissioned, built and debugged. During this time, process engineers will challenge each operation to monitor critical processes and parameter sensitivities to optimise them for commercial production success. Operators are trained and begin operating the production machinery. Larger scale product verifications are performed to confirm reliability and overcome any issues revealed at scale. The team will revisit earlier risk plans and compare current product performance to support a final determination of safety and appropriateness for use.

By continually building on its contract manufacturing track record that includes over 50 years of injection moulding experience, Stevanato Group uses moulds fabricated to the highest quality and precision which are then validated for part-to-part consistency at scale. In-house engineering teams design each element of the production line, including part feeding, assembly, labelling and packaging. The entire line is laid out, built and then debugged, while overall quality and inspection methods are validated.

Figure 2: Stevanato Group has more than 160 injection moulding machines at three locations in the US and Germany for GMP, ISO 8 and ISO 7 cleanroom production.

As the initial launch lines are finalised, long-term production solutions are concurrently being planned and ramped up. For example, a product may launch with an initial process which produces lower quantities, while a full production line producing five or 10 times the throughput is being built. Stevanato Group has extensive experience in designing, building, programming and qualifying high speed assembly and packaging equipment. With hundreds of installations worldwide, Stevanato Group has become a proven partner for scalable, modular assembly and packaging solutions featuring state-of-the-art inspection technologies.

PRODUCTION PHASE

With the initial launch line validated and ready, the first production batches can be produced. During early production, engineers keep a very close eye on all operations to make sure things are running smoothly and as expected.

Stevanato Group's manufacturing sites in Germany and the US have a combined 16,900 m^2 of controlled and cleanroom production areas (Figure 2) – and those areas are being expanded to make ready for new projects. This includes GMP or Class ISO 5, 7 and 8 cleanrooms, depending on the project requirements. There are over 160 high precision moulding machines managed by production engineers experienced in running up to 128 cavity tooling. With in-house tool shops, tooling experts can maintain, refurbish and repair tools on-site, ensuring production continuity. Additionally, there are over 40 assembly installations in-house, ranging from manual stations to fully automated equipment. Many of these systems are built internally to provide modularity and flexibility for different device projects.

With 24/7 production capability, Stevanato Group's manufacturing sites are accustomed to both high-volume projects and small-scale production. This includes extensive experience in producing low-volume, highly complex products with or without electronics, such as electronic pill dispensers or large-volume plastic components for medical devices. Thanks to its worldwide footprint, Stevanato Group has links to logistic hubs close to its customers' reference markets and can rely on a global platform of suppliers for strategic sourcing solutions.

QUALITY

Rooted deep within Stevanato Group's culture is a commitment to deliver the highest quality products and services to all partners. The company operates an ISO 15378 and ISO 13485 certified quality management system and has a US FDA audited site in Germany. Additionally, the US operations are compliant with FDA design controls, including the requirements set out

Figure 3: Stevanato Group's proprietary and licensed devices portfolio.

in 21 CFR Part 820.30. Product and process quality, risk management and user feedback are at the forefront of all decision making.

CONCLUSIONS

Through its comprehensive range of products, technologies and services, Stevanato Group has the capability to support pharmaceutical companies in taking their medical device projects from concept to launch. Its business model enables customers to access the products, technologies and services required or opt for a full end-to-end solution where all the benefits of Stevanato Group's integrated offering come into play.

Many pharmaceutical companies are attracted to the reduced overheads required to manage an integrated solution provider. This can be a significant advantage for smaller biotech firms that do not have the internal capacity to oversee various aspects of the project and co-ordinate multiple suppliers. Even for larger organisations that do have these resources, there are many benefits to a simplified supply and distribution chain.

By implementing a proven, methodical project management process, Stevanato Group leverages the synergies and knowledge from different lines of business to deliver the best possible solutions for customers. Any challenges can be handled efficiently by a single entity which sees the full picture and can solve problems from multiple angles.

Stevanato Group continues to invest in integrated solutions for contract manufacturing and in collaborations with industry partners to expand its portfolio of devices (Figure 3), including through licensing and collaboration agreements. Examples of this approach include a partnership and collaboration agreement with Duoject Medical Systems (Quebec, Canada) for the promotion and contract manufacture of Maverick, an emergency-use autoinjector; an exclusive agreement with Haselmeier (Stuttgart, Germany) related to its Axis-D technology for the development of SG Alina, a pen injector for diabetes care with support from Cambridge Design Partnership (Cambridge, UK); and ICOcap, a licensed inhaler from Iconovo (Lund, Sweden) for asthma and chronic obstructive pulmonary disease (COPD). SG EZ-be POD is a proprietary wearable device developed in-house. These examples illustrate the power of Stevanato Group's integrated approach and growing capabilities, as well as the flexibility and willingness to incorporate strong outside contributions to supplement and leverage internal capabilities to build class-leading devices for patients.

As an experienced partner serving internationally recognised pharmaceutical, diagnostic and medical companies, Stevanato Group is fully committed to providing the best combination of products, technologies, services and capabilities for an integrated solution, under one point of contact.

ABOUT THE COMPANY

Established in 1949, Stevanato Group is the world's largest, privately owned designer and producer of glass primary packaging for the pharmaceutical industry. From its outset, the group has developed its own glass converting technology to ensure the highest standards of quality. The group comprises a wide set of capabilities dedicated to serving the biopharmaceutical and diagnostic industries: from glass containers with its historical brand Ompi, to high-precision plastic diagnostic and medical components, to contract manufacturing for drug delivery devices, to vision inspection systems, assembly and packaging equipment. Stevanato Group also provides analytical and testing services to study container closure integrity and integration into drug delivery devices, streamlining the drug development process. Thanks to its one-stop-shop approach, Stevanato Group is able to offer an unprecedented set of solutions to biopharma companies for a faster time to market and a reduced total cost of ownership.

ABOUT THE AUTHORS

Steven Kaufman is Vice-President, Drug Delivery Systems at Stevanato Group, responsible for managing business development, proposal management and project management as well as strategic initiatives in the group's drug delivery systems business. He has been active in the drug delivery device field for more than 15 years, working with leading multinational biopharmaceutical companies to provide pen injectors, autoinjectors and wearable injection systems, as well as test equipment, assembly equipment and final device assembly services.

Adam Stops, PhD, is Drug Delivery Systems Product Manager at Stevanato Group, managing autoinjectors, prefilled variable and fixed-dose pen injectors, large-volume wearable injectors and inhalers. With a PhD in mechanical engineering and an MBA in business management, Dr Stops has broad experience in the design, development and product management of devices and parenteral products. Throughout his career, he has worked with innovative multinational companies, leading teams of experts in device research, design and industrialisation.

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MEDICAL ENGINEERING TECHNOLOGIES

GLOBAL EXCELLENCE IN DEVICE TESTING

VERIFICATION OF INJECTABLES IN TRANSPORT AND STORAGE

Here, Mark Turner, Managing Director, Medical Engineering Technologies, discusses the regulations and requirements around testing combination products for their stability in storage over their shelf-life and during transport.

INTRODUCTION

From the May 26th, 2021, many combination products will be included in the EU Medical Device Regulation (2017/745), commonly known as the MDR.[1] Specifically this inclusion is by Article 117 of the regulation. If your delivery device is a single integral product, including the drug, that cannot be reused, it must comply with the medical device General and Safety Performance Requirements (GSPRs).[2] These requirements include verification of the device's robustness in storage and transport.

"A dose accuracy study for a biosimilar injection will use a product that has been stored at the normal 4–8°C because the product, or other components of the formulation, could denature or degrade at 25°C and thus alter the measured dose dispensed."

STABILITY REQUIREMENTS

Pharmaceutical companies are familiar with the use of ICH guidelines[3] when demonstrating the stability of their formulations. The storage conditions outlined therein can be used for preparing combination products for performance testing at various points throughout their safe storage period, which is often the case in practice. For example, a dose accuracy study for a biosimilar injection will use a product that has been stored at the normal 4–8°C because the product, or other components of the formulation, could denature or degrade at 25°C and thus alter the measured dose dispensed.

"This standard allows the use of accelerated ageing to obtain packaging stability information, in advance of waiting for natural ageing to produce test material that has completed its recommended storage period. This is acceptable for both the secondary packaging and the CCIT."

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From the medical device point of view, the syringe is the sterile barrier packaging (GSPR 11.4).

This, for the syringe needle cover and stopper joints, would require a closed container integrity test (CCIT), an example of which can be seen in Figure 1.[4] If the combination product has secondary sterile barrier packaging, there will often be a blister or a pouch pack. Both the syringe seals and any secondary packaging will be subject to ISO 11607 Part 1 as part of the GSPRs.[5] This standard allows the use of accelerated ageing to obtain packaging stability information, in advance of waiting for natural ageing to produce test material that has completed its recommended storage period. This is acceptable for both the secondary packaging and the CCIT. A temperature of 25°C is acceptable for this accelerated ageing. Typically, the rapid ageing for a medical device is carried out at 55°C (a condition that is not found in the ICH guidelines). At this temperature, for a product that is normally stored at 4–8°C, an equivalent shelf life of three years would be attained in approximately six weeks (ASTM F1980).[6] This allows the stability of the packaging to be validated well in advance of the validation of formulation-related performance aspects.

"With regard to the formulation, arctic or desert conditions are likely to be the most severe. When thinking about the carton, tropical (38°C/75% relative humidity) is usually the most severe environment."

Figure 1: Closed container integrity testing using a trace gas technique.

Figure 2: Air bubble movement measurement in simulated air transport.

TRANSPORT REQUIREMENTS

ISO 11607 also requires confirmation of the combination product's robustness in transportation. The specific standard used for this is usually ASTM D41697.[7] This standard gives conditioning (input) recommendations to simulate transit. These include stacking, concentrated impact, vibration and manual handling. There are a variety of pre-conditioning atmospheres that need to be applied, usually for 72 hours, before subjecting a shipping carton to the transit inputs. These would not be relevant for a cold-chain product.

For a device that is shipped without temperature control, consideration must be made of environments into which a carton may be shipped. With regard to the formulation, arctic or desert conditions are likely to be the most severe. When thinking about the carton, tropical (38°C/75% relative humidity) is usually the most severe environment. Other situations should also be considered, the most common one for delivery devices being air transport. For example, it is possible that an air bubble inside a prefilled syringe would expand and contract as an aircraft changes altitude. This can cause movement of the fluid, which in turn might cause a change in the dose available, or lead to evaporation and the deposit of residue which could block the needle aperture. These effects can be simulated in an air transit test chamber (Figure 2).

CONCLUSION

Drug-device combination products are just that, multi-component systems which straddle the medicinal and medical device regulatory systems. When it comes to stability testing, both pathways must be followed to demonstrate the stability of the formulation and of the packaging

components. For the resistance to damage in transit, the two pathways largely overlap with consideration included for any product-specific hazards that have been identified in a risk analysis.

ABOUT THE COMPANY

Medical Engineering Technologies (MET) has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and North America. MET knowledgeably, reliably and effectively delivers medical device and packaging testing. Services include protocol development, laboratory testing and data analysis. The laboratory is equipped for performance testing, chemical analyses and sterile barrier verification and – with accreditation to ISO 17025 – customers can have complete confidence in the quality and accuracy of results.

REFERENCES

1. *"Regulation (EU) 2017/745". Official Journal of the European Union, published 2017.*
2. *"ANNEX I – General safety and performance requirements". EU MDR (Regulation (EU) 2017/745), published 2017.*
3. *"ICH Q1A (R2), Stability testing of new drug substances and drug products". EMA, published 2003.*
4. *"Closed Container Integrity Testing". Company Web Page, MET.*
5. *"ISO 11607-1:2019, Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems". ISO, published 2019*
6. *"ASTM F1980 - 16, Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices". ASTM International, published 2016.*
7. *"ASTM D4169 - 16, Standard Practice for Performance Testing of Shipping Containers and Systems". ASTM International, published 2016.*

ABOUT THE AUTHOR

Mark Turner is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Mr Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a perfusionist in the cardiac unit of Kings College Hospital, London, UK, providing experience of the application of medical devices first-hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales (UK) in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

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December 2020	Connecting Drug Delivery	Nov 12, 2020
January 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
January/ February 2021	Prefilled Syringes & Injection Devices	Dec 17, 2020
February 2021	Novel Oral Delivery Systems	Jan 7, 2021
March 2021	Ophthalmic Drug Delivery	Feb 4, 2021
March/ April 2021	Drug Delivery & Environmental Sustainability	Feb 18, 2021
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May 2021	Delivering Injectables: Devices & Formulations	Apr 1, 2021
June 2021	Connecting Drug Delivery	May 6, 2021
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September/ October 2021	Drug Delivery & Environmental Sustainability	Aug 19, 2021
October 2021	Prefilled Syringes & Injection Devices	Sep 9, 2021
November 2021	Pulmonary & Nasal Drug Delivery	Oct 7, 2021
December 2021	Connecting Drug Delivery	Nov 5, 2021

PACKAGING LINE FOR GSK AUTOINJECTORS: A CASE STUDY

Ivan De Sanzo, Sales and Account Manager, Marchesini UK, describes a unique automated complete packaging line provided to GlaxoSmithKline for three different autoinjectors.

Recently, during the most difficult times of the covid-19 pandemic, Marchesini UK managed to deliver a new highly automated packaging line to GlaxoSmithKline (GSK) UK to handle three different autoinjectors for key new products including biopharmaceuticals for the treatment of severe eosinophilic asthma and for the treatment of lupus.

When Marchesini won the tender from GSK to supply a complete line for packaging the three devices, at a speed of 140 per minute, its solution consisted of six machines and five Marchesini robots, capable of handling two different sizes: single device laid flat or four devices positioned next to each other.

The line, designed for rapid size change and line clearance operations, successfully completed all operation qualification (OQ) activities with performance qualification (PQ) underway.

AN EXTRAORDINARY PHARMA DEVICE PACKAGING LINE

Upstream from the GSK line there is a tray-emptying unit to feed the trays with devices. A Gigacombi followed by a Robocombi (Figure 1) empty the devices from the trays and feed them onto the conveyor belt connected to the twin-head labeller RE 302 2T (Figure 2), which wraps a label around the device and applies a label on the front and back of it too.

Figure 1: The Gigacombi (left) empties trays and stacks empty trays, and the Robocombi (right) inserts devices into pucks for downstream packaging.

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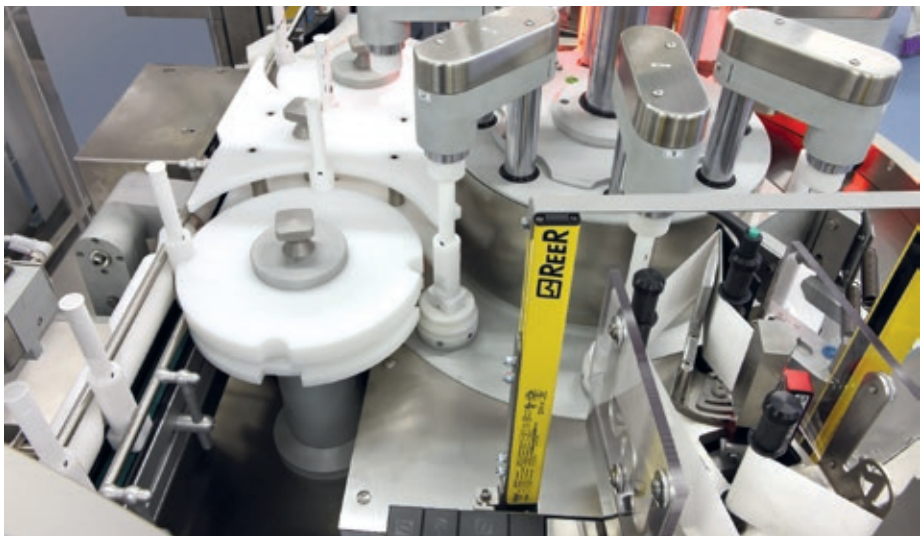

Figure 2: The RE 302 2T twin-head labeller wraps a label around the devices and applies labels on the front and back too.

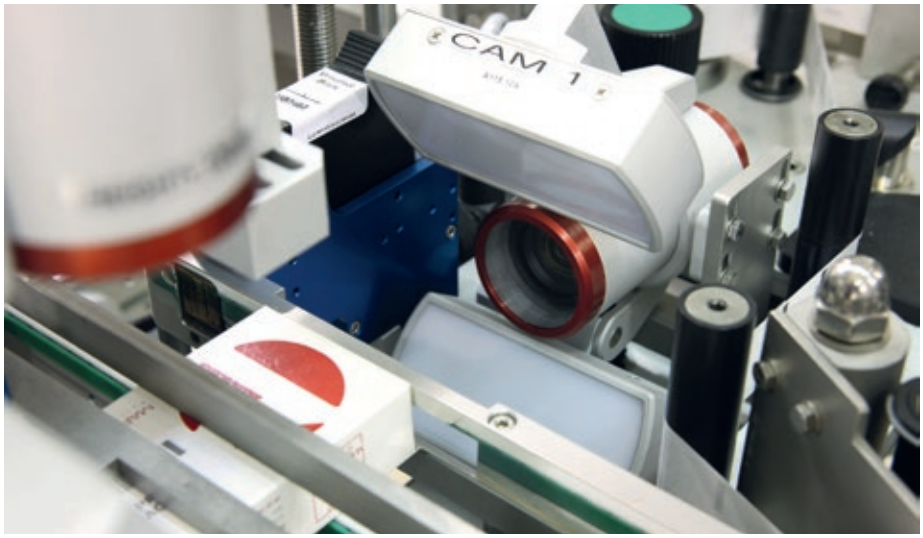

Figure 3: The BL A-420 labeller performs serialisation, stamping and sealing operations.

The RE 302 by Marchesini's Neri Division has a series of advantages for the customer: a smaller base, full access and visibility of the work area, quick size changeover operations thanks to special digital indicators and high label application precision. It's also highly versatile, being able to handle products made from different materials, from glass to plastic, but also various shapes and sizes, be they round, oval or any other unconventional shape.

A new Robocombi takes the labelled device and transfers it to the machine from Waldner (Wangen, Germany), which puts it into the moulds with the thermoformed cases.

Once sealed, the cases with the devices reach the MA 255 continuous-motion horizontal cartoner with Robocombi, which puts them into the carton together with the information leaflet. The cartoners in the MA family are one of Marchesini Group's masterpieces: impressively versatile machines that can package the widest variety of shapes and sizes for both the pharmaceutical and cosmetic industries.

The cartons are then weighed on an external weighing unit and transported towards the labeller BL A-420 (Figure 3), which performs the serialisation, stamping and sealing operations. Thanks to its outstanding versatility, the BL A-420 unit can fit all types of printing and vision systems currently available so that all the drugs packaged have their own unique code.

An MCP840 TT monobloc casepacker-palletiser equipped with a Gigacombi completes the packaging process. The MCP840 TT has a very small footprint and can handle a wide range of cartons, even those larger than average, and meets all the requirements related to drug serialisation and traceability.

> "This has been a fantastic team effort between the Marchesini, Waldner and GSK teams, delivered through the adversity of covid challenges."
>
> **Nigel Wood**, Engineering Capital Director, GSK

Both the labeller and the casepacker-palletiser are fitted with Sea Vision systems to satisfy the international regulations for visual control and labelling for fully serialised product supply assurance.

Nigel Wood, Engineering Capital Director at GSK, said: "This has been a fantastic team effort between the Marchesini, Waldner and GSK teams, delivered through the adversity of covid challenges."

ABOUT THE COMPANY

With a turnover of €430 million (£390 million) and 2,000 employees in Italy and abroad, Marchesini Group is a flagship of the Packaging Valley region in Emilia Romagna, Italy, and one of the top four worldwide manufacturers of automatic pharmaceutical and cosmetic packaging machines. To serve international markets, Marchesini Group avails of 35 agencies which, together with 14 foreign subsidiaries, represent the group in over 116 countries worldwide. 87% of the group's turnover is generated by exports, with important peaks in Europe, China, the US and Latin America.

ABOUT THE AUTHOR

Ivan De Sanzo, Sales and Account Manager, Marchesini UK, has 18 years' experience in the field of packaging machinery for the pharma industry, all within the Marchesini Group. After working in the design department and then the sales department (serving the Middle East and Italian markets) when based in the Italian headquarters, Mr De Sanzo moved to the British branch of the business, TMG Marchesini UK in 2017.

VERIFYING THE CONTAINER CLOSURE INTEGRITY OF CUSTOM PRIMARY PACKAGING

In this article, Alex Vasiev, PhD, Manager of Device Development, Connor Everett, Intellectual Property Engineer, and Steven Hay, Senior Industrialisation Engineer, all of Oval Medical Technologies, explore the challenges of verifying the container closure integrity of custom primary packaging.

For more than a decade, Oval has been developing proprietary primary drug containers (PDCs) that are specifically optimised for integration with its autoinjectors. Oval's PDC designs are therefore the result of a thorough understanding of all the functions, considerations and requirements that this integration entails. As a result, its containers use several unique design features which differentiate them from other market offerings both in terms of form and function. This is what allows the company to produce autoinjectors which are strong, compact and consistent in both delivered dose and needle-insertion depth.

While bespoke primary packaging features offer advantages in autoinjector performance and design flexibility, they also create challenges in container closure integrity

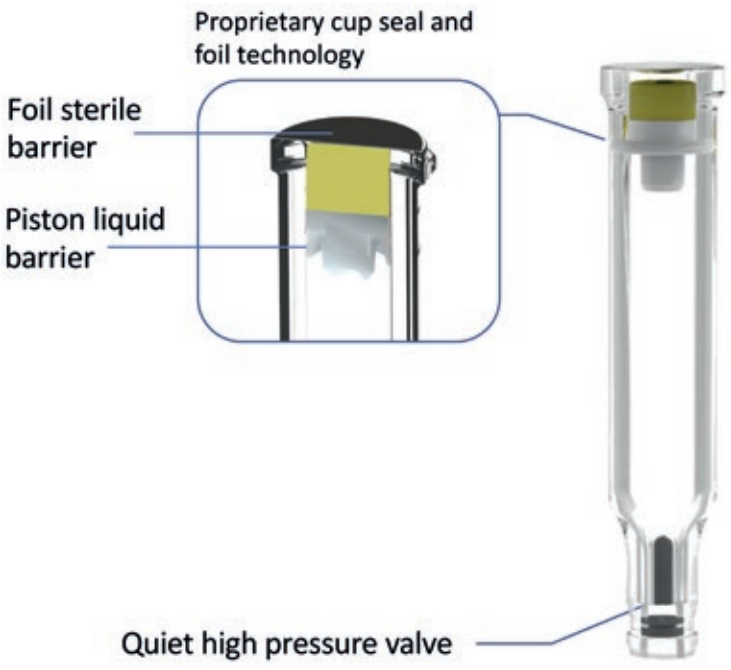

Figure 1: Illustration of seals and CCI interfaces present in Oval's ArQ Bios high viscosity primary drug container (1 mL).

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"CCI is a critical aspect of any primary packaging system. Patient and consumer health and safety is the principal reason why testing methods are put into place for its verification."

(CCI). For this reason, Oval has established a multidisciplinary industrialisation team to provide in-house expertise in the commercialisation of devices and primary packaging. This has allowed it to develop both research and development (R&D) tools for CCI feature optimisation and 100% in-line CCI inspection during manufacture.

This article explores some of the CCI features that are present in Oval's proprietary PDCs, the means by which they are optimised during the development phase and how they are tested in production.

UNIQUE CONTAINER ARCHITECTURE

Although control over the form of PDCs offers unparalleled design flexibility, there is a need to balance novelty with manufacturability and validation. Nowhere is this more apparent than in the ArQ Bios PDC for high-viscosity drugs (Figure 1).

Cup Seal And Foil Technology

Delivering high-viscosity formulations through small-gauge needles requires the generation of very high pressures within the container. It is imperative that the plunger operates effectively at these pressures, ensuring low glide force whilst preventing leakage past the seal. Traditionally, the plunger also provides a sterile barrier in storage. This is a challenge for rubber stoppers, where a low glide force and effective sterile seal present conflicting requirements.

Rubber stoppers have a large contact area which allows them to seal effectively. However, the Poisson's ratio of most rubbers approaches 0.5 – making them virtually incompressible. When a rubber stopper is subject to a high pressure within the container, much of the applied delivery force is translated into proportional friction with the container wall. To overcome this challenge, Oval has developed a high-pressure cup seal which decouples the sterile and liquid barrier functions from one another.

The piston design consists of a high-density polyethylene (HDPE) self-energising seal. The lubricious nature of HDPE, and the limited contact area it has with the container, act to reduce glide force. CCI is then maintained by a layer of aluminium foil, induction welded across the back of the container to form the sterile barrier. Process optimisation of the induction welding process, and therefore container closure integrity testing (CCIT), is critical.

High-Pressure Valve

The release of a high-force delivery spring in an autoinjector, as it impacts the plunger at the start of drug delivery, can cause a significant level of frightening noise and haptic feedback for a patient.

For this reason, the front of the ArQ Bios PDC incorporates a proprietary hydraulic valve release mechanism. The valve enables quiet and gentle activation of the device, even when the drug is pressurised to 300 bar. The activation is performed by a sliding contact between a seal and the fluid path. While advantageous for the patient, the incorporation of additional seals and moving parts creates additional challenges for container closure. This makes an in-house capability in CCIT invaluable for developing and optimising these types of novel designs. The process of optimisation can include a variety of changes to component design, material and fit, as well as the arrangement and surface finish of tooling.

CONTAINER CLOSURE INTEGRITY

CCI is a critical aspect of any primary packaging system. Patient and consumer health and safety is the principal reason why testing methods are put into place for its verification. CFR Title 21 part 211.94[1] stipulates that container closure systems must provide adequate protection against anticipated external factors that can cause deterioration or contamination of the drug product, both in storage and in use.

For common CCIT methods, such as dye ingress, the expectation from US regulatory agencies is that it should be capable of detecting defect sizes ≤ 20 µm in diameter. This defect criterion is applied to routine test methods and is an expected positive control.[2] Is this leak threshold sufficient when ensuring CCI? Recent updates to USP 1207.1 define a maximum allowable leakage limit (MALL) rather than a physical defect size for CCIT methods.[3] The reason for this is that there is a large difference in the leak sizes which correspond to compromised sterility in the literature. Some researchers found that metal cans left to cool in an E. coli challenge media required leaks > 5 µm for contamination to occur.[4] Others exposed glass vials to challenge media containing P. diminuta and E. coli, and omitted samples with airlocked leaks. Of the remaining samples, only those with leaks of ≤ 0.2 µm diameter demonstrated sterility.[5]

This discrepancy can be attributed to the variety of methods in which bacterial ingress can be inhibited. Most bacteria require a liquid medium through which to travel and will not cross a leak in the absence of a continuous fluid path or in the presence of adverse differential pressure. Bacteria can also be excluded by size. There are therefore numerous factors that influence the outcome of microbial challenge testing:

- Fluid driving force (wicking or differential pressure)
- Fluid properties (surface tension, viscosity)
- Material properties (hydrophobicity)
- Leak geometry (length, tortuosity, diameter)
- Size, shape and motility of the microbes in question.

The size exclusion approach is a common method adopted in sterile barriers. Most sterilising grade filters rely on tortuosity and a narrow pore size distribution to exclude particles of a certain size in moving fluid, described by a "rating". The current 0.2 µm sterilising grade filter rating is based on the discovery in the 1960s that Brevundimonas diminuta could pass through the 0.45 µm rated filters standard at the time.[6]

"When developing primary packaging, it is preferable to assume the worst case; i.e. the presence of pinhole defects with ideal shape and minimal length."

When developing primary packaging, it is preferable to assume the worst case; i.e. the presence of pinhole defects with ideal shape and minimal length. To facilitate the exclusion of bacteria, a critical leak diameter is defined as being ≤ 0.2 µm.

CONTAINER CLOSURE INTEGRITY TESTING

Leak detection guidelines specify that container closure testing methods should use analytical detection techniques which are appropriate to the method and compatible with the specific product being tested. Oval uses a combination of high-sensitivity methods during development and high-throughput methods in production when establishing the CCI of its proprietary PDCs.

Tracer Gas CCIT

A high-sensitivity sniffer test is used to characterise the CCI interfaces during container development and process optimisation. The sensitivity of this technique allows the critical seal geometry, influence of production variability and material selection to be evaluated and optimised to produce a reliable and stable sterile barrier.

The CCI interface being tested is placed between a test and an accumulation chamber. A tracer gas is introduced to the test chamber around the specimen. If a leak is present, the tracer gas concentration within the accumulation chamber will rise (Figure 2). The tracer gas concentration depends on the leak size, type of gas, pressure difference and temperature. The increase in tracer gas concentration can be approximated by the relationship:

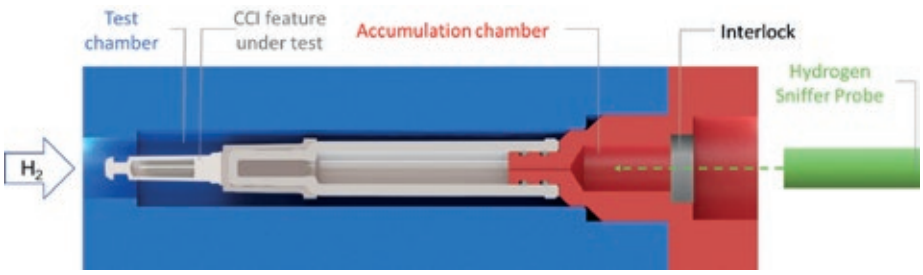

Figure 2: Illustration of a tracer gas CCI fixture. Gas is supplied to the test chamber. If a leak is present, the gas concentration will increase in the accumulation chamber.

$$\frac{\Delta m}{\Delta t} = \frac{q_L M}{RT} \quad where, q_{L,gas} = \Delta p c_{gas} A$$

Where: $\Delta m/\Delta t$ is the rate of mass change, $q_{L,gas}$ is the leak rate, M is the molar mass, R is the gas constant, T is the temperature, Δp is the driving pressure gradient, A is the orifice area and c is the speed of sound within the gas.

> "A component can have several conflicting functional requirements such as pull off force, friction and the integrity of the sealing interface."

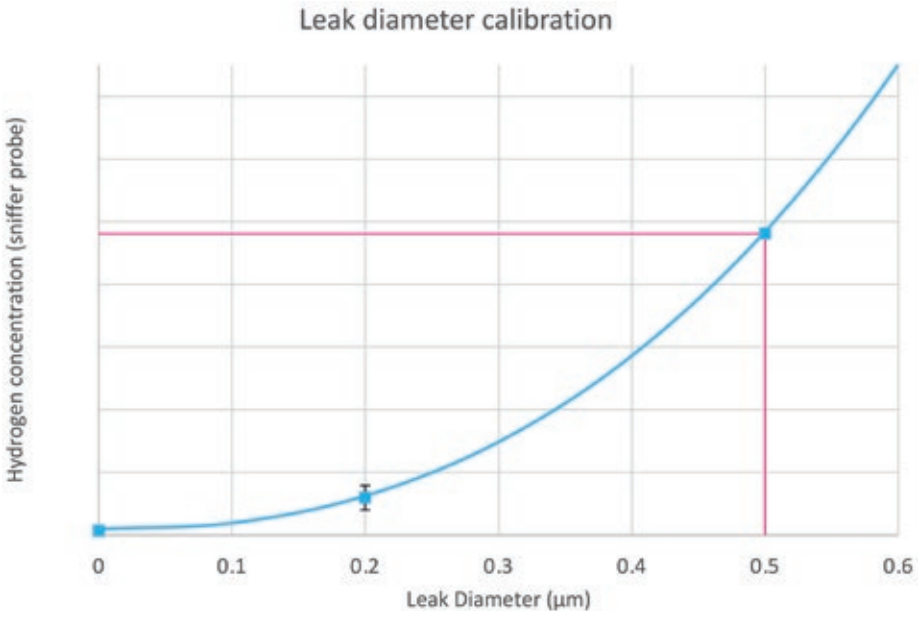

Figure 3: Graph showing a typical calibration curve for hydrogen a sniffer test fixture. Error bars: 1σ (n=5).

Helium and argon are often used as tracer gases. The small size of helium atoms, and the high speed of sound in helium, result in a threefold increase in sensitivity compared with air. Argon does not undergo chemisorption, giving it specific uses depending on the environment. Both these options are costly, with hydrogen offering a sustainable and cost-effective alternative. Because hydrogen is flammable, Oval uses a tracer gas mixture of 5% hydrogen/95% nitrogen (non-flammable concentration). The hydrogen gas is highly mobile, filling volumes and passing through leaks quickly. It also does not stick to surfaces as much as helium, reducing background interference from large leaks or residual gas in tested fixtures.

A microelectronic hydrogen sensor probe containing a thin film of palladium (Pd) is used to detect hydrogen concentration in the accumulation chamber. When hydrogen molecules reach the Pd surface, the former dissociate into elemental hydrogen which is occluded by the film, forming palladium hydride. This produces several physical effects, including a rise in electrical resistance proportional to the ambient hydrogen concentration. The reaction is reversible, the hydrogen atom desorbs from the Pd film surface when ambient hydrogen concentration decreases.

The sniffer probe is introduced into the accumulation chamber before the test to set a baseline and again after a fixed time interval to take a reading. A rise in hydrogen concentration (ppm) is detected if a leak is present. The probe reading is calibrated to the defect size using engineered leaks of a predefined size. This allows a calibration curve to be produced (Figure 3). A solid (blocked) control sample is used to determine a baseline value for the fixture.

Any CCI interface needs to be optimised to compromise on the needs of different design features. A component can have several conflicting functional requirements, such as pull off force, friction and the integrity of the sealing interface.

The design of the seal geometry in a needle shield is provided as an example. An equivalent leak size of ≤ 0.2 µm is used as an acceptance criterion. Initial geometry optimisation leads to an improvement in the efficacy of that CCI interface, whereas other changes which aid manufacturability or address other, non-CCI related functional improvements can have unintended consequences. Learning from the effect of previous design iterations allows the designer to find an optimum solution (Figure 4). The ability to establish CCI efficacy at an early stage of development offers several advantages:

- Provides useful feedback to designers during development
- Helps separate important design features from those which are less effective
- Provides insight into batch-to-batch variation and process capability.

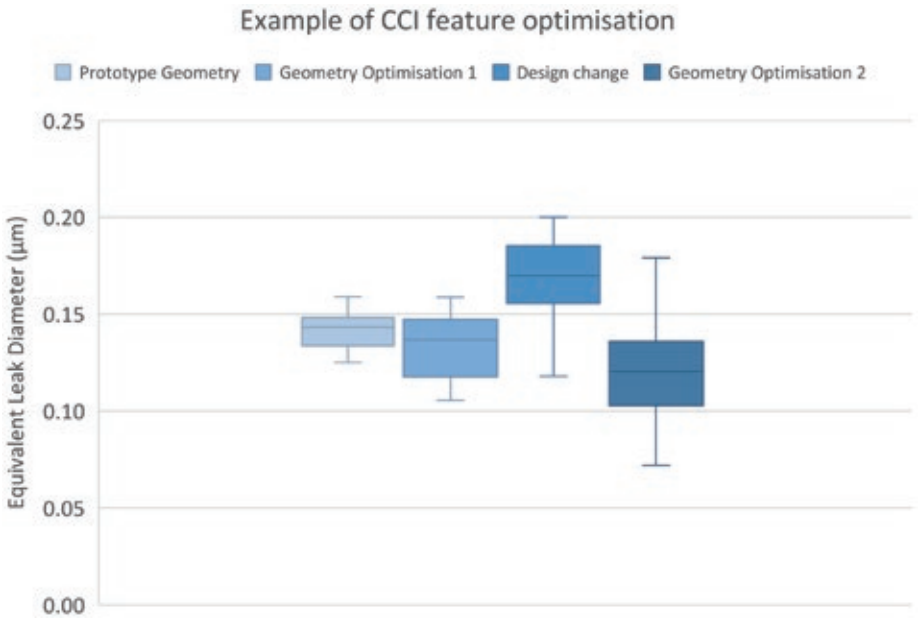

Figure 4: Boxplot showing an example of CCI performance optimisation using hydrogen leak testing. Tests performed at room temperature (23±5) °C and (50±25) % relative humidity (left to right: Plots 1-3 n≥10, Plot 4 n=30).

Real-World Variability

The calibration curve is the product of idealised defects. Actual leaks tend to present in a variety of shapes and flow paths. Care needs to be taken when interpreting the results and outputs of a test:

- Tortuous leak paths can reduce the flow rate of tracer gas, reducing the leak rate. These tortuous paths also tend to inhibit the migration of bacteria
- The presence of multiple smaller leaks can produce a larger combined flow path which may increase the leak rate without ever compromising the sample sterility
- Seals can deform and deflect due to the slight pressurisation during the test. This can cause leak paths to deform in ways that do not reflect normal conditions, exaggerating or masking the true leak size.

Hydrogen leak testing does not require pressurisation, as the test is conducted at low (0.1 bar) gauge pressure. This avoids unintentional deformation of the seals. The test method, like any gas-based leak detection method, would fail a component which had a multitude of smaller leaks, resulting in false positives (critical leak detected but not actually present). This makes the test a worst case, providing an appropriate impression of the quality of an interface.

Vacuum Decay (In-Line) CCIT

While hydrogen leak testing offers excellent sensitivity, it is slow and cannot be applied to Oval filled containers in-line due to the number of CCI interfaces present (need to access both sides of the seal). EU GMP regulations also stipulate that containers such as Oval's, which are closed by fusion, should be subject to 100% integrity testing.[7] A more rapid method is therefore required for in-line testing.

To achieve this, Oval uses a non-destructive vacuum decay system. The system creates a vacuum around the sample whilst monitoring chamber pressure over a short cycle time. The use of negative pressure prevents contamination being forced through any defects which are under the threshold of detectability. It also prevents the pressurisation of sealing interfaces which could mask potential leaks.

Qualification of this approach requires the creation of positive and negative controls which are tested together with the filled PDCs. Positive controls are created by laser drilling calibrated holes (calibration of leak flow rate and hole diameter) in a sample to mimic leak defects. Negative controls (free from leaks) are created by

Figure 5: Image of an in-line vacuum decay CCIT method used during production. Photo courtesy of Bonfiglioli Engineering Srl.

precision machining a solid form of the PDC. Acceptance criteria are also set such that all negative controls pass while all positives fail. A lower and an upper limit of detection are also established, followed by relevant validation processes. Validation is essential to prove test accuracy, repeatability and detection limit.

Oval uses a 5 µm positive control for in-line testing; this is an industry standard and the performance limit for CCIT at higher throughputs. The 5 µm leak diameter threshold is considered appropriate in production because the component design itself is optimised using the more sensitive technology of hydrogen leak detection, as previously discussed. In addition, none of the sterile CCI interfaces in Oval's PDCs are in contact with the formulation, which mitigates the risk of a liquid path facilitating bacterial ingress.

Two pressure readings are taken after fixed time intervals, following pressure stabilisation. If the difference is greater than the threshold determined from positive controls, the container has a leak. If the value meets expectations, the container closure is integral. Leaks manifest as sharper vacuum decay profiles as they allow air inside the container to equilibrate the vacuum generated outside. Oval's system uses proprietary technology which helps to overcome the challenge of differentiating between micro and macro leaks (Figure 5).

CONCLUSION

The development of this expertise has allowed for the efficient optimisation of the sterile seal geometries in Oval's primary packaging. Control of this critical aspect of Oval's PDCs allows for implementation of features to suit the needs of a particular formulation and autoinjector architecture, with confidence that they will not impact on the demands of CCI.

The ability to perform 100% inspection of PDCs in-line helps guarantee patient safety when manufacturing a commercial drug delivery device at scale. The proprietary technology facilitating this is just a small part of the expertise offered by Oval's in-house industrialisation team. It is adapted specifically to meet the needs of commercialising Oval's novel primary packaging.

> "The ability to perform 100% inspection of PDCs in-line helps guarantee patient safety when manufacturing a commercial drug delivery device at scale."

ABOUT THE COMPANY

Oval Medical Technologies is a drug delivery company whose patient-centric autoinjector platforms enable pharmaceutical companies to deliver a wide range of drug formulations for both subcutaneous and intramuscular injection. Oval's flexible, robust drug delivery platforms can be tailored precisely, providing unprecedented scope for pharmaceutical companies to address the needs of current patient populations and develop and market new products. With its patented integrated primary drug container technology at their core, Oval's devices are safe, reliable and easy to use in their target patient populations. The company is certified to ISO 13485 (2016).

ABOUT THE AUTHORS

Alex Vasiev, PhD, is an engineer with a wide range of experience in medical and biomedical R&D gained in academia and consultancy. Before joining Oval in 2019, his primary focus was the interface of engineering, physics and biological systems. In the space of drug delivery, Dr Vasiev has developed everything from smart hydrogel microcarriers to patch pumps, inhalers and several high-viscosity autoinjectors. As a Manager of Device Development, he is responsible for leading technical teams and device development programmes at Oval. He graduated with an MEng in mechanical engineering with aeronautics, and a PhD in biomedical engineering from the University of Glasgow (UK).

Connor Everett is an Intellectual Property Engineer at Oval and manages its innovation and intellectual property portfolio, maintaining and curating all the proprietary knowledge within the company. His broad knowledge of the biomedical space allows him to assist in the design and development of Oval's novel autoinjectors, as well as associated systems and processes, such as container closure integrity testing. Mr Everett joined Oval after graduating with an MEng in biomedical engineering from Queen Mary University of London (UK).

Steven Hay has been with Oval for the past three years. As a Senior Industrialisation Engineer, he has worked on the industrialisation of Oval's PDCs and autoinjector devices. He focuses on PDC and device assembly, fill/finish, and subsequent test and inspection processes. Mr Hay has previously worked in the medical devices sector, having held roles in process engineering management, process development and new product introduction. Prior to joining Oval, he managed the process engineering team for a point-of-care medical monitoring and diagnostic device company – and has broad prior experience from the auto catalyst and optical data storage industries. Mr Hay graduated from Anglia Ruskin University (Cambridge, UK) with a BEng in mechanical and manufacturing engineering.

REFERENCES

1. *"CFR – Code of Federal Regulations Title 21". US FDA, part 211.94.*
2. *Hughes PF, "Aseptic Processing of Biological Products: Current Regulatory Issues". Presentation at WCPB 2016 conference, pp 26–28.*
3. *"USP<1207> Package Integrity Evaluation: Sterile Products". US Pharmacopeial Convention, 2018.*
4. *Gilcrist J et al, "Helium Leak Test for Micron-Sized Holes in Canned Foods". J Food Prot, 1985, Vol 48 (10), pp 856–860.*
5. *Kirsch LE, Nguyen L, Moeckly CS, "Pharmaceutical container/closure integrity. I: Mass spectrometry-based helium leak rate detection for rubber-stoppered glass vials". PDA J Pharm Sci Technol, 1997, Vol 51(5), pp 187–194.*
6. *Meltzer TH, Jornitz M, "The sterilizing filter and its pore size rating". Am Pharm Rev, 2003, Vol 6, pp 44–52.*
7. *EU GMP Annex 1, section 8.18.*

THE WHOLE PACKAGE: CONDUCTING EFFECTIVE AND INFORMATIVE EVALUATIONS OF INJECTION DEVICE PACKAGING

Here, Allison Strochlic, Research Director, and Andrea Dwyer, Associate Research Director, both of Emergo by UL's Human Factors Research & Design team, discuss the often overlooked aspect of a combination product user interface: the packaging. With a specific look at injection devices, the authors cover how to perform proper human factors testing of a combination product's packaging, and the advantages doing so can confer to a project.

INTRODUCTION

When you hear about an injectable product, you might immediately envision some type of drug injection device, such as a prefilled syringe, autoinjector or pen injector. Such a product could be based on an existing device platform or it might reflect a novel design developed to accommodate specific drug characteristics or enable a company to differentiate its offering from others in the competitive commercial landscape. Although the injection device itself is often "the star of the show", a product's packaging, labelling and instructions are also integral components of a product's user interface.

Designing, evaluating and validating a medical device's packaging is essential to produce a safe and effective product. In fact, there is an explicit regulatory imperative from the US FDA to carefully consider the design and evaluation of packaging throughout the device development process. Packaging often serves as a key risk mitigation factor for critical tasks, such as selecting the proper dose strength of a given injectable drug. Despite this important role, packaging is too frequently neglected from a human factors (HF) engineering and design perspective compared with other user interface elements and user touchpoints, such as the injection device hardware, companion software applications and accessories.

In this article we put the spotlight on packaging and present methods for conducting effective and informative evaluations of product packaging.

Packaging for medical and drug delivery products can come in many shapes and sizes.

> "Packaging can support or hinder proper device use by the way it provides critical information – such as storage, usage or disposal instructions."

Common types of medical packaging include cartons, pill bottles, peel packs, sterile kits, vials and blister packs. Considering this issue of ONdrugDELIVERY's focus on prefilled syringes and injectables, we will focus on cartons, vials and medication kits as the most relevant types of packaging.

WHY EVALUATE PRODUCT PACKAGING?

There are several reasons it is important to evaluate product packaging. As previously mentioned, packaging is part of a product's "user interface". As such, even though packaging is not the direct means by which a given drug is administered, packaging can affect users' ability to interact with a given injection device safely and effectively. Specifically, packaging can support or hinder proper device use by the way it provides critical information – such as storage, usage or disposal instructions. A product's packaging is responsible for communicating key drug information to the user, including the brand and generic names and dose strength. And, almost always, packaging is a user's first point of interaction with a given product.

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Packaging is often much more than a protective or convenient container in which to distribute a product. Rather, packaging presents or contains information that often serves as a risk mitigation factor for critical tasks, for example presenting information intended to help someone distinguish their prescribed insulin pen injector from that of their partner when both are stored in the same place. Packaging-based risk control measures need to be designed initially based on users' needs and regulatory requirements. They should then be evaluated throughout the product development cycle, from formative evaluations to HF validation testing, just like the injection device itself.

Finally, FDA and other regulators expect manufacturers to evaluate packaging design during product development, along with software, hardware and labelling. Despite this expectation, packaging is sometimes relegated to an afterthought.

Going forward, this article will focus on two primary reasons to evaluate product packaging:

1. Product differentiability
2. How packaging guides proper use.

But first, we'll provide a quick primer on key methods that can be employed to evaluate any aspect of a product in development, including, of course, product packaging.

USABILITY TESTING – A BEST PRACTICE PRODUCT EVALUATION METHOD

There are a number of HF engineering methods that can be employed to evaluate a product in development. Such methods include one-on-one and group interviews, cognitive walkthroughs, design or heuristic reviews, and formative usability tests. Each method has its place in the development process and yields key insights when leveraged at the right time with the right stimuli (e.g. early-stage prototype versus representative product samples). Moreover, each method can be designed to evaluate every aspect of a product's user interface or to test just a select few.

This article focuses on evaluating product packaging during usability testing, an activity that involves representative users interacting with, and providing feedback on, a product in development to evaluate the product's interactive qualities (Figure 1). In the case of an injection device, the representative users – or test participants – would likely be lay users who might self-administer medication for a certain medical condition, non-professional caregivers who might support medication administration for others, or healthcare professionals who typically prescribe and/or train end users on a product. Researchers present participants with a product in its packaging, along with any labelling and accessories, and ask the participants to simulate using the product, for example by administering a simulated injection into an injection cushion. The researchers then seek feedback regarding various product attributes. Such attributes often include usability (whether something is easy or difficult to use), clarity, learnability and perceived use safety, depending on the test objectives.

Figure 1: Scene from a usability test evaluating a pen injector and its packaging.

There are several types of usability tests, but the most common ones conducted during injection device development are formative and HF validation tests. A formative test is one conducted iteratively and frequently as the design is being formed, whereas an HF validation test is one conducted to validate that the device can be used safely and effectively. Sometimes, usability tests focus exclusively on product packaging but, more often, packaging is one component included in the usability test alongside the device and potentially other accessories.

> "One of the most common objectives of drug delivery device packaging evaluations is to assess representative users' ability to differentiate between various drug products and/or dose strengths."

KEY OBJECTIVE 1: EVALUATING PRODUCT DIFFERENTIABILITY

One of the most common objectives of drug delivery device packaging evaluations is to assess representative users' ability to differentiate between various drug products and/or dose strengths. We state this objective in terms of the users' ability, but the true test is directed at the product packaging: whether or not it has been designed in a thoughtful and error-resistant manner.

The following is an outline of the key steps to take when planning and conducting an evaluation of a product's differentiability. The steps are described in the context of a usability test although, as noted earlier, other types of evaluations can be conducted to serve the same objective.

Simulate a Representative Product Storage Area

In a pharmacy, injection device packages (usually, cartons) are typically lined up on standard shelving units or stored in a refrigerator if necessary for the drug contained within (Figure 2). Products are

likely to be sorted according to a logical scheme, such as alphabetically by generic name, but any given facility will have its own, possibly idiosyncratic, method. Automated medication dispensing systems are common sights in hospitals. At home, injection devices are stored in perhaps the widest range of places – including, but not limited to, household refrigerators, medicine cabinets and storage closets. For an effective usability test, you don't need to rent out a pharmacy or visit tens of patients' homes to evaluate product packaging in their actual storage conditions. However, you should simulate a reasonably representative set-up rather than simply present a given product's packaging on a table or in another isolated manner. For example, a refrigerator can be a good choice to represent a typical storage set-up.

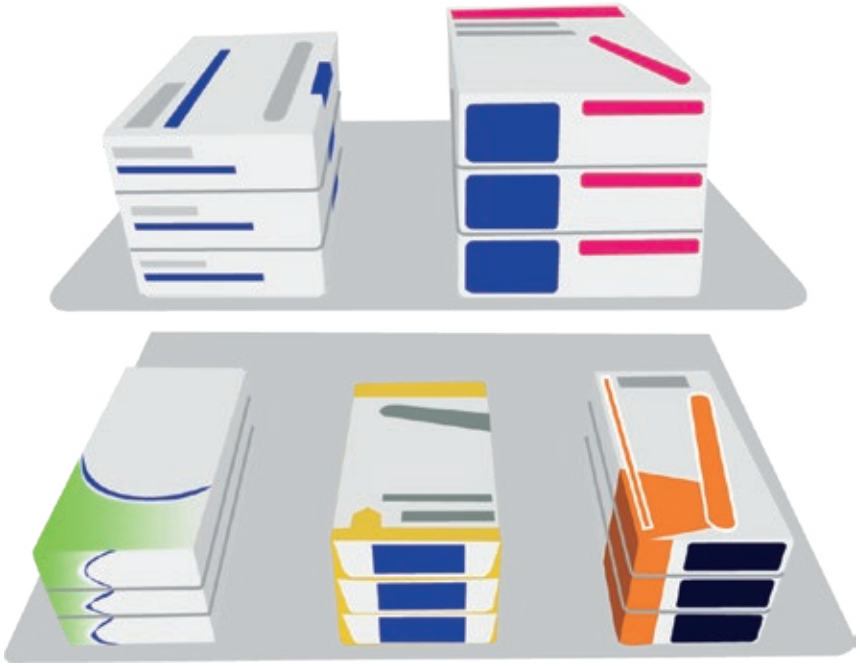

Figure 2: Insulin pen injector cartons as they might be arranged in a pharmacy refrigerator. *(Illustration by Jacqueline Edwards, User Interface Design Associate at Emergo by UL)*

Present the Target Product in Various Strengths and Among Representative Comparators

In addition to presenting the product within a representative setting, it's best to present the product being evaluated in its available dose strengths and among realistic "comparators." The goal is to add the context of realistic use to your evaluation. By presenting a product in multiple dose strengths, you can evaluate a participant's ability (read: the packaging's ability to enable the participant) to select a specific prescribed dose strength from among other dose strengths. By presenting the target product alongside different products that might be stored or used in the same environment, you can evaluate whether the packaging is distinct enough from that of other comparator products with which it could commonly be found. At certain stages in development, the most productive evaluation is one that presents an opportunity for a high-risk or worst-case mix-up to occur. Presenting such mix-up opportunities gives injection device manufacturers the best chance of detecting any potentially harmful differentiation errors during development, rather than after launch.

Have Each Participant Perform Representative Selection Tasks

Once you've set up a representative use environment and context, it's time to bring in your test participants and put your product packaging to the test. With a focus on packaging differentiation, the primary task is one of product selection or retrieval. You want to see if the participant can select the target product – the one you're evaluating – from among the various comparators and other items in the storage environment. Be sure to present selection tasks in a representative manner. You might present the task information to a pharmacist participant via a sample, printed prescription and give a layperson participant a verbal prompt asking the participant to retrieve "your medication," medication which the participant would have previously seen.

Present the Target Product in Packaging Representative for That User

The fundamental task of selecting a product might be the same for different types of users, but not all users will interact with a given product in the same packaging. For example, pharmacists handle injection devices most often within their outer cartons, and lay users at home interact with the product first in its outer carton, and then might also need to differentiate unpacked products – for example, a single pen injector that is in use and stored among other, often similar, pen injectors without their cartons. Be sure that you consider and evaluate each of these packaging variations during usability testing and other evaluation activities.

> "In some cases, packaging is simply an outer enclosure intended to protect an injection device and other items contained within the packaging. However, in other cases, packaging serves a dual, and arguably equally important, purpose of helping users understand how to prepare, use and/or store a product."

KEY OBJECTIVE 2: EVALUATING HOW PACKAGING GUIDES PROPER USE

In some cases, packaging is simply an outer enclosure intended to protect an injection device and other items contained within the packaging. However, in other cases, packaging serves a dual, and arguably equally important, purpose of helping users understand how to prepare, use and/or store a product. During development, it's important to evaluate whether the packaging does in practice help users as intended, and confirm that the packaging effectively complements a well-designed product and other labelling.

There's no doubt that having informative and instructive packaging is beneficial for all products. That said, evaluating how packaging guides proper use is particularly valuable for more complex products, such as injection systems comprised of multiple components (e.g. an injection device packaged with lyophilised drug and diluent vials and a transfer device) or other "kits" that require users to assemble components or otherwise prepare the product before injecting.

The following is an outline of the key steps to take when evaluating packaging's effectiveness in guiding proper use. Again, the steps are described in the context of a usability test.

Present the Product and Labelling in Representative Packaging

This might be self-evident but, to conduct an effective evaluation of product packaging, you want to be sure the packaging is representative. Early on in development, you might want to collect users' feedback on a few different design concepts you are considering – ideally, all options that reflect any known technical, production or financial constraints (for example, in terms of packaging size and materials). Towards the end of your development efforts, you want to provide all product components and labelling in production-equivalent, or commercial-equivalent, packaging. For example, use representative cardboard thickness and opening/closing mechanisms, and place the products, accessories and labelling in the exact planned locations a user would see them when opening the commercialised product for the first time (Figure 3). Presenting the real-world solution will enable participants to interact fully with your proposed packaging and provide valid, context-appropriate feedback.

Have Participants Perform Naturalistic, Hands-On Tasks

Similar to presenting representative selection tasks to evaluate product differentiability, you should present representative tasks that require test participants to interact with the packaging and items contained within it in a realistic manner. Such tasks might include asking someone to use the product for the first time (to simulate injecting a drug), or asking someone to do anything they might need to before injecting later in the day or week (which can help evaluate someone's ability to properly unpack and store a product). You want to confirm a user can open a package properly to access the items within, and then see how packaging elements – such as integrated instructions, trays with dedicated spaces for different components, and the placement of various documents – help enable someone to prepare, use and, ultimately, discard a product as intended.

Include Untrained Users in Your Evaluation

Some injection devices might not be dispensed to a patient until the patient receives training on proper device use from a clinician or company representative. If your goal is to evaluate how packaging can guide proper use, you should "stress test" the packaging by including untrained users, at least in your early-stage evaluation activities. Users who do not receive training are more likely to rely on other product user interface elements – namely, packaging and labelling – to determine proper product use.

> "Injection device packaging deserves attention – perhaps more than you've given it in the past – from a design and evaluation perspective; it is often tested to evaluate product differentiability and how packaging guides proper use, but there are other objectives served by evaluating packaging as well."

In these packaging-centric evaluations, you want to put the onus on the packaging and what's contained within to lead users down the right path.

CONCLUSION

Injection device packaging deserves attention – perhaps more than you've given it in the past – from a design and evaluation perspective; it is often tested to evaluate product differentiability and how packaging guides proper use, but there are other

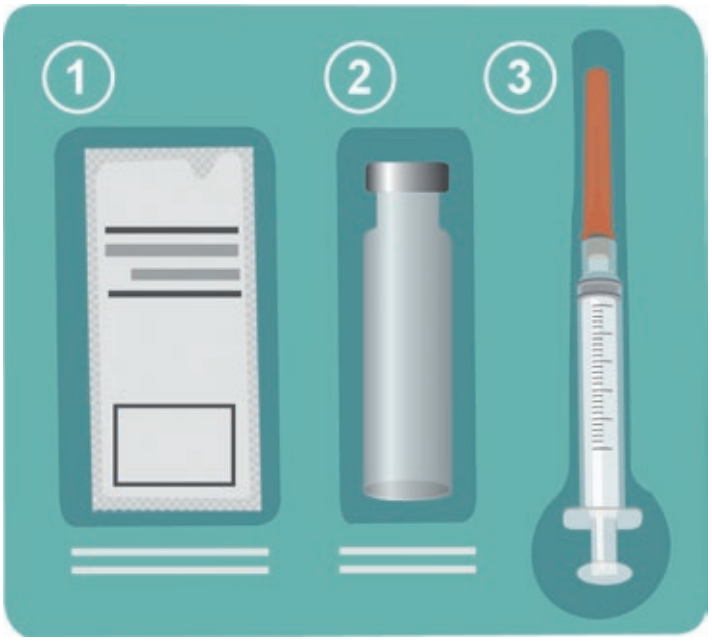

Figure 3: Medication kit with moulded inlays that create designated sections for specific components, thereby grouping related items and guiding sequential use. *(Illustration by Jacqueline Edwards, User Interface Design Associate at Emergo by UL)*

objectives served by evaluating packaging as well. For example, packaging can be evaluated to confirm legibility of printed or graphical information, sometimes from an expected viewing distance, for example, considering oral medication bottles in a pharmacy.

Furthermore, while this article focuses on evaluating packaging, it's worth noting that the design of packaging also warrants careful consideration. Don't spend the development process only focusing on an injection device's design; ensure you also give due attention to the packaging and labelling. A well-designed product package is a strong start to a user's safe and effective interaction with an injection device and an overall positive user experience.

ABOUT THE COMPANY

Emergo by UL's Human Factors Research & Design (HFR&D) team is a an experienced global team that specialises in early-stage user research, product design, usability testing and user interface design. With a primary focus on medical devices and combination products, the team has over 15 years' experience helping clients bring safe and effective products to market and ensuring best-in-class user experiences. The team's injectable device experience includes novel and platform-level prefilled syringes, needle safety devices, autoinjectors and on-body injectors, among others. The team includes over 70 specialists and has offices in the US, the UK, the Netherlands and Japan.

ABOUT THE AUTHORS

Allison Strochlic is a Research Director in Emergo by UL's Human Factors Research & Design team, and was one of the team's co-founders in 2005. She contributes to a wide range of activities that serve to identify user needs and evaluate and validate combination products and other medical technology. Ms Strochlic also advises clients on meeting FDA and other regulators' expectations, is co-author of "Usability Testing of Medical Devices" and several technical articles, and speaks frequently on applying human factors to medical technology development. She is a board-certified human factors professional, and has undergraduate and graduate degrees in human factors.

Andrea Dwyer is an Associate Research Director with Emergo by UL's Human Factors Research & Design team, and has been with the team for 10 years. A board-certified human factors professional, Ms Dwyer leads research activities required to meet regulators' expectations for applying human factors engineering during medical device development. She frequently conducts workshops, speaks at industry events and advises clients on how to implement human factors engineering in the medical device development process. Ms Dwyer is co-author of "Medical Device Use Error – Root Cause Analysis." She holds a BS in human factors and an MS in engineering management, both from Tufts University (Medford and Somerville, MA, US).

UNISAFE® 2.25: SEAMLESSLY TRANSITIONING TO NEW-GENERATION BIOLOGICS

In this article, George I'ons, Head of Product Strategy and Insights at Owen Mumford, discusses the benefits of subcutaneously administering new drug formulations, and the factors that manufacturers need to consider when designing delivery devices.

As new-generation biologics increase in volume and viscosity, developers of drug delivery devices must revisit previous designs to accommodate new formulations. If these drugs could be subcutaneously administered, this would help to alleviate some of the pressure on healthcare systems, as this route is more suitable for home administration than intravenous drug delivery. However, to ensure effective administration outside of a healthcare setting, it is critical that manufacturers develop drug delivery solutions with the needs of patients and carers in mind, as well as healthcare professionals. Regardless of the benefits, patients may struggle to adhere to therapies if drug delivery is too painful or difficult, if the procedure is too complex or lengthy, or if they have to inject frequently. Human factors specialists and design engineers must, therefore, ensure optimal comfort, ease of use and safety in delivery device design, especially when adapting to the challenges of increased volumes and viscosity.

> "Human factors specialists and design engineers must ensure optimal comfort, ease of use and safety in delivery device design, especially when adapting to the challenges of increased volumes and viscosity."

Figure 1: UniSafe® 2.25 is the latest addition to the established UniSafe® platform.

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Owen Mumford
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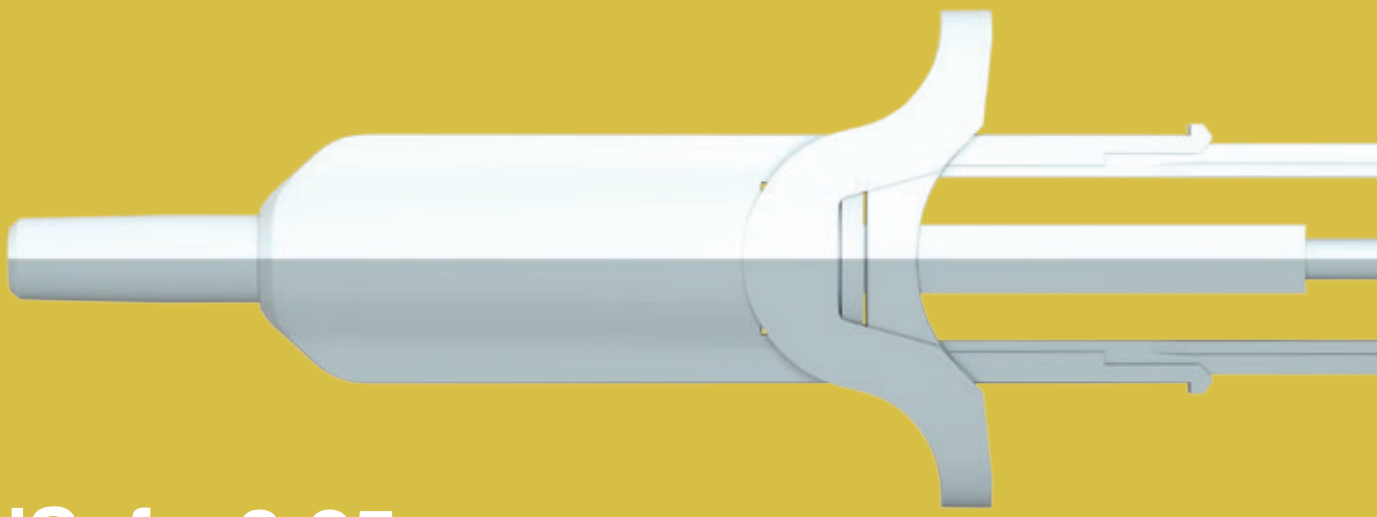
Evolving
UniSafe® Platform



UniSafe® 2.25

Spring-free simplicity for higher volume formulations

A springless, passive safety device for 2.25mL pre-filled syringes, designed for simple assembly and use.

From concept to reality. Find out more at ompharmaservices.com/unisafe-2-25/

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Resolving this challenge was the impetus for UniSafe® 2.25, the latest addition to Owen Mumford Pharmaceutical Services' established UniSafe® platform (see Figure 1). For subcutaneous administration, standard prefilled syringes (PFSs) and safety devices have been designed typically for 1 mL fill volumes and a viscosity that is under 10 cP. The UniSafe 2.25 safety device is designed to contain 2.25 mL PFSs, which are now being developed for higher volume and viscosity drugs, usually biotherapeutics.

CONTROLLING INJECTION TIME AND FORCE

Drug viscosity has a significant impact on the injection experience. To help ensure that patients have as little discomfort as possible, it is recommended that injection force does not exceed 10 N and that the procedure is no longer than 10–15 seconds, as human factors data show that patients typically struggle to continue holding a device in place after this duration. When viscosity is higher, it can be difficult to remain within these parameters. Prefilled safety syringe devices facilitate injections by allowing patients greater control over force and speed, and to an extent, the level of pain. To ensure easy operation, the UniSafe 2.25 device has a large comfortable plunger head and a smooth, integrated finger flange. In particular, these features assist patients who may have additional difficulty with injecting biologics, due to impaired strength or dexterity.

PREVENTING DRUG WASTAGE

As biologics often require small dosage volumes, it is critical that patients deliver the full dose and that the device prevents any possibility of drug leakage and wastage. This is a real concern for manufacturers as well, since biologics are often costly. One method of preventing leakage is to ensure that the syringe plunger at the rear of the device cannot be removed, and this serves the additional purpose of preventing tampering and possible multiple use. Drug wastage can also happen in the supply chain during transit as internal springs, which are typically used in safety syringes to activate the safety mechanism, can cause the device to activate accidentally before reaching patients. This is one of the reasons why the UniSafe 1 mL safety device was developed without a spring – a first for this type of product – and the 2.25 iteration retains this valuable feature. A further benefit of a springless device is that patients have clear visibility of the syringe contents before administration, and can check for drug clarity and that the dosage has been delivered fully following injection.

> "It is important that medical devices used for self-administration are intuitive, which is why the injection technique for UniSafe 2.25 is the same as a conventional syringe."

PROTECTION FROM INJURY

It is important that medical devices used for self-administration are intuitive, which is why the injection technique for UniSafe 2.25 is the same as a conventional syringe. The injection procedure for both the 1 mL and 2.25 UniSafe designs are also the same. The product includes a safety shroud, which fully encases the needle and is automatically positioned as the user carries out the injection. When the plunger is fully depressed, the device's safety mechanism is automatically deployed and the needle retracts into the safety shroud. In compliance with sharps safety regulations, patients and users are immediately protected from the risk of needlestick injury as the needle is no longer exposed once injection is complete. As the mechanism is automatic or "passive", there are no additional instructions or techniques; patients can simply carry out injection as usual.

MANUFACTURING SIMPLICITY

As well as being simple to use, UniSafe 2.25 allows for a simplified manufacturing process. Adding a spring to a safety syringe device is complex as it must be done under high tension, so removing this element is highly advantageous for manufacturers. The product has only five moulded plastic components, which can be assembled easily with a PFS to create the final combination product. To allow pharmaceutical manufacturers a wider choice of suppliers, UniSafe 2.25 is compatible with ISO-standard small round flange and cropped flange PFSs. For viscous biologics, smaller gauge needles with a large diameter facilitate delivery, but patients may remove the device too early if they experience pain, and fail to fully deliver the dose. 29 G or 27 G needles, or even 25 G needles, are therefore most commonly used for subcutaneous injections, while thin-wall needles have been developed for highly viscous formulations to assist the flow of the drug in needles of a small diameter.

To encourage patient self-administration, there is an increasing focus on reformulating intravenous drugs for subcutaneous administration. However, the design of a drug delivery device must be given appropriate attention for subcutaneous administration to be effective and to encourage compliance. Although the molecular structure of biological drugs makes subcutaneous injection a preferred route of administration, the viscosity of these drugs can make comfortable injection challenging. As a result, the vast benefits of biologics may not be gained fully if delivery devices do not allow for a smooth injection procedure that is as intuitive as possible, for patients, carers and healthcare professionals alike. As more discoveries are made in this area of drug development, drug delivery device designers must rise to the challenge of providing innovative devices that enable a seamless transition to new formulations.

ABOUT THE COMPANY

Owen Mumford is a medical device manufacturer that develops products for its own brand and custom device solutions for pharmaceutical and diagnostic companies. Owen Mumford provides research, design and manufacturing capabilities for device production.

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.

GERRESHEIMER

GERRESHEIMER INCLUDES STEVANATO GROUP INTEGRATED TWIST-OFF CLOSURE SYSTEM FOR GX RTF SYRINGES

In this article, Maximilian Vogl, Head of Product Management at Gerresheimer Regensburg, reveals the latest user-friendly addition to its Gx RTF Luer lock syringes using Stevanato Group's integrated twist-off closure technology.

Gerresheimer is to offer its Gx RTF (ready-to-fill) syringes with the SG ITC (integrated tip cap) twist-off closure from the Stevanato Group. With this technology, which is often asked for on the market, Gerresheimer is adding an especially user-friendly system solution for Luer lock syringes to its programme.

> "The integrated seal cap consists of two components – an elastomeric component, which is available in different formulations, and a rigid, translucent polymer cap."

Figure 1: The twist-off closure system responds to the containment needs of different drugs.

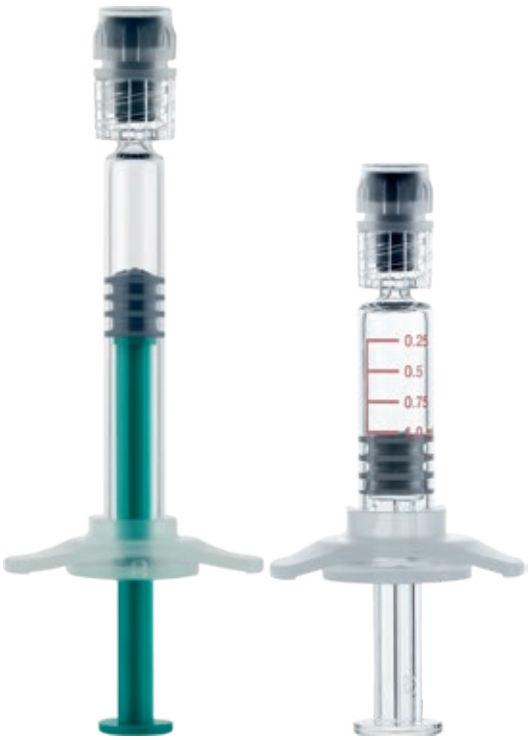

Figure 2: Gerresheimer will begin by offering 1.0 mL long and 1.0 mL short Luer lock syringes with the integrated twist-off closure.

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The integrated seal cap consists of two components – an elastomeric component, which is available in different formulations, and a rigid, translucent polymer cap. The elastomer component is inserted into the plastic cap, screwed together with a Luer lock adapter, and pre-assembled on the syringe. Compared with traditional Luer cone systems, this solution offers a syringe closure with increased stability, thus protecting the drug product.

The twist-off closure system (Figure 1) responds to the containment needs of different drugs: vaccines, hyaluronic acid, biotech drugs and other viscous formulations. It has been developed and produced according to the ISO 11040-7 standard and fits perfectly on Gx RTF syringes. Gerresheimer will offer 1.0 mL long and 1.0 mL short Luer lock syringes with the integrated twist-off closure as a first step (Figure 2), with additional formats to follow.

> "The seal cap is securely screwed onto the Gerresheimer Luer lock syringe, so that accidental removal of the cap is prevented."

INCREASED SAFETY AND USER FRIENDLINESS

The seal cap is securely screwed onto the Gerresheimer Luer lock syringe, so that accidental removal of the cap is prevented (Figure 3). The familiar twist-off function offers medical specialists improved user friendliness without impairing the integrity of the prefillable syringes. The structured surface simplifies the removal of the cap.

The system components of Gerresheimer syringes are primarily aimed at user friendliness and safety – and the company says the new SG ITC twist-off closure suits these aims outstandingly. Gerresheimer already delivers syringes equipped with the seal cap, which can be processed on existing filling lines, under the name Gx TWILC (twistable integrated Luer lock closure).

Figure 3: The seal cap is securely screwed onto the Gerresheimer Luer lock syringe, so that accidental removal of the cap is prevented.

The 100-hole nests are packaged in a tub and sterilised with ethylene oxide gas (EtO).

ABOUT THE COMPANY

Gerresheimer is a major supplier of speciality glass and plastic products to the healthcare sector, in particular pharma, with a strong presence in parenteral delivery devices. Its product range includes insulin pens, inhalers, micropumps, prefillable syringes, injection vials, ampules, bottles and containers for liquid and solid medications with seal and safety systems, as well as packaging for the pharmaceutical and cosmetics industries. It has around 10,000 employees worldwide, with operations in Europe, Asia and North and South America.

ABOUT THE AUTHOR

Maximilian Vogl studied engineering, patent management and innovation management at the University of Applied Sciences Amberg-Weiden (Germany). Ten years ago he started his career at Gerresheimer. Today he is part of the business development team of Gerresheimer Medical Systems. In his role as Head of Product Management, Mr Vogl focuses on market analysis and new product developments in the field of primary packaging and injection devices for drug delivery.

Gx InnoSafe®

Integrated Safety System

- Protection against needlestick injuries
- Eliminates the possibility of reuse
- Fully passive safety function:
  protection mechanism is activated automatically – no additional actions required
- Fully integrated system:
  delivered pre-assembled in nest and tub

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GERRESHEIMER

BESPAK by Recipharm

THE CHANGING FACE OF AUTOINJECTOR TECHNOLOGY

In this article, Reenal Gandhi, Business Development Director, Bespak by Recipharm, discusses the advantages offered by liquefied gas as a power source for autoinjectors compared with conventional spring-based systems, as well as covering the benefits of using a platform model for drug delivery device development.

Over the past 20 years, drug delivery via an autoinjector has helped improve the patient experience and increase treatment adherence, with this trend continuing today. The autoinjector market has been growing, providing an easier alternative for patients to self-administer treatments that would otherwise be given by a healthcare professional. An autoinjector is often used to reduce dosage errors associated with self-administration, to alleviate patient concerns relating to needle phobia and to combat dexterity challenges. Typically, self-injections with autoinjectors are recommended to take less than 10–15 seconds to complete but with high viscosity products this can pose a challenge.

OPTIMISING INJECTABLE DRUG DELIVERY

The injectable drug delivery market is expected to grow from US$362.4 billion (£280.6 billion) in 2016 to $624.5 billion (£483.6 billion) by 2021.[1] This growth is, in turn, helping to drive the global autoinjector market size, which is expected to be worth in the region of $3.2 billion (£2.5 billion) by 2026, growing at a compound annual growth rate of 19.6% between 2019 and 2026.[2]

This rapid growth is driven by many factors. There has been an increase in the number of treatment options for chronic diseases involving biologics. In an effort to increase patient care and remain competitive in the growing biologics market, more products are moving towards reducing injection frequency, which often leads to increased concentration and higher viscosities.

There are also significant cost benefits to be achieved by healthcare providers in moving the administration of some medicines out of the clinic and into patients' homes. In addition, a greater market acceptance and transition to autoinjectors has been fuelled by increased convenience and ease of use.

Many biologic therapies are monoclonal antibodies that require high doses, resulting in high-viscosity liquids which are challenging to inject with a syringe or typical spring-based autoinjector. Using a device to appropriately deliver the product demands a complex and balanced combination of power to apply the necessary force, while managing the forces applied to fragile components, such as the syringe.

Novel autoinjectors are emerging to address these needs, delivering substantial benefits for both patients and drug developers.

> "Today, the use of liquefied gas, such as liquefied hydrofluoroalkane (HFA), as a power source for autoinjectors has presented several benefits over traditional spring-driven devices."

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NOVEL ADVANCEMENTS IN AUTOINJECTOR DESIGN

Today, the use of liquefied gas, such as liquefied hydrofluoroalkane (HFA), as a power source for autoinjectors has presented several benefits over traditional spring-driven devices. One of the main advantages is that it provides a near constant force over the duration of the injection. To achieve full injection, HFA-powered autoinjectors require lower peak forces compared with a typical spring autoinjector because the force does not decay. This applies lower stresses on the syringe and results in lower variation of force during drug delivery.

Figure 1 shows how an HFA-powered device provides a constant force and stopper velocity. As the liquefied HFA converts to gas, the expansion leads to a soft start of injection. The initial force peak can be much lower compared with a spring. As the gas continues to expand, the stopper velocity remains near constant, providing a steady force as the complete dose is injected. This is a major advantage compared with a spring-based autoinjector's kick start, where the spring can apply a high impact to the syringe. The resulting forces are centralised to weaker locations, such as the syringe flange or shoulders, increasing the chance of a breakage. For example, with technologies such as Bespak's VapourSoft, the forces are contained within the can until the device is used, which virtually removes any long-term loads on the device components compared with a conventional spring-based autoinjector.

Figure 2 demonstrates the steady pressure afforded by HFA-powered autoinjectors for a more constant rate of injection.

> "With technologies such as Bespak's VapourSoft, the forces are contained within the can until the device is used, which virtually removes any long-term loads on the device components compared with a conventional spring-based autoinjector."

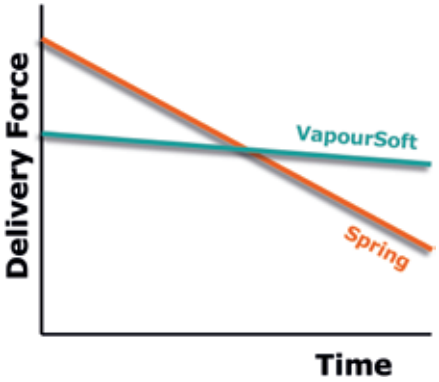

Figure 1: Change in force applied to a syringe in an autoinjector with a standard spring (red) and a liquified gas-powered system such as Bespak's VapourSoft (blue).

ADAPTING TO CHANGING REQUIREMENTS: ADDRESSING THE NEED FOR FLEXIBLE PLATFORMS

The development of an autoinjector traditionally proceeds through several stages:

- Concept evaluation and feasibility
- Product validation
- Transfer to manufacturing
- Scale-up.

By leveraging a platform development, these "off-the-shelf" options can now offer drug developers multiple configurations that allow for fast changes to a device according to the needs of a specific therapy. For example, a liquefied gas-powered autoinjector has the advantage that different force profiles can be obtained by simply changing the HFA gas, making it easy to adapt the platform to different drug products and different fill volumes without requiring complicated and lengthy device customisations.

When working with a platform, development has undergone the iterative process of prototyping, analysis and design modification to produce a reliable product. Designers work with an array of drug formulation properties, such as flow, viscosity and volume, and functionality requirements, including end user needs and scalability, to drive the design input requirements. Prototyping and technical guidance is a crucial element of the development process to ensure all components can be robustly scaled up for high-volume production.

Progress at every stage of production must be evaluated via a gated review by the programme team and key stakeholders to decide if the criteria to progress to the next stage have been fulfilled. This helps ensure a smooth transition from early-stage design to commercial manufacture. By performing design reviews, adjustments can be identified to help define the specification and build the process parameters.

The process parameters will be defined from the learnings during the development as products transition from prototype to small scale. This opportunity to work at a low-volume scale means that adjustments can be made to study performance, building confidence in the product capabilities. As products progress to higher volumes, process scalability needs to be proven. In most programmes, a stepwise approach will allow

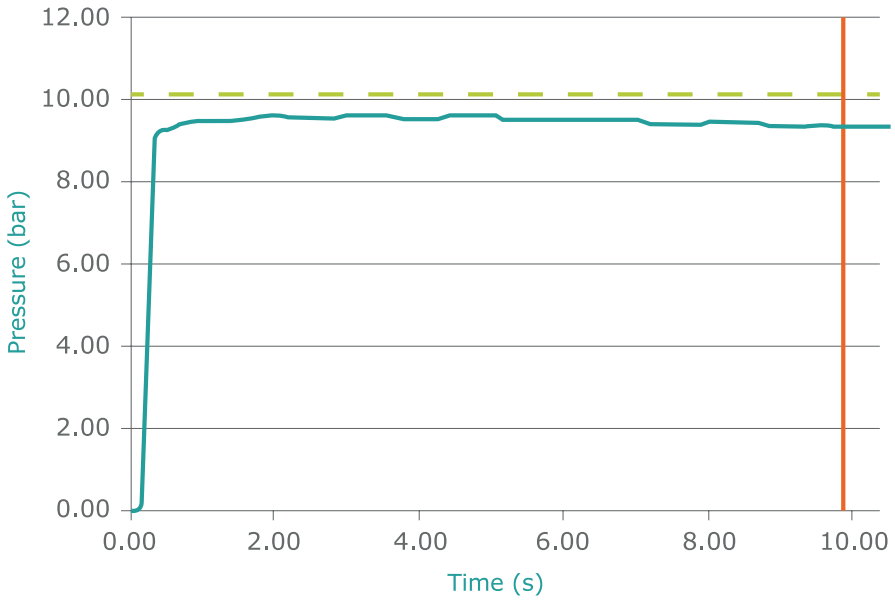

Figure 2: Pressure in a liquefied gas-powered autoinjector during injection.

for smart process design and predictable results. Working with a device partner that has the experience and capabilities to take the device design platform through to full scale and commercial manufacturing provides experience and development that can be flexible enough to meet unique product needs.

During pharmaceutical development, once a device requirement has been integrated, it can then be streamlined by analysing filled syringes and then assembling them into an autoinjector to study performance and identify potential areas for product-specific adjustments. By using the platform approach to design, the validation requirements of the final device are then based on a risk assessment of the gap between the basic device and the drug-specific variation. This type of approach can ensure that specifications are designed appropriately to ensure a drug product and device work together in the best possible way, while reducing the necessary time and resources for development.

REGULATORY AND QUALITY CONSIDERATIONS

Regulatory requirements should be incorporated from the initial stages of product development, as doing so will help to ensure that submission processes are as straightforward as possible further down the line. Requirements to be met include 21CRF820.30 and ISO 13487 for design control parts and ISO 10933 materials compliance, as well as the ISO 11608 series of standards specifically for autoinjector products, amongst several other more specific standards and industry guidance.

The complexity of a combination product filing and the level of detail regulatory agencies need is important to consider up front. Drug developers will want to work with partners that are able to support them during the filing phase and have proven experience of dealing with regulatory aspects. Rigorous in-process testing should also underpin all operations to provide the highest levels of style guide says no need to define – so just cGMP control, regulatory compliance and quality.

For example, in the US, vendors should be able to supply a medical device master file (MAF) filing which will contain all the detailed device information. The MAF can be used in the submission approach or, alternatively, the device information can be included within the drug product filing itself. This judgement should be made based on several factors, including the level of device experience within the pharma company and the regulatory strategy. One benefit of an MAF filing is that any device-related questions from the US FDA can be directed to the device partner, who will be able to provide answers to the device questions based on their prior experience of dealing with the FDA.

LOOKING TO THE FUTURE

Longer lifespans and greater numbers of patients being diagnosed with chronic conditions are calling for greater significance to be placed on the self-administration of medications. In line with this, more drug developers are looking to improve therapies to reduce dose frequency, achieve better convenience and ensure comfortable delivery for patients. The industry is increasingly realising that the success of products no longer relies solely on the therapeutic success of the drug itself, but on maintaining patient satisfaction and adherence.

As the sector continues to evolve, further advances will be forthcoming. There is a great opportunity for connectivity to be incorporated into devices, with steps towards these capabilities already being made by many device developers. This will make it possible to monitor injection data through data analytics and visualisation portals to help improve medication regimes.

In addition to higher concentrations, new drug formulations are also trending towards higher volumes (greater than 3 mL). Device vendors are now also addressing the market needs for high-volume injection devices.

The autoinjector market has established itself as a promising sector within the pharmaceutical industry. With improved capabilities of platforms and better understanding of regulatory processes, we are going to see more and more therapies delivered via autoinjectors, which is a positive step for patients living with chronic diseases.

ABOUT THE COMPANIES

Bespak by Recipharm delivers market leading design, development and manufacture of drug delivery devices to the global pharmaceutical market. This includes inhaler, nasal technologies and autoinjectors, as well as development and manufacturing services. Bespak's VapourSoft® platform offers full flexibility and capability to deliver high-viscosity formulations with ease. Syrina®, a VapourSoft®-powered autoinjector, has completed design verification testing and low-volume commercial and clinical supply is now available.

Recipharm is an innovative drug delivery device company. Driven by customer and patient demand, Recipharm's innovations have the potential to create new treatments and opportunities across the globe, as well as accelerating routes to market.

REFERENCES

1. *"Injectable Drug Delivery Market by Type (Device, Formulation), Therapeutic (Cancer), Usage Pattern (Immunization), Administration (Skin, Musculoskeletal), Distribution Channel (Hospital), Patient Care Setting (Hospital, Home Care) - Forecast to 2021". Market Report, Markets and Markets, February 2017.*
2. *"Auto-Injectors Market (By Product Type: Disposable Auto-Injectors, Reusable Auto-Injectors; By Disease Indication: Rheumatoid Arthritis, Multiple Sclerosis, Diabetes, Anaphylaxis, Other Therapies; By End-use: Home Care Settings, Hospitals & Clinics, Ambulatory Surgical Centers) - Global Industry Size, Share, Trends and Forecast 2019 - 2026". Market Report, Acumen Research and Consulting, 2018.*

ABOUT THE AUTHOR

Reenal Gandhi is Business Development Director at Bespak by Recipharm and has more than 15 years' experience in both the drug delivery device and pharma industry, developing and commercialising drug delivery solutions for biotech, vaccine and pharma. She has an MBA and has experience in business development and licensing for innovative and generic products. Ms Gandhi is responsible for business development activities related to nasal devices and injectable devices such as autoinjectors and wearable injection systems.

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POLYMER SYRINGE CONSIDERATIONS FOR DRUG APPLICATIONS AND ADMINISTRATION

In this article, Tibor Hlobik, Senior Director, Product Management, West Pharmaceutical Services, compares cyclo-olefin polymers and copolymers with glass as the material of choice for prefilled syringes, in particular discussing the benefits of polymers when it comes to biologic drug products and prefilled syringes for use in autoinjectors.

BACKGROUND

Manual prefilled syringes offer a number of benefits, including cost advantages, simpler manufacturing processes and ease of administration. However, there are several limitations, including dosing/medication errors if not used as prescribed and the potential for needlestick injuries resulting in a safety risk. Patient adherence and outcomes may be improved with the addition of an autoinjector to the syringe that is relatively easier to use, has integrated needle safety features and allows for self-administration that decreases the need for visiting a healthcare centre for treatment. Autoinjectors are also considered a valuable lifecycle management approach, used by many pharmaceutical players to expand marketing exclusivity periods of proprietary drugs.

The demand for prefilled syringe-based autoinjectors continues to be strong. Historically, these were widely used as an emergency treatment option for anaphylaxis and autoimmune treatments. Now they are being applied in multiple treatments for chronic diseases that require frequent injections, such as diabetes, rheumatoid arthritis, psoriasis and multiple sclerosis. The strong pipeline of biologics is further driving the growth of autoinjectors.

Glass prefilled syringes have traditionally been the standard in autoinjector applications. Recently, cyclo-olefin syringes are being combined with autoinjectors for complex drug delivery applications, with several drugs on the market already approved by regulatory agencies. This combination can bring differentiated value to the patient. One publicly announced example[1] is Ypsomed's (Bergdorf, Switzerland) YpsoMate® with a Terumo (Tokyo, Japan) PLAJEX™ syringe for the drug Hulio® (adalimumab); a biosimilar to Humira® (AbbVie, Lake Bluff, IL, US) developed by Fujifilm Kyowa Kirin Biologics (Tokyo, Japan) and marketed in the EU by Mylan (Canonsburg, PA, US).

CYCLO-OLEFIN POLYMER – MATERIAL REVIEW

There are two primary types of engineered polymers used to manufacture prefillable syringes: cyclo-olefin copolymer (COC) and cyclo-olefin polymer (COP). To date, COP syringes have been a primary choice for biologic drug applications. A chemistry overview of each material type is provided for reference.

COP is made by ring-opening metathesis polymerisation of norbornene (or a derivative) with Grubbs catalyst (e.g. $Ru[P_2C_3H_2(C_6H_5)_8]Cl_2$), followed by solution-phase hydrogenation with a diimide compound (Figure 1). Diimides, such as 4-methylbenzenesulfonhydrazide, are well known compounds for hydrogenating double bonds. From a commercial standpoint, they offer the great advantage of

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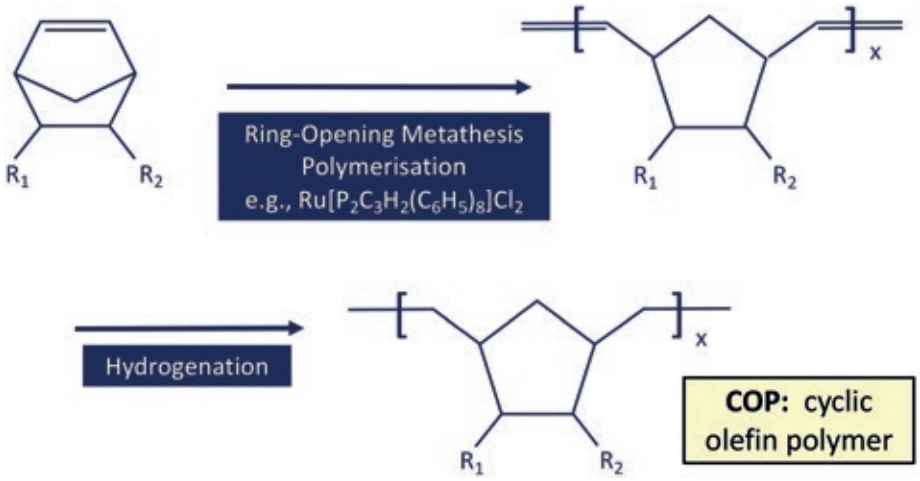

Figure 1: Structure and synthesis of a COP. Poly(norbornene) is represented where R1 and R2 are hydrogen.

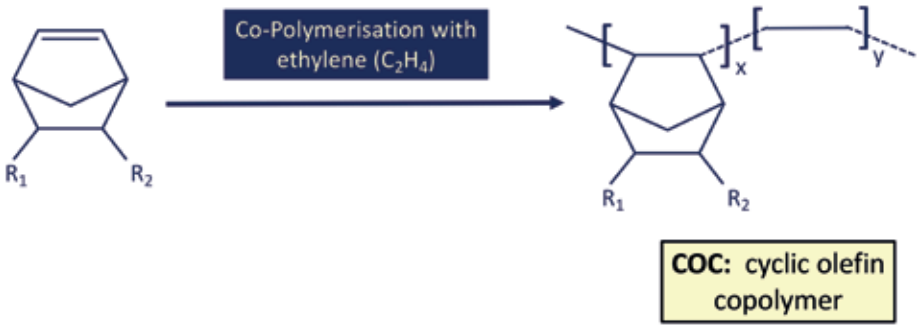

Figure 2: Structure and synthesis of a COP. Poly(norbornene-co-ethene) is represented where R1 and R2 are hydrogen.

avoiding the need to use gaseous hydrogen. By-products of the reaction are nitrogen gas and compounds that can be removed easily by washing. The molecular weight (Mw) of COP is typically ~ 7 x 104, with a polydispersity of ~ 2.

In contrast, COC is made by metallocene-catalysed (e.g. $Ti[(C_5H_5)_2]Cl_2$) co-polymerisation of norbornene (or derivative) with ethene (Figure 2). While this has some advantages, there are likewise drawbacks. Advantages are employment of a low-cost monomer (ethene) and no need to hydrogenate after polymerisation (one step versus two steps). Both points offer a cost advantage. However, a typical commercial product that has a glass transition temperature (Tg) that can withstand autoclave sterilisation (steam at greater than 120 °C) will have a high norbornene content (offsetting the ethene cost benefit) and is brittle.

"Polymers such as polyethylene comprise essentially only carbon and hydrogen (constituents of all drug products) and thus, intrinsically, the risk of a leachate causing an issue is reduced substantially."

	Glass (Mw %)	Polymer (Mw %)
SiO_2	70–82	–
B_2O_3	5–13	–
Al_2O_3	2–7	–
CaO/MgO/BaO	0–7	–
Na_2O/K_2O	4–12	–
C	–	85
H	–	15
Catalyst	–	trace

Table 1: Chemical composition of typical tubular Type I borosilicate glasses and typical polymer (polyethylene).

Chemistry Comparison

Glass used for pharmaceutical primary containers is typically Type I borosilicate (according to the United States Pharmacopoeia and European Pharmacopoeia). The compositions of Type I glass and an analogue polymer for COP (e.g. polyethylene, $[C_2H_4]_x$), are given in Table 1. Glass comprises at least five oxides, the cations of which can leach into a drug product. According to ICH Q3D (Guideline for Elemental Impurities) for new finished drug products, a strategy to limit elemental impurities must be developed. The table of impurities listed in ICH Q3D cites several ions that are present in glass.

Certain proteins or drug products, due to the buffer or excipient, are sensitive to certain elements that can leach from glass, such as aluminium, barium or calcium. In contrast, polymers such as polyethylene comprise essentially only carbon and hydrogen (constituents of all drug products) and thus, intrinsically, the risk of a leachate causing an issue is reduced substantially.

Surface Interaction and Silicone Oil Risk

Glass has a high surface energy, while lower energy materials (e.g. butyl rubber) tend to adhere. Practically, this means that an elastomer plunger made of butyl rubber will tend to adhere to the inside wall of a glass syringe. To assist movement of the plunger in the syringe, a layer of silicone oil is placed on the inside of the syringe. This is done for almost all glass syringes and facilitates easier movement of the plunger, which is a desirable feature.

As noted prior, the inner surface of a glass syringe must be siliconised (i.e. have a thin coating of silicone oil applied, typically sprayed, with sometimes resultant coating being baked) in order to provide lubricity to enable effective plunger movement. This is necessary because the lower surface-energy elastomer stopper will tend to adhere to the higher surface-energy glass surface. However, there are two issues with the presence of silicone oil:

- **Particles:** The presence of silicone oil intrinsically creates the risk of introducing visible and sub-visible particles into the drug product – particles that will be injected into the patient. This is clearly a risk to patient safety.
- **Protein Aggregation:** Proteins can aggregate to form particles in the presence of silicone oil and the drug efficacy can be compromised.

It is well known that silicone oil can cause alteration/denaturation of protein molecules, resulting in the formation of particulates which are unacceptable, as particulates can result in diminished/deleterious effects. A substantial amount of literature addresses the issue of protein aggregation and resultant particle formation.[2-7] In syringes comprising lower surface energy polymers, siliconisation is not needed. Thus, a lower-risk solution is to employ a COP-based syringe, which has a lower surface energy and thus enables plunger movement without the need for silicone oil.

Physical Properties – Modulus/Strength/Brittleness

Glass Type I borosilicate has a very high modulus of elasticity (Young's modulus), and thus stiffness (Table 2). This manifests as a high brittleness compared with many polymer materials, which instead show high ductility. The energy that is introduced from a strong impact cannot be absorbed by glass, but instead causes it to fracture. Due to its amorphous nature, glass strength is not a material constant, but rather depends on the intactness of the surface. This intactness is strongly influenced by manufacturing and processing, starting with tubing production, through the converting process and filling line, up to point of administration.

Glass has an impact resistance of only ~20 J – as compared with ~ 550 J for a polymer

Property	Glass	Polymer
Elastic Modulus – GPa	~ 70	0.8 (a)
Tensile Strength – MPa	70–100	15 (a)
Impact Strength – J (c)	~ 20	~ 550 (b)

Table 2: Mechanical properties of glass versus polymers (a: Polyethylene, b: Poly(norbornene) – Daikyo Crystal Zenith® cyclo-olefin polymer, c: Tested with a Dupont (Wilmington, DE, US) impact tester).

Material	Force to Break (N)
Glass	~ 250
Daikyo Crystal Zenith® cyclo-olefin polymer	>500

Table 3: Syringe flange strength.

"What is expected, based on theoretical considerations, has been demonstrated experimentally – proteins interact much more strongly with glass than polymer."

(Table 2). This means that the chances of glass breakage are substantially higher. In syringes, this has been demonstrated experimentally. Flange strength of syringes comprising glass was compared with those comprising a poly(norbornene)-based COP polymer (Table 3). This may appear counterintuitive, that a polymer requires more force to break even though glass has a higher tensile strength. The reason is this: a polymer can undergo deformation under stress, whereas glass cannot, and thus a polymer can accommodate a higher force prior to fracture. This is reflected by the higher impact strength of polymers. The net result is that a polymer syringe provides a much more durable product (i.e. less likely to fracture) in an autoinjector.

Protein Adsorption Consideration

In addition to having a higher surface energy than a polymer, and therefore being more likely to interact with a protein molecule (promoting the issues just noted), glass carries a net negative charge, resultant from SiOH groups.

This enables an electrostatic interaction between glass and protein. A polymer surface, in contrast, has only a marginal charge, due to the general absence of ionisable groups (except a possible small amount of alcohol (R-OH) or carboxylic acid (R-COOH) groups). Interactions between polymer and protein, therefore, would be governed not by stronger electrostatic effects, as is the case with glass, but by much weaker dispersion forces. What is expected, based on theoretical considerations, has been demonstrated experimentally – proteins interact much more strongly with glass than polymer. Several studies have compared the adsorption of proteins with vials comprising glass and polymer.[8,9]

The adsorption of proteins to the surfaces of container systems is an issue for two reasons:

- **Concentration:** For drug products formulated at a high concentration of API, such as monoclonal antibodies, the amount adsorbed is likely insignificant. However, where the drug product is formulated at a low API concentration (e.g. tens of µg/mL), the amount adsorbed can represent a significant fraction. As a consequence, the manufacturer may need to formulate at a higher API concentration than medicinally necessary, resulting in higher cost for the patient.
- **Performance:** Of more concern, protein adsorbed to a surface can serve as a nucleation site leading to the formation of protein particles. It has been demonstrated by Philo and Awakara[10] that proteins can aggregate by five different methods. These particles may become dislodged (e.g. due to mechanical stress such as agitation), potentially leading to the formation of larger aggregates. This has been demonstrated by Gerhardt *et al.*[4] Furthermore, a growing body of evidence suggests that protein aggregates can be immunogenic, for example as reported by Rosenberg.[11] This is an extremely serious issue.

Proteins interact much more strongly with glass than polymer, which leads to issues of diminished API concentration in drug product and, worse, formation of particles that may be immunogenic. Clearly, with a biologic drug product, the lower risk option is a cyclo-olefin polymer.

CONCLUSION

Greater scrutiny must be paid to the interaction between the drug and prefillable syringes. Drug stability over the shelf life, particulate burden, the prevention of

"High-quality cyclo-olefin polymer prefillable syringes are a proven solution and have differentiated benefits over glass in areas of chemistry, physical properties and protein adsorption."

breakage (e.g. body and flange) and ease of delivery are some important factors to consider. In addition, regulatory agencies and pharmaceutical companies have increased their quality expectations in an effort to enhance patient safety.

High-quality cyclo-olefin polymer prefillable syringes are a proven solution and have differentiated benefits over glass in areas of chemistry, physical properties and protein adsorption. Engineered polymer syringes present attractive benefits that are gaining increased attention from drug manufacturers seeking new answers to growing drug challenges.

ABOUT THE COMPANY

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

West is headquartered in Exton, PA, US, and supports its customers from locations in North and South America, Europe, Asia and Australia. West's 2019 net sales of US$1.8 billion reflect the daily use of approximately 112 million of its components and devices, which are designed to improve the delivery of healthcare to patients around the world.

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REFERENCES

1. *"First market entry of YpsoMate autoinjector from Ypsomed". Press Release, Ypsomed, December 7, 2018.*
2. *Jones LS, Kaufmann A, Middaugh CR, "Silicone oil induced aggregation of proteins". J Pharm Sci, 2005, Vol 94(4), pp 918–927.*
3. *Thirumangalathu R et al, "Silicone oil- and agitation-induced aggregation of a monoclonal antibody in aqueous solution". J Pharm Sci, 2009, Vol 98(9), pp 3167 –3181.*
4. *Gerhardt A et al, "Protein Aggregation and Particle Formation in Prefilled Glass Syringes". J Pharm Sci, 2014, Vol 103(6), pp 1601–1612.*
5. *Chisholm CF et al, "In Vivo Analysis of the Potency of Silicone Oil Microdroplets as Immunological Adjuvants in Protein Formulations". J Pharm Sci, 2015, Vol 104(11), pp 3681–3690.*
6. *Krayukhina E et al, "Effects of Syringe Material and Silicone Oil Lubrication on the Stability of Pharmaceutical Proteins". J Pharm Sci, 2015, Vol 104(2), pp 527–535.*
7. *Waxman L, Vilivalam V, "Evaluation of End-Over-End Rotation/Agitation of Protein Solutions in Prefilled Syringes Made from Glass or Plastic as a Preliminary Indicator of Protein Aggregation". Technical Bulletin, West Pharmaceutical Services, 2011.*
8. *Qadry SS et al, "Evaluation of CZ-resin vials for packaging protein-based parenteral formulations". Int J Pharm, 2003, Vol 252(1–2), pp 207–212.*
9. *Eu B et al, "Direct visualization of protein adsorption to primary containers by gold nanoparticles". J Pharm Sci, 2011, Vol 100(5), pp 1663–1670.*
10. *Philo JS, Arakawa T, "Mechanisms of Protein Aggregation". Curr Pharm Biotechnol 2009, Vol 10(4), pp 348–351.*
11. *Rosenberg AS, "Effects of protein aggregates: an immunologic perspective". AAPS J, 2006, Vol 8(3), pp E501–E507.*

ABOUT THE AUTHOR

Tibor Hlobik is a Senior Director, Product Management, at West Pharmaceutical Services, with 30 years' experience in the pharma industry. He is responsible for managing a portfolio of prefilled system and device products. Mr Hlobik has global responsibility for strategic planning, identifying new product development and directly leading brand product managers, as well as cross-functional teams. Previous roles and experience at West include marketing, technical services, quality assurance and research & development.

MITSUBISHI GAS CHEMICAL

OXYCAPT™ MULTILAYER PLASTIC VIAL AND SYRINGE

Here, Shota Arakawa, Research Manager, and Tomohiro Suzuki, Associate General Manager, of Mitsubishi Gas Chemical, discuss MGC's OXYCAPT™ vial and syringe primary containers, including the OXYCAPT™ material and product offering, as well as where MGC sees OXYCAPT™ fitting into the modern pharmaceutical market.

INTRODUCTION

Although essential for humans, oxygen is basically unnecessary for processed foods and drugs. Over 40 years ago, Mitsubishi Gas Chemical (MGC) developed an oxygen absorber called AGELESS® which prevents the oxidation of foods. Since then, AGELESS® has been used in a variety of food products worldwide and MGC has been a leading company in the oxygen-absorber field. AGELESS® has also been used for drug products, such as intravenous (IV) solutions, prefilled syringes, ampoules and tablets, for many years, especially in the Japanese market. It significantly contributes to stabilising the efficacy of drugs and extending their shelf life. However, the use of an oxygen absorber is not as common in the US or Europe, as additional items, including dispensing machinery, sealing equipment and secondary packaging with high gas barrier, are needed to apply the absorber.

Therefore, MGC began developing alternative technologies to the oxygen absorber. Firstly, MGC developed a new oxygen-absorbing polymer, which featured a very low level of extractables and demonstrated no degradation, even after absorbing oxygen. Secondly, MGC sought an improvement on the existing multilayer-moulding technology which has often been used in the beverage industry to enhance the oxygen and carbon dioxide barrier provided by the packaging. By combining these two technologies, MGC has successfully developed a multilayered plastic vial and syringe called OXYCAPT™ (Figure 1).

Figure 1: The OXYCAPT™ multilayer plastic vial and syringe.

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"The COP layers give OXYCAPT™ the traditional characteristic advantages of polymer syringes, while the new polyester plays a role as an oxygen and UV barrier to address the weaknesses inherent in using COP alone."

OXYCAPT™ PRODUCT OVERVIEW

The OXYCAPT™ vial and syringe consists of three layers (Figure 2). The inner and outer layers are made of cyclo-olefin polymer (COP), the most reliable polymer used by the pharma industry. The middle layer is made of a novel polyester that has been developed by MGC. The COP layers give OXYCAPT™ the traditional characteristic advantages of polymer syringes (high water vapour barrier, very low extractables, high pH stability, low protein adsorption, high break resistance, etc.), while the new polyester plays a role as an oxygen and UV barrier to address the weaknesses inherent in using COP alone.

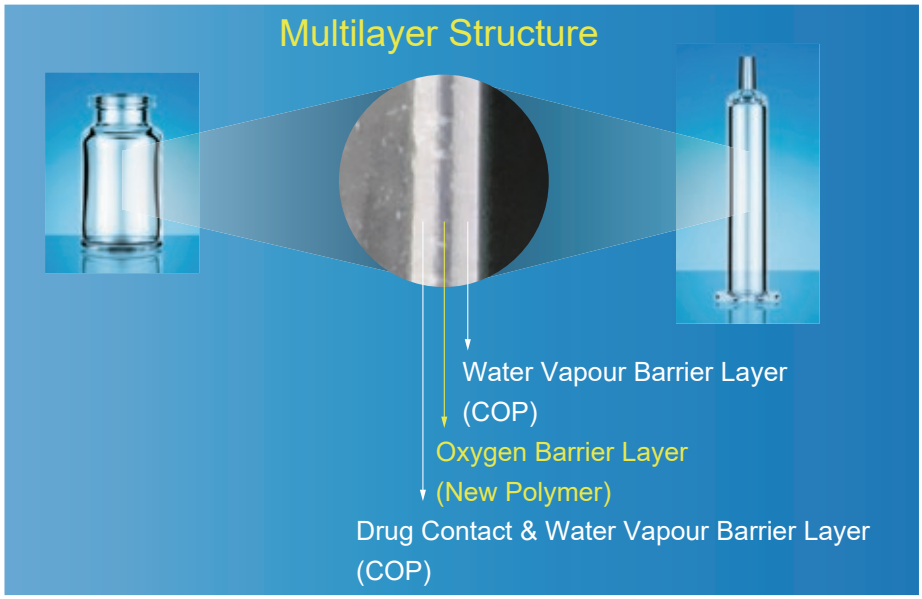


Figure 2: Multilayer structure of OXYCAPT™.

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, thanks to its oxygen-absorbing function, OXYCAPT-A can maintain lower oxygen concentrations in the headspace than Type 1 glass. OXYCAPT-P has also achieved an excellent oxygen barrier, although there is no oxygen-absorbing function. For example, the oxygen barrier of the OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial (Figure 3). OXYCAPT-A is particularly suitable for oxygen-sensitive drugs and OXYCAPT-P is recommended for all drugs.

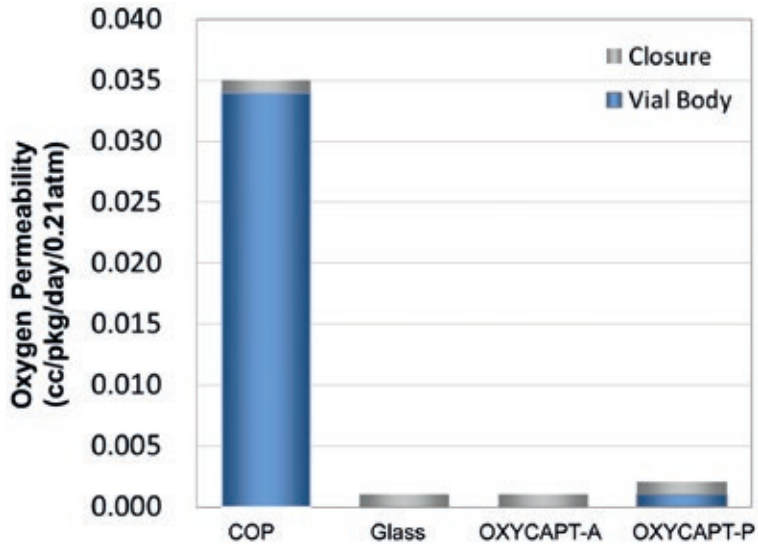


Figure 3: Oxygen permeability comparison of a typical COP, glass, OXYCAPT-A and OXYCAPT-P.

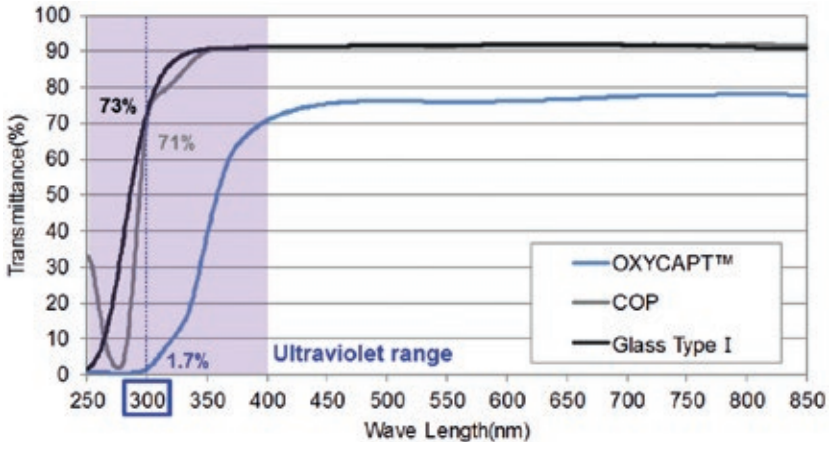


Figure 4: UV light transmittance comparison of a typical COP, Type I glass and OXYCAPT™.

Barrier Properties

OXYCAPT™ is an excellent UV barrier. Although about 70% of UV light of 300 nm transmits through glass and COP, only 1.7% of UV light transmits through OXYCAPT™ (Figure 4). MGC has confirmed this feature also contributes to the stability of biologics.

Regarding the 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 in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

Extractables

Studies have shown extremely low extractables from OXYCAPT™. One study was conducted to confirm volatile, semi-volatile and non-volatile impurities from OXYCAPT™. Water and four solutions (50% ethanol, NaCl, NaOH and H3PO4) were selected, and impurities were measured by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the blank, impurities were not detected in OXYCAPT™ containers. A second study confirmed that inorganic extractables levels from OXYCAPT™ were similar to those from COP, which is well known as an extremely pure polymer, and with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contribute to better pH stability in drug products (Figure 5).

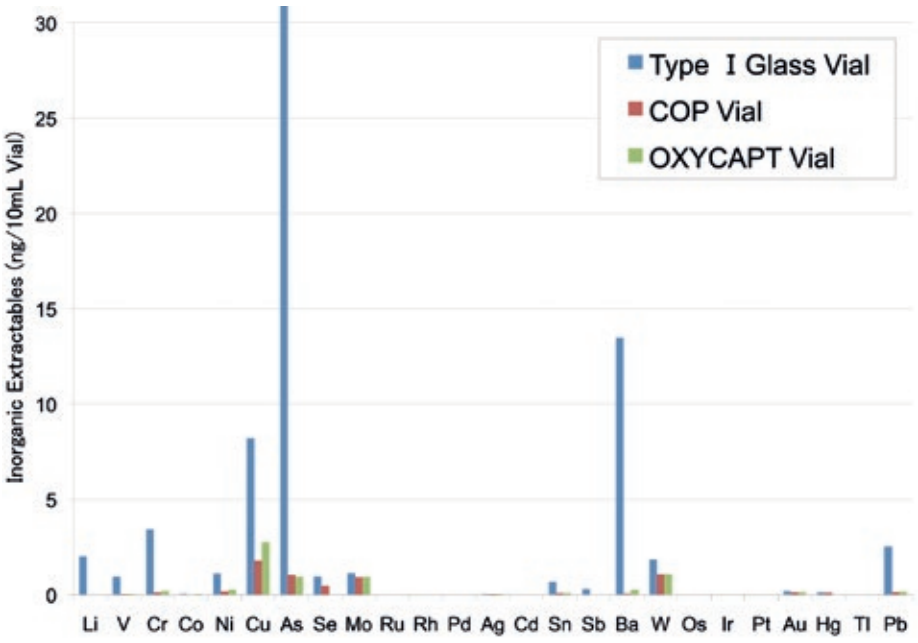


Figure 5: Inorganic extractables comparison of a typical COP, Type I glass and OXYCAPT™.

Syringe Construction

The OXYCAPT™ syringe consists of a tip cap, a barrel, a polytetrafluoroethylene-laminated stopper and a plunger rod (Figure 6). Although a very small amount of silicone oil is sprayed on the stoppers of OXYCAPT™ syringes, no silicone oil is baked on the barrel. According to our internal studies using existing antibodies, MGC has found that this feature leads to much less protein aggregation compared with existing Type 1 glass syringes.

The OXYCAPT™ vial and syringe is produced by co-injection moulding technology. Although this technology has been applied to beverage bottles for many years, MGC is the first company that has succeeded in applying it to multilayer plastic syringes. MGC has also developed the

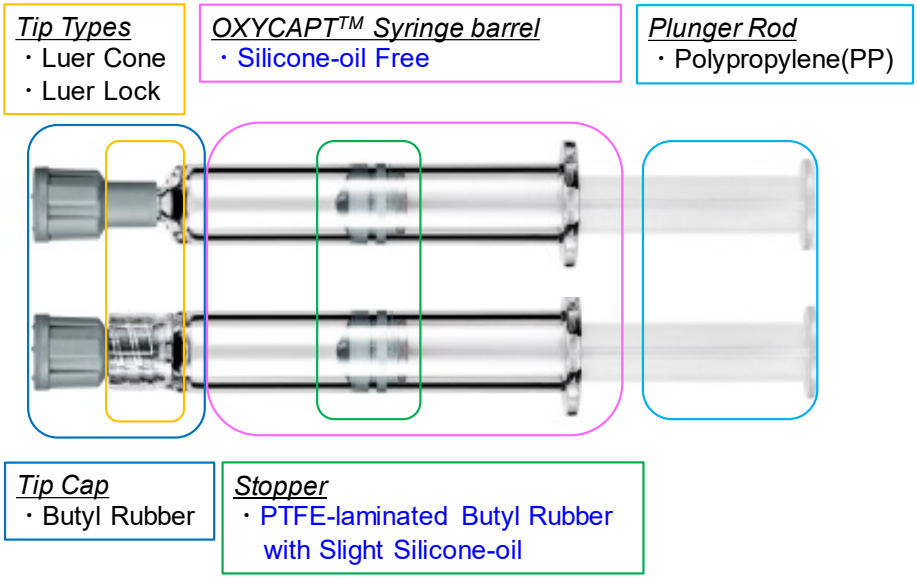


Figure 6: Components of an OXYCAPT™ syringe.

inspection methods for the oxygen barrier layer. All the containers are 100% inspected by state-of-the-art machinery.

The latest dropping tests for these syringes were conducted based on ISO 11608-1:2014 (requirements and testing methods for needle-based injection systems). Gamma-sterilised OXYCAPT™ 1 mL long syringes and existing Type 1 glass syringes were dropped from a height of 1 m three times (once horizontally and twice vertically) onto a steel plate. Although 90% of the glass syringes were broken, no breakage was observed in the OXYCAPT™ syringes (Table 1).

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 1: Data from MGC's latest drop testing of OXYCAPT™ and glass syringes.

Figure 7: Nest and tub storage for OXYCAPT™ vials and syringes.

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 2: MGC's OXYCAPT™ product portfolio.

OXYCAPT™ ON THE MARKET

MGC can offer bulk vial, ready-to-use (RTU) vial and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-based nest and tub formats (Figure 7). The nest and tub are mainly sterilised by gamma ray. There are 2 mL, 6 mL, 10 mL and 20 mL for vials, and 1 mL long and 2.25 mL for syringes (Table 2). MGC is willing to provide samples for initial testing free of charge.

Each polymer meets the requirements of USP 661, USP87, USP88 and EP, and has been filed in the US FDA's drug master file (DMF). The vials and syringes are also compliant with each pharmacopoeia and have been filed in the DMF. The syringes are produced and controlled in accordance with ISO 13485.

The primary target market for OXCAPT™ is the therapeutic application of biologics. As mentioned in ICH Q5C (Stability of Biotechnological/Biological Products), oxidation is one of the causes of protein instability. As such, the oxygen and UV barrier properties of OXYCAPT™

> "MGC believes that OXYCAPT™ would be very suitable as a primary container material for epinephrine, because it is well known as an oxygen-sensitive drug."

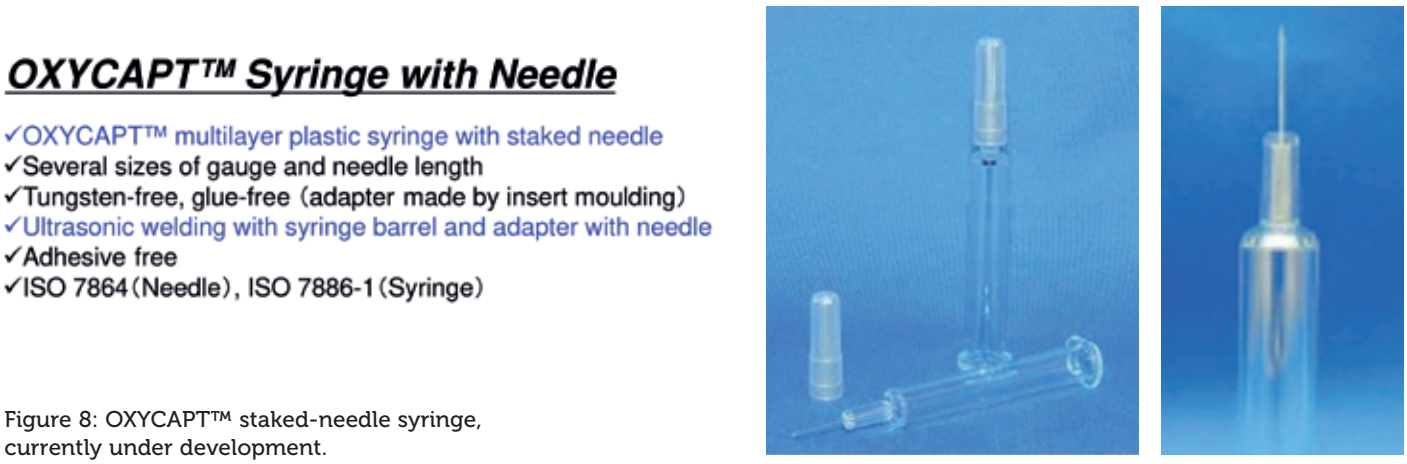


Figure 8: OXYCAPT™ staked-needle syringe, currently under development.

will definitely contribute to the stability of biologics stored within. Also, some drug developers have started evaluating the OXYCAPT™ vial for their gene and cell therapy recently; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

In addition, MGC believes that OXYCAPT™ would be very suitable as a primary container material for epinephrine, because it is well known as an oxygen-sensitive drug. Storing epinephrine in glass also has the problem of glass breakage, a serious issue for an emergency drug, and therefore some suppliers have tried to develop new pen injectors using polymers as the primary container.

MGC has previously been asked to develop staked-needle multilayer plastic syringes by some of its customers. As such, MGC started tackling development a few years ago and recently decided to invest in a production facility for staked-needle syringes. The necessary equipment will be installed by March 2021. OXYCAPT™ syringe, with staked needle, has some special features, such as being free from tungsten, glue and adhesives, and will be available with several gauges and lengths (Figure 8).

CONCLUSION

In conclusion, OXYCAPT™ has been developed to solve the current problems in the pharmaceutical industry. In addition to the special features of COP, such as a strong water vapour barrier, high breakage resistance, very low extractables and low protein adsorption, OXYCAPT™ provides a strong oxygen and UV barrier. MGC believes that OXYCAPT™ brings a lot of benefits to the rapidly growing biologics and regenerative medicines market.

ABOUT THE COMPANY

Mitsubishi Gas Chemical does business in a wide range of fields, from basic chemicals to fine chemicals and functional materials. MGC established an Advanced Business Development Division in 2012 as a centre for continually creating new businesses, and developed the OXYCAPT™ plastic vial and syringe as an alternative to glass containers.

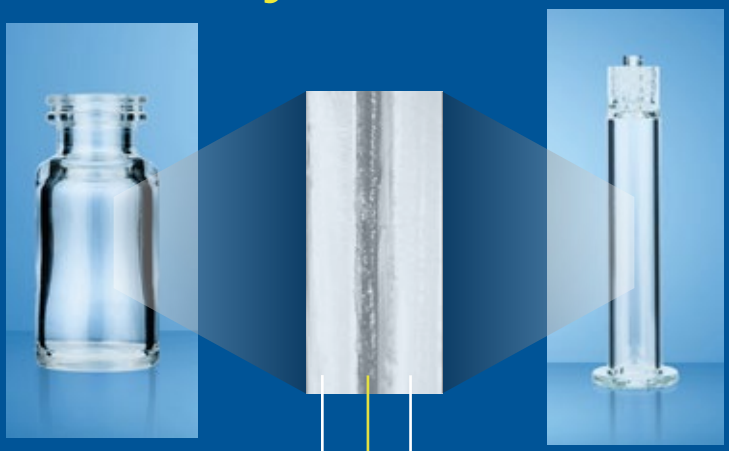
ABOUT THE AUTHORS

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 Masters Degree of Science in 2009 from Osaka University (Japan). Since April 2009 he has been in charge of macromolecular science, especially in synthesis of polymers and material development, for MGC. In 2012 he joined the development team for OXYCAPT™.

Tomohiro Suzuki is an Associate General Manager at Mitsubishi Gas Chemical, having joined the company in 1998. He belonged to the Oxygen Absorbers Division until 2011, and was transferred to the Advanced Business Development Division in 2012 to be a member of the OXYCAPT™ development team. Since then, he has been in charge of marketing of the OXYCAPT™ plastic vial and syringe.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



- Excellent Oxygen Barrier
- 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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