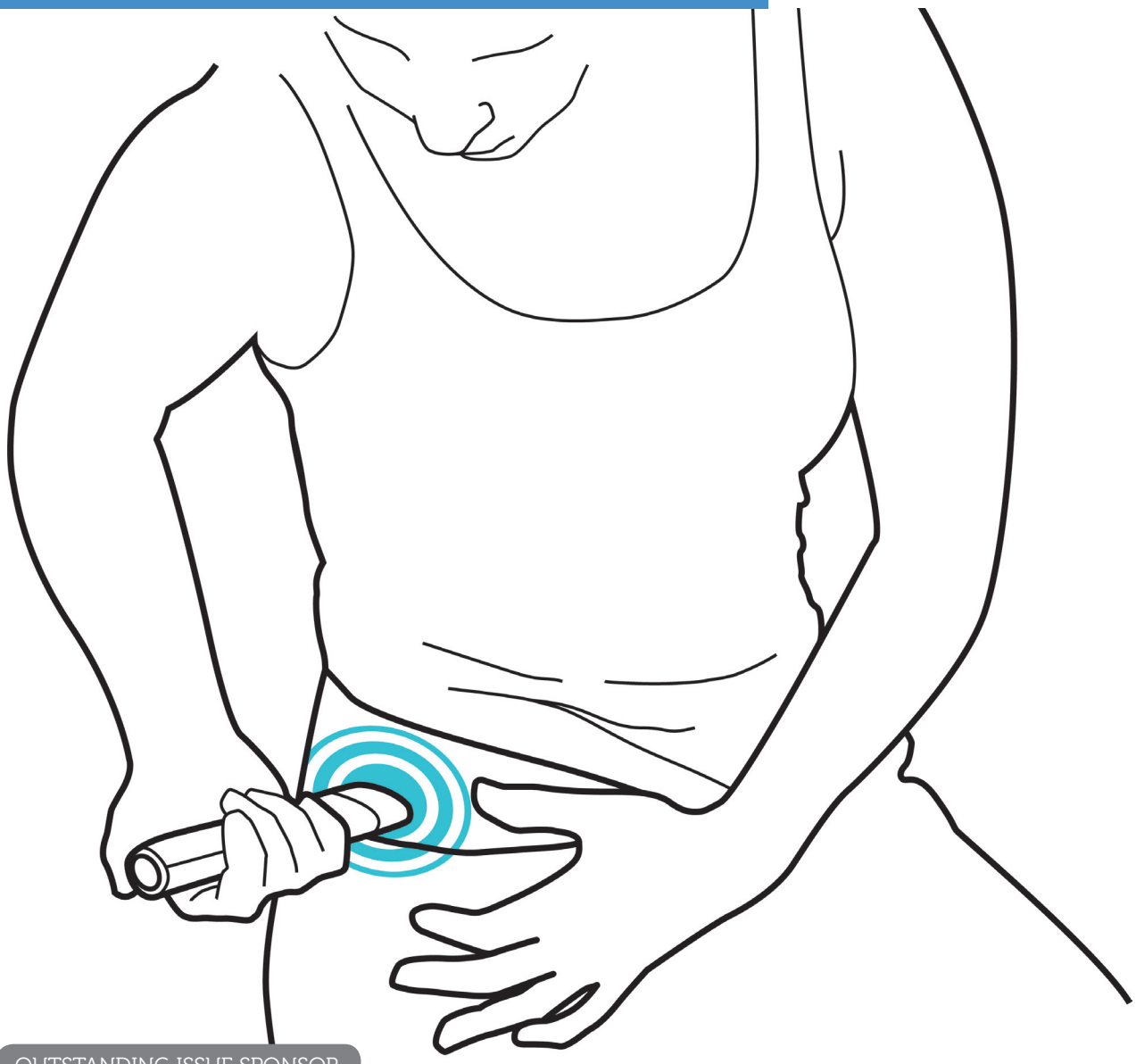
INJECTABLE DELIVERY: DEVICES FOCUS

ON drugDELIVERY



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ONdrugDelivery Issue N° 75, May 8th, 2017

INJECTABLE DELIVERY: DEVICES FOCUS

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

12 MONTH EDITORIAL CALENDAR

Jun	Connected Delivery Devices
Jul	Novel Oral Delivery Systems
Sep	Wearable Injectors
Oct	Prefilled Syringes
Nov	Pulmonary & Nasal Delivery
Jan '18	Ophthalmic Delivery
Feb	Prefilled Syringes
Mar	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Devices Focus

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Front cover image: "A self-administered drug injection allows patients around the world to take control of their quality of life." courtesy Key Tech Inc (www.keytechinc.com). Reproduced with kind permission.

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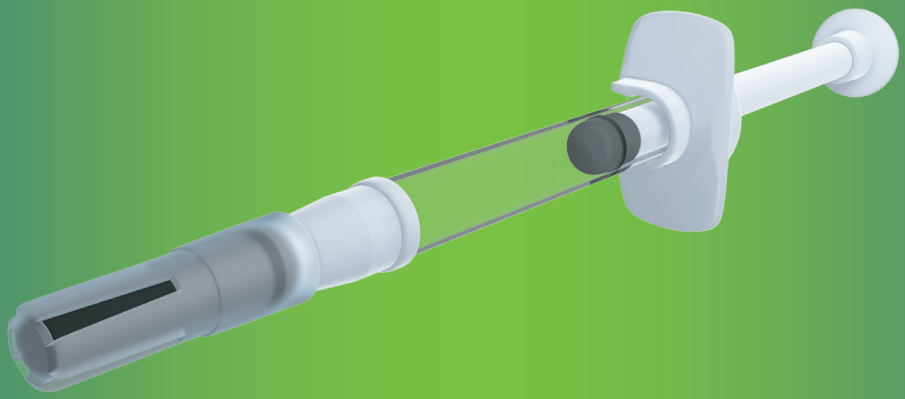

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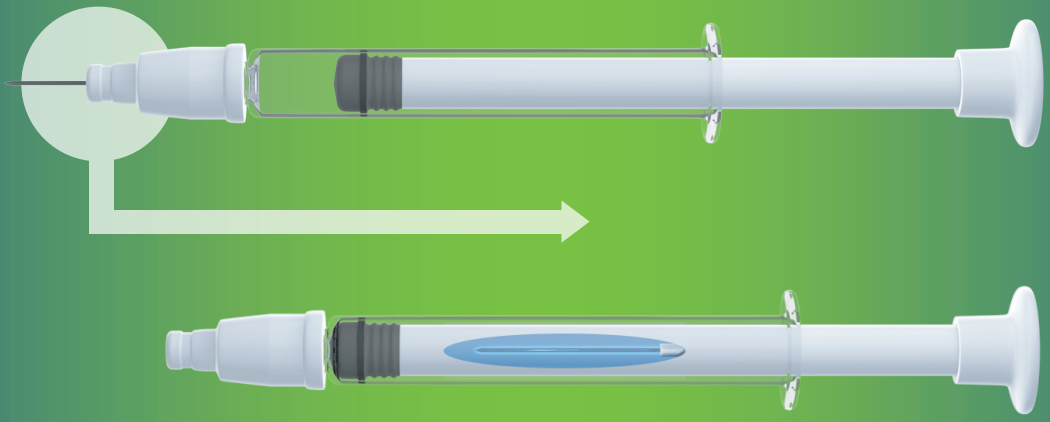

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SHL GROUP

SAFEGUARDING USER NEEDS: THE LONG-TERM LEGACY OF SHL'S PATIENT-CENTRIC DESIGNS

Despite being founded in an age when medical devices were more about getting the job done than providing optimum patient experience, SHL Group, has from the very beginning placed emphasis on users and usability. At the center of SHL's design hub, safeguarding these fundamental values, is SHL's Director of Industrial Design, Jochen Ratjen. In this article, we talk to Mr Ratjen about his personal experiences, what patient-centricity means to SHL, and how SHL's designs are moving ahead with the changing trends.

Today human factors, patient-centricity, and usability are terms strongly connected with the healthcare sector as well as the development of medical devices. However, just 30 years ago, the idea of focusing on patient-centricity in designs was more of an idealistic concept than a determining factor for the medical industry.

It was not until 2011 that the US FDA, in response to the increasing emphasis on the patient experience, updated its guidelines for applying human factors in medical devices into a new guidebook – "Applying Human Factors and Usability Engineering to Optimize Medical Device Design".[1,2] Later, the FDA announced that the document would officially supersede its 2000 predecessor as of April 3, 2016. This marked the shift from simply designing products that work to creating devices that place patient comfort and safety first.

A MAN OF PASSION & PRACTICALITY

Jochen Ratjen started his career in an industrial design consultancy in 1988. He played important roles in award-winning healthcare projects for the elderly and the disabled, and worked on a variety of consumer and medical technology products in different segments. Later in his career, he became more invested in auto injectors, reusable and disposable pen injectors, pill dispensers, and inhaler systems. It was during that time that he began working with plastic components for mass production, an experience that would lend itself to his expertise working on in-house manufacturing at SHL.

> "After all these years participating in user studies, I still find there is always something new to learn."

In 1995, a more seasoned Jochen Ratjen was approached by SHL's management team to design the company's first auto injector – PenInject 2.25 (Figure 1). This was a time, he notes, when the medical industry focused more on device functionality rather than patient usability, and when terms such as "usability," "ergonomics," and "human factors" were not mentioned by pharma companies as they are today. He was, as a result, struck by SHL's passion for industrial design as well as by the company's foresight to involve the end user at the very beginning of the design process.

Prior to becoming an industrial design expert, Mr Ratjen was educated as a precision tool maker in Germany. This experience influenced his interest in as well

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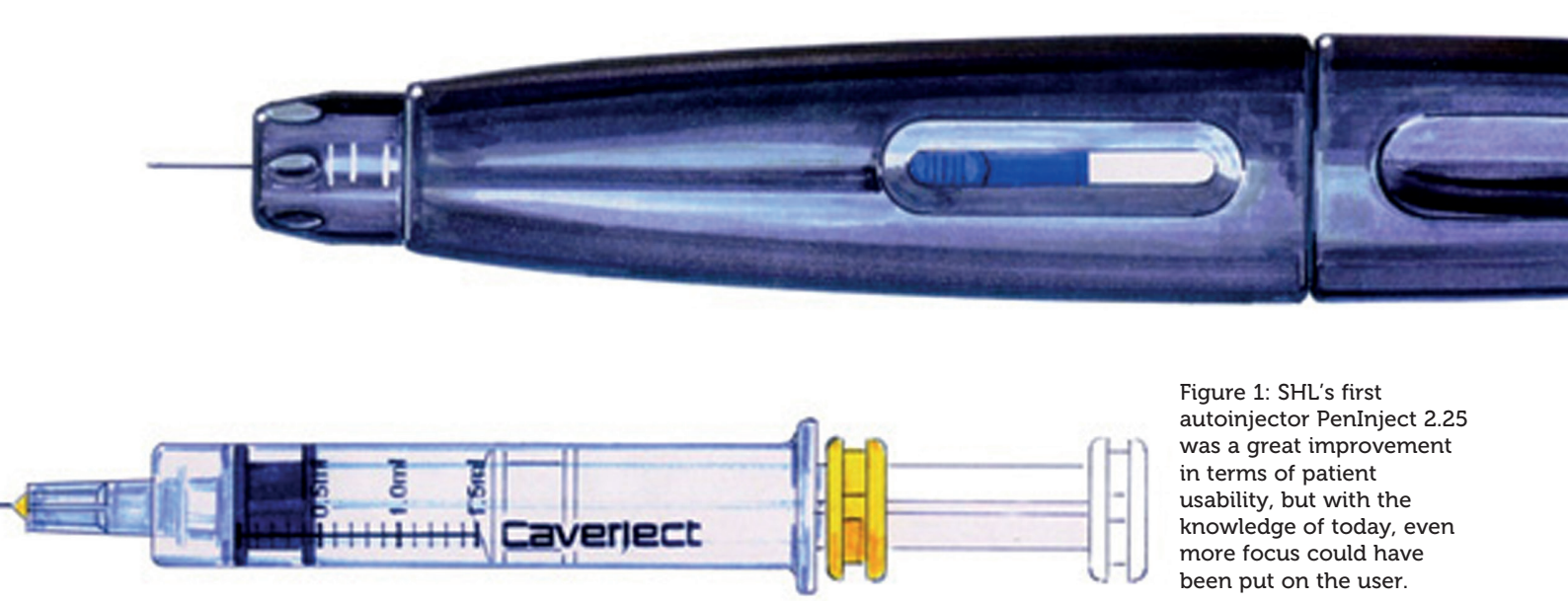

Figure 1: SHL's first autoinjector PenInject 2.25 was a great improvement in terms of patient usability, but with the knowledge of today, even more focus could have been put on the user.

as eye for the mechanical details inside auto injectors and other systems. His training has also allowed him to consolidate the exterior design with the inner components to design products for enhanced user experience.

ALWAYS DEDICATED TO USER NEEDS

Over the years, SHL has participated in an extensive amount of user studies, some led by pharmaceutical partners in collaboration with human factors firms and some within the company involving different target groups. "SHL has from day one been engaged in user experience and user needs studies," says Mr Ratjen. With a smile on his face he adds that such emphasis was "not just so that we adhere to regulations set by authorities such as the FDA".

Participation in user studies is extremely important as it provides new insights into how real patients interact with devices. Since the idea of patient-centricity has changed so drastically, it is now more important than ever to continue investigating the unmet needs of patients. Mr Ratjen notes, "Each treatment is different and each patient is unique. After all these years participating in user studies, I still find there is always something new to learn."

In order to know if a design works, SHL is also invested in getting real user feedback. Personally looking into social media support groups, Mr Ratjen found that a majority of users responded positively to the treatment carried in one specific auto injector designed with high-level usability features.

Further investigation also revealed that there were no complaints made about the SHL device. Mr Ratjen feels that "the greatest reward as an industrial designer is knowing that your design works and that you have made a positive impact on somebody's life".

With the changing times, SHL's in-house design team has grown significantly throughout the years. Today's team includes individuals with multi-disciplinary backgrounds including mechanical design, industrial design, human factors engineering, and usability research. Now, this group of talented individuals, each with their own range of expertise, works with determination to create better designs focused on the user. With the range of competencies now more comprehensive than ever, Mr Ratjen is confident that SHL is ready to take on the challenges of the future.

CASE STUDIES ARE MORE THAN JUST STATISTICS

SHL also believes in the importance of looking beyond statistics in case studies and paying attention to the unmet needs of the patients, the unsung heroes of patient-centric designs.

Mr Ratjen remembers being inspired by a group of elderly rheumatoid arthritis patients who had extreme difficulty gripping and holding onto objects. Speaking to them, he learned that the patients had volunteered in quite a few other studies as a way of giving back to society. This drove the SHL design team to work even harder to help them accomplish their mission and design a product that they could really use. After rounds of improvements, the patents were finally able to handle the device with ease, giving the SHL team more confidence that others could do so too.

Mr Ratjen also recalls one of his first and most heartfelt lessons learnt as a young industrial designer working in medtech. During one of his earliest case studies, he met a young lady in a wheelchair who spoke to him about the devices she was using at home and how she had to manoeuvre them to work in her favour. "It was then that I learnt she was undergoing fertility treatment and was already familiar with self-administered injections. Immediately, I knew that I had made assumptions about her because she was in a wheelchair. Admittedly, I felt guilty for failing to see her beyond her condition," he explained.

Having learned the hard way, Mr Ratjen shares his story to remind himself as well as his team always to look beyond the numbers and statistics in user studies, and treat patients with sincerity and true compassion.

> "To stay ahead of the trend, SHL has invested in a brand-new design centre that will include a dedicated interview studio featuring state-of-the-art equipment for recording and documenting patient experience and feedback."

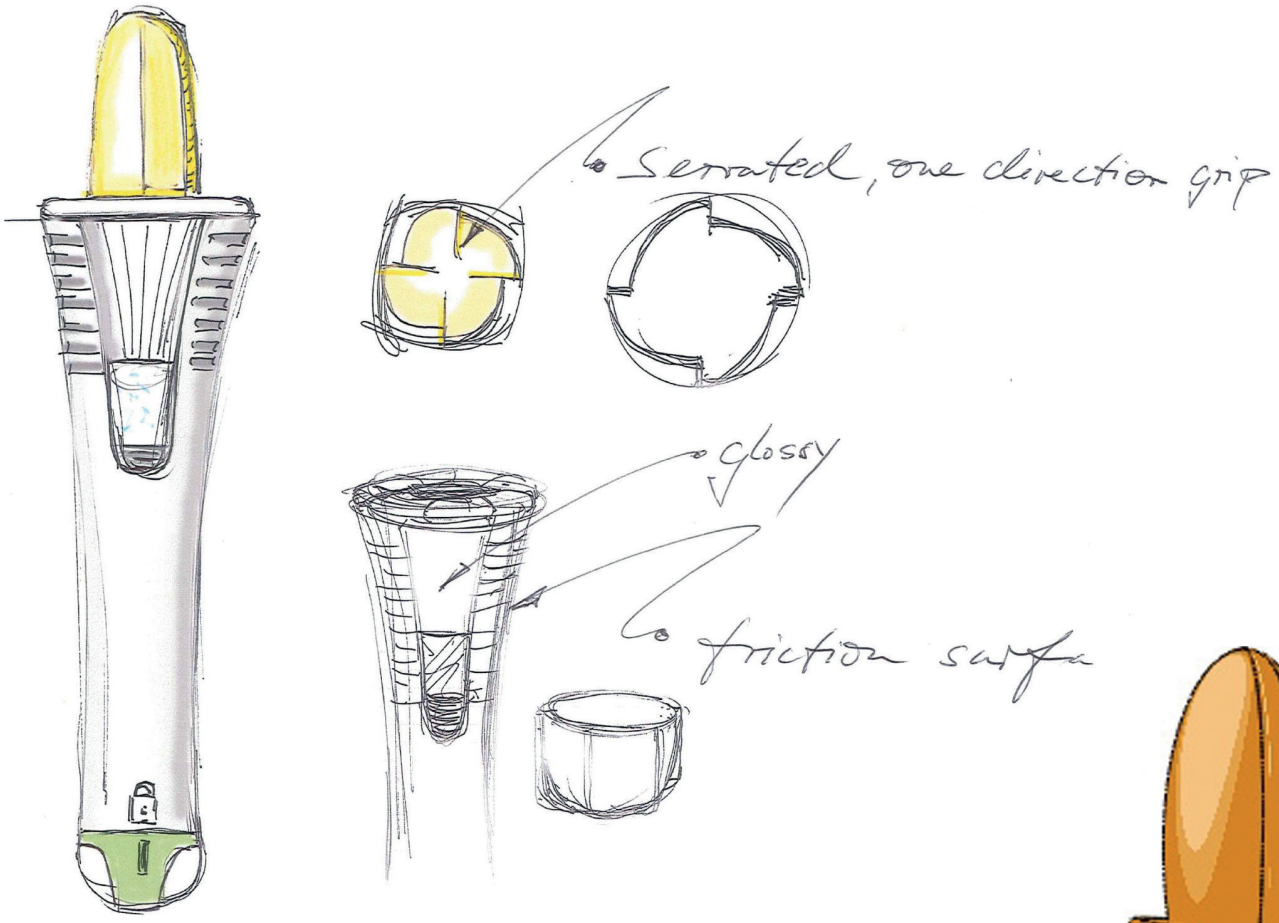

Figure 2: While all patients are different, a good device must be intuitive and self-instructing.

STAYING AHEAD OF THE CURVE

While there is no "one size fits all" method for patient centricity, SHL is able to capitalise on its near three decades of experience when it comes to launching new projects. Building on this foundation, SHL is in the final stages of completing its "usability process," a project that will standardise the methods in which usability and human factors are incorporated in SHL's internal design and development process. Once the project is complete, all involved, from design to development to manufacturing, will understand what usability means to SHL and how specific requirements are to be carried out throughout the entire organisation for optimum outcomes.

For this purpose, the company has built a database to help it effectively investigate how different types of treatments using SHL devices or other similar devices are perceived. Data from every project conducted throughout the years are fed into the database so that the experiences can serve as invaluable reference points for improvements when a new project is launched.

Ratjen points out: "As a provider of drug delivery solutions, we often have to be ahead of our customers in terms of understanding how the administration of injectable drugs affects the patient." The upkeep of the database is especially important because the knowledge can help speed up a new project's time-to-market. The data also becomes the foundation of SHL's solutions for auto and pen injectors.

MOVING AHEAD

According to the FDA, human factors and usability engineering focuses on "the interactions between people and devices," and in between them is the "device user interface."[3] A well-designed device interface, for Mr Ratjen, is not just about how one grips and holds a device, but also about how the device is understood and accepted by the user. While this will include such basic elements as grip and hold (Figure 2), a truly user-centred device interface will also feature proper visual, audio and tactile feedbacks to help the user understand what is going on both outside and inside the medical device.

In the future, Mr Ratjen believes that industrial design will play an even more important role as the differentiator for injectable drugs. Standardised functions,

Figure 3: All SHL devices are designed to meet various user expectations.

such as SHL's two-step uncap and inject procedure, will be incorporated with more specific patient-centric designs to meet the needs of specific user groups. In other words, the industry will see more product specific designs for injectable drugs and user need (Figure 3).

To stay ahead of the trend, SHL has invested in a brand-new design centre that will include a dedicated interview studio featuring state-of-the-art equipment for recording and documenting patient experience and feedback. The centre, in co-ordination with SHL's usability process and user study database, will allow SHL to continue creating time-tested designs to meet future industry challenges.

Jochen Ratjen concludes that most patients are nervous when they start a treatment, and there is without a doubt always a long way to go before anyone can feel comfortable enough to treat themselves with a self-administered injection. "At the end of the day," he says, "nobody really wants to be sick and need treatment; this is why we try our best to make this scary experience become as easy and comfortable as possible."

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ON drugDELIVERY

2017/18 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
June 2017	Connected Drug Delivery Systems	DEADLINE PASSED
July 2017	Novel Oral Delivery Systems	May 22nd
Sept 2017	Wearable Injectors	July 24th
Oct 2017	Prefilled Syringes	Aug 21st
Nov 2017	Pulmonary & Nasal Drug Delivery	Sept 25th
Jan 2018	Ophthalmic Drug Delivery	Nov 20th
Feb 2018	Prefilled Syringes	Dec 22nd
Mar 2018	Skin Drug Delivery: Dermal, Transdermal Microneedles	Jan 20th
April 2018	Pulmonary & Nasal Drug Delivery	Feb 19th
May 2017	Injectable Drug Delivery: Devices Focus	Mar 19th

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PUTTING PATIENTS FIRST: INNOVATING DRUG CONTAINMENT AND DELIVERY

Wearable drug delivery technology offers patients an easy-to-use, reliable and integrated system for managing self-injection. However, to be safe and effective, manufacturers need to consider the interface between the drug, the device and the patient. Chris Henshall, Senior Director, Strategic Marketing – Biologics, West Pharmaceutical Services discusses how one such device – the SmartDose platform – can meet these requirements.

> "For most patients, an easy-to-use, integrated delivery and administration system can be key to creating the reliability that can help to bring about compliance with treatment plans."

For patients with chronic conditions, the use of injectable biologic therapies is on the rise, making it increasingly important for patients to be fully engaged and invested in their treatment regimens. While providing considerable therapeutic benefit, biologics can also present several challenges for both drug manufacturers and patients.

In particular, many biologics are highly viscous and others require large doses to be injected slowly over time. Additionally, ongoing management of chronic conditions is increasingly shifting from doctors' offices and hospitals into the patient's home in an effort to provide patients with more independence and control over their treatment while helping to stem growing healthcare costs.

For patients tasked with self-injection, this can be difficult to do consistently and effectively every time, potentially impacting medication adherence. This is especially true for patients with chronic conditions such as diabetes, haemophilia, rheumatoid arthritis and multiple sclerosis, which often require repeated injections for effective, long-term care.

One of the most promising options to help patients managing chronic conditions is wearable drug delivery technology. For most patients, an easy-to-use, integrated delivery and administration system can be key to creating the reliability that can help to bring about compliance with treatment plans. A truly successful wearable delivery system must also consider the needs of the end-user during the different stages of a patient's journey.

> "The next generation of prefilled products will include a preloaded option, with the objective of reducing patient handling steps."

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One such example is West Pharmaceutical Services' SmartDose® platform, which is designed to integrate easily into a patient's lifestyle. The SmartDose platform is a single-use, electronic wearable injector that adheres to the patient's body, usually on the abdomen. Discreet, intuitive and designed to minimise discomfort, the SmartDose platform currently incorporates a polymer-based drug container (made from Daikyo Crystal Zenith® cyclic olefin polymer) with a drug delivery device that can be pre-programmed to deliver high volumes of viscous or sensitive drug products over time, making it easier for patients to self-administer medication outside of the clinical setting (Figure 1).

SAFE, EFFECTIVE DELIVERY

Safety and effectiveness are the top priority when designing a wearable drug delivery system. To accomplish this, it is critical for biopharmaceutical companies to have a thorough knowledge of the potential interactions between a drug and its packaging.

In order to design a drug delivery system that helps to address the needs of both the drug and the patient, pharmaceutical manufacturers must consider the interface between the drug, container, delivery device and, of course, the patient. As such, it is critical to consider the ultimate method, location and person involved in the preparation and administration of the medicine.

For the development of any delivery system – and certainly in the development of the SmartDose platform – the following considerations are key:

- **Primary container format:** The selection of a drug's primary container is an important consideration for drug efficacy and stability. Vials may be necessary for initial use, but a syringe or cartridge system may provide a desirable solution for the patient when the system reaches the market. Custom systems may also help to differentiate the product and should be considered early in the development process.
- **Drug/container compatibility:** The container material must be safely and effectively paired with the drug product when selecting the type of primary container. While glass is suitable for many pharmaceutical products, high pH drugs or otherwise sensitive products may require vials or syringes made from alternative materials such as cyclic olefin polymers.
- **Container/delivery system interface:** Once the primary container has been selected, efforts must be made to ensure that it works with the delivery system. Dimensional tolerances and functionality should be tested to ensure proper activation and glide force. If the interface between the primary container and the delivery system is not effectively understood, the performance of the combined system may suffer.
- **Patient interaction:** Perhaps the most essential consideration is how the patient will use the drug delivery system. Even the most innovative drug can only provide the appropriate therapeutic benefit if it can be delivered effectively and the patient adheres to a prescribed treatment regimen. It starts from a thorough understanding of patient needs, including the fact that these needs may change during the journey from diagnosis through ongoing treatment. These same inputs also ensure that risks from user-based errors are identified early in the development process and provide critical user information for risk mitigation measures.

Figure 1: The SmartDose platform.

TAKING A PATIENT-CENTRIC APPROACH

While developing the SmartDose platform, it became clear that when patients deem a system inconvenient, there can be a negative effect on the emotional attitude and motivation to sustain adherent behaviour. As a result, the SmartDose platform was developed with extensive human factors testing to address potential obstacles to compliance:

- **Improved patient comfort:** The SmartDose platform was designed to maximise comfort throughout the drug delivery process thanks to the hidden 29 gauge needle featured in the automatic needle protection design that prevents accidental needle injuries. Upon safely completing the injection, the SmartDose platform can be easily removed.
- **Keeping it discreet:** Many patients prefer a delivery mechanism that is not visible to others. Special consideration was taken with the SmartDose platform to ensure that it is easily concealed to avoid calling undue attention to the system, creating distractions to others or creating feelings of stigmatisation.
- **Ease of use:** Because injectable medications are administered completely by the patient with the SmartDose platform, the process needed to be so intuitive that only minimal instruction is required. To this end, the SmartDose platform currently allows for the patient to load the cartridge containing the drug. A user-friendly activation button on the front of the device and LED indicator lets the patient know that the dose delivery is in progress.
- **Dose notification:** A critical aspect of the SmartDose platform is its patient-focused design elements that address the possibility a user did not receive the full dose, or did not receive their medication at all. To account for this possibility, the device is equipped with a microprocessor that is designed to offer immediate feedback via a dose confirmation window and visual and audible cues indicating whether the prescribed medication was delivered.

USING TECHNOLOGY FOR GOOD

One way to increase a patient's affinity for their self-injection system – and ultimately increase the likelihood for adhering to a prescribed treatment regimen – is to connect it to another device that they already use: their smartphone. Smartphones and other intuitive apps can also be used to make information about medications and step-by-step instructions on how to administer them easily accessible in patients' daily lives.

When setting out to design the next generation of drug delivery systems, West understood the vast potential of smartphone apps for helping to improve the patient experience and medication adherence. To that end, West collaborated with HealthPrize Technologies (Norwalk, CT, US) to incorporate its dynamic software-as-a-service platform that engages and educates patients into the SmartDose platform. Through this collaboration, an electronically connected drug delivery system can track when patients take their medication, educate and engage patients to help increase adherence and medical literacy, and reward them for compliance with their prescribed regimen.

THE POWER OF COLLABORATION

Partnering with a company like West that can provide expertise in the field of drug packaging and delivery systems should be an important part of the launch plan for any biologic to be delivered in a wearable system. By developing a thorough understanding of the drug's intended use and the patient's needs, packaging manufacturers can lend their expertise to drug manufacturers to develop a delivery system that differentiates the drug in the market and helps to ensure that the patient's needs are met.

West assists pharmaceutical and biopharmaceutical customers every day in the development of innovative delivery solutions, and there are multiple active programmes at various stages of pre-commercial development utilising the SmartDose platform. Additionally, West is currently in the process of expanding the SmartDose platform to ensure continued leadership and innovation in this area. The next generation of prefilled products will include a preloaded option, with the objective of reducing patient handling steps.

CONCLUSION

Looking ahead, it's imperative that the pharmaceutical industry remains focused on better understanding the interaction between a medication, the drug delivery system and the patients using it, as this relationship may have a substantial impact on patient experience and outcomes. Through close collaboration between the pharmaceutical industry and their manufacturing partners, there is an opportunity to truly innovate the care and experience for patients managing chronic conditions.

SmartDose® is a registered trademark of Medimop Medical Projects Ltd, a subsidiary of West Pharmaceutical Services, Inc. West seeks partners for its SmartDose drug delivery technology platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company.

ABOUT THE AUTHOR

Chris Henshall leads the strategic marketing efforts in global biologics for West. In this role, he is responsible for the development and delivery of strategic and operational commercialisation plans across the biologics portfolio. Working in partnership with the sales and customer-facing teams and other functional leadership, Mr Henshall drives performance, ensuring the success of West biologics is optimised for both the short and long term, securing organisational alignment from strategy through execution.

Mr Henshall has a wealth of pharma and biotech experience across his 20 plus years in the industry. He has led and launched multiple brands in his career both domestically and globally. He is an entrepreneur at heart who brings a new dimension to the team with his diverse background and unique blend of professional experience.

Mr Henshall is a native of South African where he received his undergraduate degree. He is now permanently in the US, where he also received his MBA.

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TONY BRATT, NORDIC PHARMA

Graduating in Chemistry, Tony Bratt has more than 30 years' experience in the pharmaceutical industry following marketing and commercial functions through both blue-chip (e.g. Novo Nordisk) and SME companies (e.g. Elan). Mr Bratt gained a Diploma in Company Direction from the UK Institute of Directors in 2007 before starting a consultancy business in 2010 providing expertise to both client companies and investing in start-ups. In 2016, he was appointed to lead the UK & Ireland business for the Nordic Pharma group.

In this interview, Mr Bratt provides an illuminating view, from the pharmaceutical company perspective, of how the right parenteral delivery device can open up opportunities and markets for a drug product – in this case methotrexate – by enabling delivery by the patient, at home. He explains that Nordic Pharma's business model is focused on very specialised markets and how he believes drug delivery systems, and in particular the platform device concept, can play an important role in this niche product field.

Q For those of our readers who are not already familiar with the Nordic Group, I wondered if you could briefly introduce the group, its business strategy and model, its structure, and Nordic Pharma UK's place within the overall organisation?

A The Nordic Group was founded in 1995 and, as the name of the group suggests, it was originally in Scandinavia. Since then Nordic has evolved to become a pan-European business with affiliates in most of the major European countries, with reach from Portugal to Russia. The group headquarters is in Paris, as is our French affiliate, which is our largest operating group, followed by Scandinavia, and then the UK affiliate Nordic Pharma UK. So the UK affiliate is the third-largest of our operating companies.

Our business model is that we look to supply niche products, which are initiated by specialists. We are not a primary care business although, that said, our most recent product Nordimet® is often used in primary care markets but the product was not initiated there. So we look for products that are below the hurdle rate of even the mid-sized pharma companies now.

We have a strong offering to pharma companies in terms of partnering, which puts us in good stead. But from the outset we have been very much driven by products initiated by hospital specialists. We don't want to go into the mass market space and in fact over the twenty years since Nordic was founded that mass market space has declined in terms of its importance in the market.

In terms of the organisational structure, Nordic Group is a privately held company whose shareholders have a variety of interests. The Nordic Group has grown steadily over the last 20 years and is poised to grow even faster as we introduce our most exciting product to-date in Nordimet®.

Q Very recently, Nordic Pharma launched Nordimet®, a new methotrexate product presented in an auto-injector for self-injection, for the treatment of rheumatoid arthritis (RA), in the UK. Please could you tell us more about the product? How does it fit with Nordic's business model?

A Nordimet® is very important for us. It's a fascinating product. Our interest is based on having had history with methotrexate in our operating company in France, where we are distributors for another supplier. We built up experience in that space but clearly recognise some of the gaps and opportunities in that marketplace and set about developing our own franchise in which we actually have three different products available in different countries.

So we supply oral methotrexate, we supply methotrexate in a prefilled syringe or "semi-auto-injector" which meets modern safety standards in terms of retractable needles and, two weeks ago, in the UK and Ireland, we introduced Nordimet®, which is methotrexate in an auto-injector device.

In the UK we offer the prefilled syringe, which we call Zlatal, and now Nordimet®. In Ireland we have only introduced Nordimet®, and in France we offer all three products – oral, prefilled syringe and Nordimet®. So it varies across different countries.

The auto-injector behind Nordimet® is a very interesting development by SHL Group (Nacka Strand, Sweden), the designers of the device, who have really taken the evolution a long way in terms of simplicity of patient handling, healthcare professional

> "There is a second click when the injection has finished, which is unique to Nordimet®. So the patient knows when the dose has started and, crucially, when the dose has finished. The needle is of course only retracted when the dose is finished and so we think this end-of-dose click is also a really important safety feature."

"Literally only two-to-three weeks after launch, what we are experiencing in our conversations with healthcare professionals is that they believe the Nordimet® device will enable them to initiate injectable therapy where they may have otherwise failed to do so."

confidence in drug delivery, and in terms of patient safety.

There are three key messages we have about the advantages of Nordimet®. Firstly, patients with rheumatoid arthritis very often have dexterity issues and with Nordimet® there is no button to press on the device whereas the other pen device available in this marketplace requires the patient to press a button.

Secondly, Nordimet® has a compact design. All of these products have to be disposed of in cytotoxic bins and the essence of it is that you can get a lot more of our devices into a 1.5-2 L bin that you can the other products currently available. And of course the size of the device impacts on patient handling and transport.

Thirdly, and very importantly, the Nordimet® device has a unique two-click mechanism. There is a click when the formulation starts to be delivered after the pen has been pressed onto the injection site, and there is a second click when the injection has finished, which is unique to Nordimet®. So the patient and/or healthcare professional knows when the dose has started and, crucially, when the dose has finished. The needle is of course only retracted when the dose is finished and so we think this end-of-dose click is also a really important safety feature.

Q **Patient centricity and the move to self-injection at home are incredibly important themes in the parenteral delivery industry today and it seems Nordimet® is a great example of a product that, if it required administration in a clinical setting by a healthcare professional, simply would not be viable, yet thanks to delivery device innovations it is perfectly feasible to develop it for self-injection at home and it is therefore a very viable product.**

A It's a once a week delivery and so, yes, the burden on the system would be unsustainable. It is very much a patient-at-home self-injection system. If you look at the alignment with the anti-TNF (tumour necrosis factor inhibitor) space, it fits very well. The first generations of anti-TNF products were infused and patients had to literally go in – be it weekly, fortnightly, monthly – to have their anti-TNF treatment, which is used alongside methotrexate. And of course those products with time have moved to patient self-administration with ever increasingly improved pen devices.

So we're following that trend and really it's not unique to here. I was fortunate enough in the 1980s to work at Novo Nordisk when the NovoPen insulin pen was introduced – the very first pen, which was designed by Bang & Olufsen. We are now thirty years on and these devices are more standardised but there are always improvements – as demonstrated by Nordimet®.

Q **What are Nordimet®'s advantages in terms of benefits for the patient, and also commercially speaking? Methotrexate is effective orally and is widely available in oral dosage forms. What are the advantages of parenteral administration of methotrexate? To what extent does the auto-injector remove barriers to acceptance of the parenteral version?**

A Looking to Ireland provides a good example to answer this. In Ireland at the moment, apart from Nordimet®, they are still using a prefilled syringe to deliver methotrexate. Nordimet® will be the first methotrexate auto-injector in the Irish market. Literally only two-to-three weeks after launch, what we are experiencing in our conversations with healthcare professionals is that they believe the Nordimet® device will enable them to initiate injectable therapy where they may have otherwise failed to do so because of patients not being comfortable using a syringe device where the needle is on show. With Nordimet®, of course, the needle is always hidden, and it is protected after the injection meaning there is no risk of accidental needlestick injury.

Injecting the product enables a higher plasma level of methotrexate than can be achieved with oral. If you could deliver enough oral methotrexate to achieve high enough plasma levels to gain the required clinical effect, then of course you would always go for the oral route rather than any parenteral route. The issue though is that the side-effect profile of oral methotrexate, delivered in such doses, for many patients is just unsustainable. It is not uncommon for some patients, particularly younger patients, to have a very severe reaction even becoming nauseous at the sight of methotrexate tablets, before they have taken their dose.

So I think, for healthcare professionals, yes in an ideal world if we could deliver oral methotrexate safely in some form of protected oral delivery system which would cut down the GI side-effect profile, that would be great. It doesn't exist though and none of the drug delivery houses have successfully managed to overcome that barrier. So parenteral – for achieving the right dose – has to remain the way forward.

The other question is, once patients are on methotrexate as the gold standard of DMARD therapy, how long can you keep them on methotrexate with the right clinical effect before moving up to a biologic where you face significant changes in drug acquisition costs? The right delivery device can enable healthcare professionals to keep patients on higher doses for longer – and this is what they are aiming to achieve by having an injectable methotrexate product that they and their patients are confident with.

If with Nordimet® we can expand the window for injectable methotrexate by either pushing down on oral or up onto biologics, then we believe that this will of course be good for us commercially

"If you could deliver enough oral methotrexate to achieve high enough plasma levels to gain the required clinical effect, then of course you would always go for the oral route rather than any parenteral route. The issue though is that the side-effect profile of oral methotrexate, delivered in such doses, for many patients is just unsustainable."

"Products that are small in terms of revenue can still provide a great deal of support for healthcare professionals in treating specific patients. Nordic fulfils a really important role in these areas where large companies cannot operate because it is not worth their while. This is where we think Nordic, as we become more focused, will become more established as we unify pan-European brands."

by having the right product available at the right time but, more importantly, it could enable healthcare professionals to have a greater window of use for this kind of agent than they have had in the past. If patient convenience improves, compliance can also be improved and therefore efficacy of disease management.

Q Please could you tell us more about the selection of the delivery device for Nordimet®? Was it developed in-house or by a third party?

A Whilst I was not directly involved in this process, what I can tell you is that right from the start, having had the experience of working in France (where our corporate headquarters is) for the competitor product, we knew the space very well indeed. We recognised that there was an opportunity to address some of the issues both with the standard prefilled syringe version and with the pen device that, at that time three or four years ago, would shortly be coming to market.

Nordic Group set about scouring the world really to find the optimal device, which could also be assembled in our manufacturing company in Sweden, QPharma. Where would you want to go if you wanted an injection device for once weekly self-administration of a cytotoxic agent? We have to remember that it's not all that long ago that these products were made up by galenic compounding pharmacists with all the challenges that this entails.

We wanted to make sure that we took this product as far as we could as an organisation for the best patient acceptability and patient safety, and for the confidence of the healthcare professional in terms of safe, full-dose delivery of a cytotoxic agent.

The device that was eventually selected, SHL's Molly, really stood out. It ticked the following boxes:

- We didn't want a button to press because our customers and the market told us that this is difficult for RA patients.
- We wanted a compact device because we knew that the bigger the device is, the more intimidating it can be, particularly if it's a patient's first injection.
- The innovative double-click mechanism meant that we could say with absolute 100% confidence to healthcare professionals, your patients will know that the drug has been delivered because they can see, hear and feel when it has worked.

In terms of what we wanted to achieve for patients, it came down to these three key elements.

Q From the point of view of a pharma company focused on developing cost-effective specialist, niche and orphan products, there is a constant dynamic, when looking at new product opportunities, between seeking out new molecules or, as was the case with Nordimet®, seeking out new ways to add real value to existing molecules. Could you talk about this from Nordic's point of view?

A It's a fascinating dynamic because taking an established generic molecule and innovating with device can be a very successful business strategy. If you look back to the insulin and growth hormone markets before the advent of biosimilars or analogues, then insulin was insulin and growth hormone was growth hormone, but if you had a superior device to add differential, then you gained an advantage in the marketplace.

So on one hand, it is possible, and Novo Nordisk did it extremely well, to put up enormous barriers to competitors encroaching on your market using manufacturing technology and also devices. However of course on the other hand this is not as robust, early in the lifecycle, as having a patentable new molecular entity. Having said that, if you manage the lifecycle successfully including by the use of delivery devices, you don't face the traditional generic exposure at the loss of exclusivity and your business model can run for longer.

These are the kinds of tensions you're looking at and Nordic has been down both routes. Every asset has to be treated on its own merits but there is usually a reason why they have missed that Phase I / Phase II "mop-up" by big- and mid-pharma and you have to be extremely careful about moving into areas where you may have only one single asset. Franchise identity is really important in specialised areas and becomes more important with new chemical entities.

There are times when we have been innovative in different ways. For example, we have a pan-European haematology product called Nordic Aprotinin, which used to be called Trasylol. The marketing authorisation was suspended by the EMA in the late 2000s but Nordic continued to supply it in the UK at the request of the MHRA as an unlicensed medicine and it has recently been re-introduced and the marketing authorisation brought back by the EMA. This is an instance of a very small company being able to maintain a niche product, working in partnership with the regulator, because it was adding clinical value.

Those kinds of products that are small in terms of revenue can still provide a great deal of support for healthcare professionals in treating specific patients. Nordic fulfils a really important role in these areas where large companies cannot operate because it is not worth their while. This is where we think Nordic, as we become more focused, will become more established as we unify pan-European brands.

We can go to the US, go to Asia, go to Eastern Europe and say to organisations, if you have an asset that is worth potentially €20-30 million, don't even bother trying to talk to large pharma companies as it is way below their hurdle rate, whereas we have stretched from Portugal to Russia and an asset of €20-30 million would potentially be of interest to us and we are equipped to support healthcare professionals by bringing it to market.

I believe a unique strength of Nordic is that whilst being able to focus on niche products we also have that true pan-European footprint. It is possible to go and find a small family-owned pharma business in France, one in Germany, another in Italy. But if you want one single partner across Europe who has that scale but can also handle small

specialist products, I cannot think of another company, other than Nordic.

Q Finally, in an ideal world where anything is possible (within reason!) what would you like to see coming out of the drug delivery sector over the coming years – in terms of innovative technologies or indeed innovative ways of working and doing business – that would really help Nordic achieve its objectives?

A Broadly speaking, we want to continue being as successful as possible in the spaces in which we operate.

The drug delivery environment – historically – had sought big market opportunities to apply their technologies. Particularly on oral dosage forms, thinking back to companies like Alza and Elan, there were huge cardiovascular franchises in global primary care markets and it was all about developing modified-release dosage forms for different products – to minimise dosing frequency, evergreen the product, and potentially reduce the side-effect profile.

In terms of what we would like the drug delivery sector to bring to the table if we imagine that anything is possible, we touched on it earlier. Across all of our core areas we have established molecules with different risk-benefit profiles and different side-effect profiles.

Let's stick to rheumatology, as mentioned previously if someone could develop a patentable oral formulation of methotrexate you can dose up to 25 mg with no GI side effects, that would be a very welcome product – by healthcare professionals and their patients. For us, we would love to be able to get hold of something like that because it would enable us to become a more established partner with our healthcare professionals. Being in a position to provide an offering that covers the entire therapeutic platform means that it becomes a more adult-to-adult conversation. Rather than simply saying to customers, "Our product is better than theirs", we are able to say "We have the entire range, what is best for your patient?"

Beyond improving the oral product, we continue to see significant innovation in rheumatology in developing new chemical entities, such as the area of interleukin 17 inhibitors. But whilst this level of innovation continues I still believe we can look at products that come earlier in the treatment paradigm – like methotrexate, but there are other DMARDS too – where we can enhance the drug delivery mechanism to give healthcare professionals and their patients more choice.

Unfortunately, these products are not always the most attractive, financially, for drug delivery firms because, in contrast to the blockbuster oral cardiac therapy markets we just mentioned, these are the smaller products, and that is the dilemma.

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NEEDLE-FREE JET INJECTION IN WORKPLACE INFLUENZA CLINICS

Here, Tara Miller, MS, Clinical Affairs Manager, PharmaJet; Chris Galloway, MD, Medical Director, Aspyrian Therapeutics; and William E Gannon Jr, MD, CSO/Medical Director, Capital City Consulting, evaluate an unmet need for increasing immunisation coverage in workplace influenza clinics by offering needle-free injection technology as an alternative to needle and syringe delivery.

INTRODUCTION

Needle-free Injection System (NFIS) technology has evolved significantly over the last 50 years and has been accepted in many routine immunisation settings as a safe and effective vaccine delivery method.

Company-hosted influenza (flu) clinics are an effective way to make getting a flu shot easy and convenient for employees. Therefore, flu shots can be administered to employees at their place of work by trained healthcare professionals as part of workplace health influenza clinics. The benefits of needle-free injection technology in such clinics are significant.

It is safe:

- No needle, therefore no risk of needle stick
- Auto-disabling syringe which means no re-use
- Accurate and consistent injections
- Reduces sharps disposal which reduces cost and waste
- Delivers vaccines to the desired tissue depth.

> "Surveys were completed by patients, caregivers, and event co-ordinators to collect feedback regarding the acceptability and usability of the device, whether it should be an option for next year, the potential to increase influenza immunisation coverage at a particular site, as well as information on the event itself."

It is fast:

- Delivers the vaccine into the muscle in about one-tenth of a second
- Most healthcare providers are self-trained within 20 minutes.

It is easy:

- 95% of patients would choose it again for their next vaccination[1]
- Minimises injection associated fear and anxiety for the patient and provider resulting in a better experience.

BACKGROUND ON INFLUENZA

Influenza is one of the most common preventable infectious diseases. In the US alone, approximately 10-20% of the population contracts influenza each year, which accounts for about 226,000 hospitalisations and 36,000 deaths annually. While morbidity and mortality affect mostly the young and old, all age groups are affected. This includes the more than half of adults aged 20-64 years that are employed, and results in about 111 million lost working days every year.[2-4]

Workplace health influenza immunisation programmes are an important factor to consider for addressing decreased productivity, when a simple flu shot could decrease work absenteeism[3] and significantly reduce the risk of spread of influenza to others. According to the US National Institute for Occupational Safety and Health (NIOSH), the costs associated with sick days and lost productivity are approximately US$7 billion (£5.5 billion) in the US annually.[4,7] In spite of the potential benefits of vaccination, one study showed that only about 20% of healthy working

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age adults aged 18-49 years receive an annual flu shot.[5]

In addition to improving employee productivity and decreasing absenteeism, there are strategies to immunisation practices that can influence the success of influenza vaccination programs such as:

- Obtaining upper management and employee buy-in
- Providing incentives to employees for getting vaccinated
- Offering convenient times and locations
- Educating employees about influenza vaccination
- Offering a needle-free option as a safe and effective alternative to needle and syringe.

The measures above could increase compliance of influenza vaccination in the workplace. Increased vaccination rates will reduce employee absenteeism, increase productivity and reduce healthcare utilisation and expenditures.

WORKPLACE INFLUENZA VACCINE SURVEYS

During the 2016-17 influenza season, the PharmaJet Stratis® Needle-free Injection System was used in multiple workplace health influenza clinics. Immunisations were administered by either Affiliated Physicians (New York, NY, US) nurses, Sam's Club (Bentonville, AR, US) pharmacists, or occupational health nurses employed by a particular company or organisation. There were 35 vaccination events, which included employees from BP Oil, Cargill, Denver International Airport, Ernst & Young, Morgan Stanley, Terumo BCT, TriNet, and Xerox, among others.

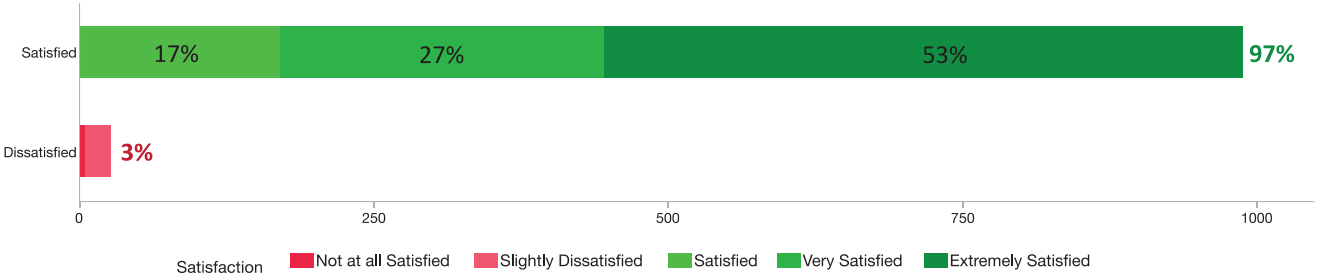
Surveys were completed by patients, caregivers, and event co-ordinators to collect feedback regarding the acceptability and usability of the device, whether it should be an option for next year, the potential to increase influenza immunisation coverage at a particular site, as well as information on the event itself.

The results of these surveys by audience are summarised in the following text and in Figures 1 and 2.

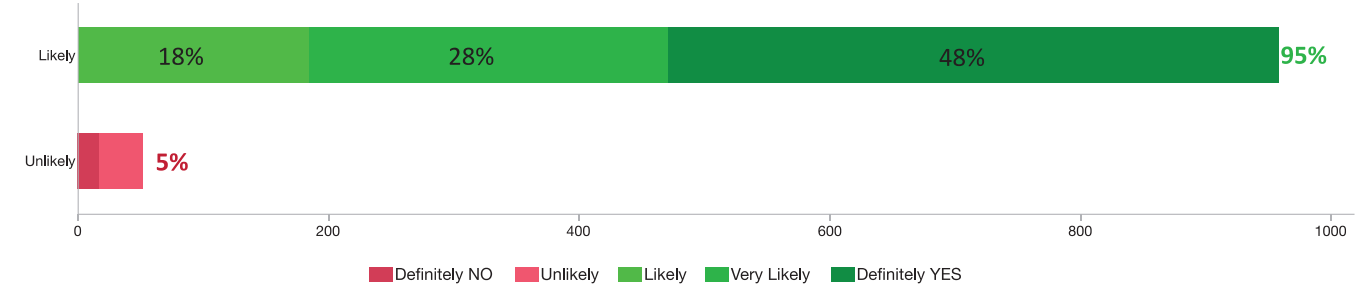
Patient Surveys

Overall, 1,018 surveys were completed by working individuals, 18-64 years of age, who received a needle-free flu shot at one of the influenza vaccination events. Figure 1 shows results for each of the three key questions regarding satisfaction, likelihood of choosing a needle-free injection next year, and likelihood of

a) How satisfied were you with today's needle-free flu shot?



b) For next year's flu vaccination, will you choose to receive your flu shot with a needle-free injection?



c) How likely are you to recommend a needle-free flu shot to your family and friends?

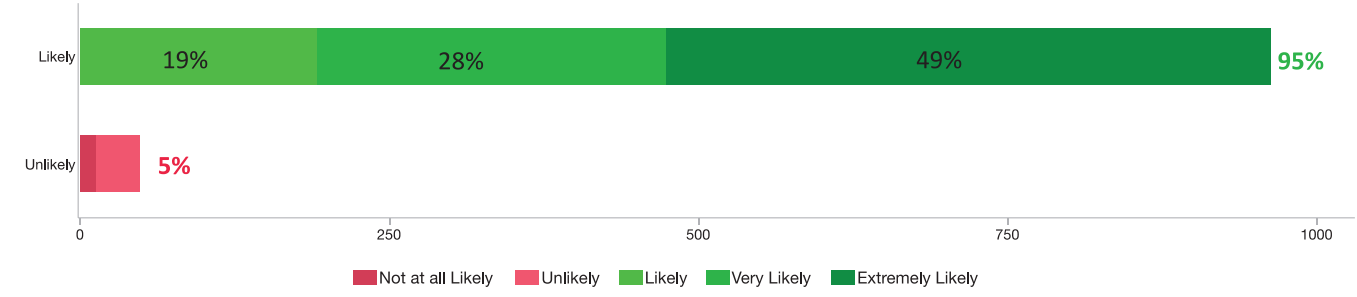
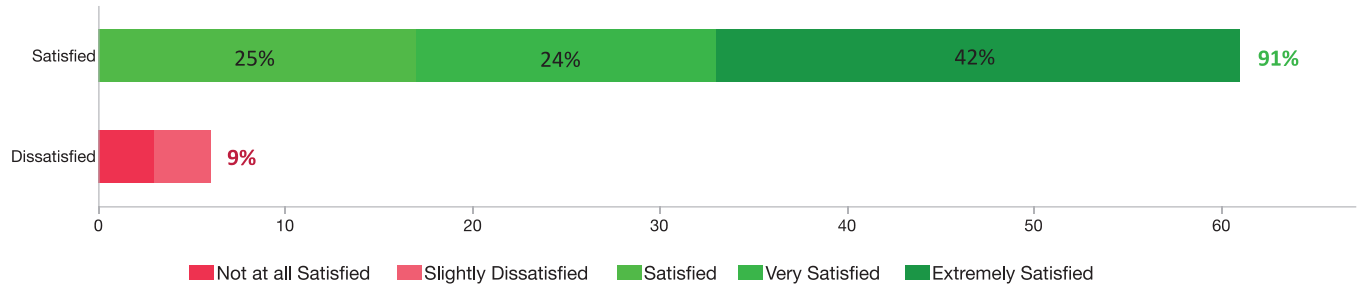
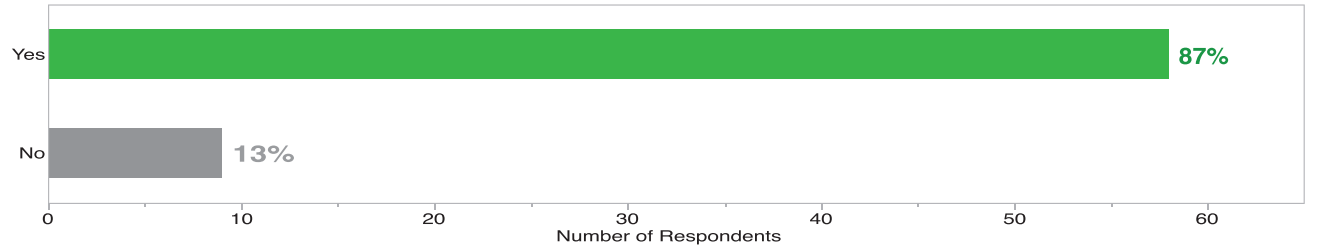


Figure 1: Patient survey results regarding: a) satisfaction with the needle-free injection they had just received; b) likelihood of choosing a needle-free injection next year; and c) likelihood of recommending a needle-free injection to family or friends.

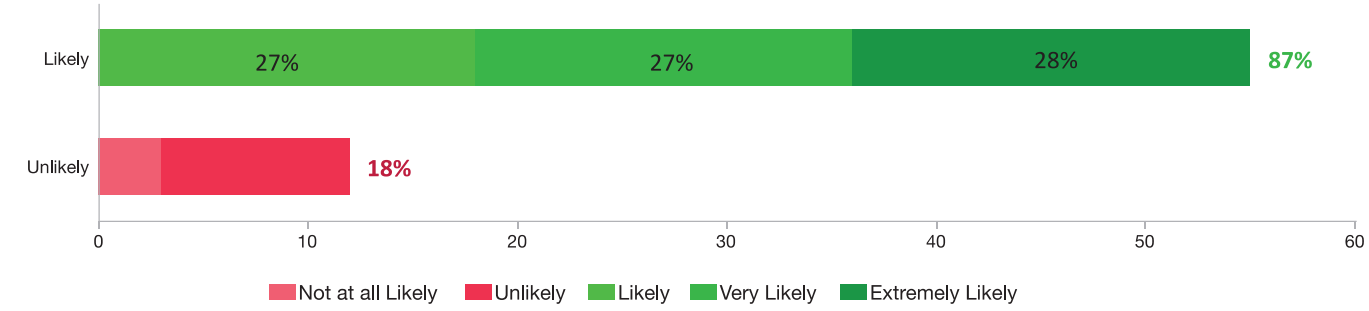
a) How satisfied were you with the ease of use?



b) For next year's flu vaccinations, would you like the option of needle-free shots at your facility?



c) How likely are you to recommend needle-free flu shots to your colleagues?



d) How much could your flu vaccinations increase next year by offering the option of a needle-free flu shots?

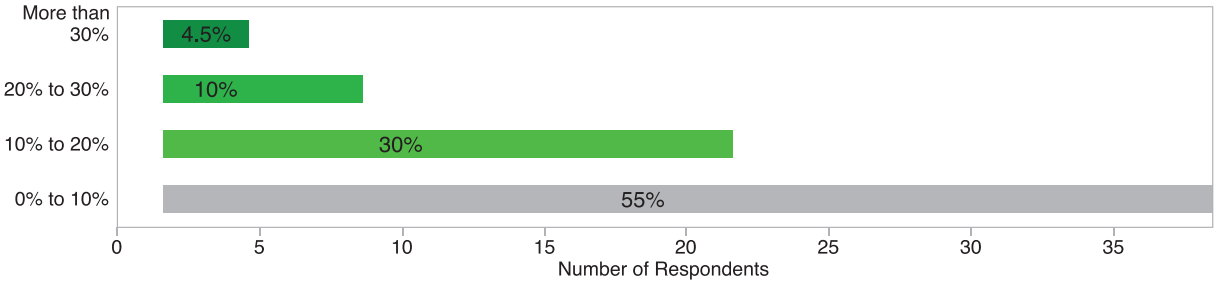


Figure 2: Healthcare provider survey results regarding: a) satisfaction with ease of use; b) needle-free option for next year; c) likelihood to recommend to colleagues; and d) how much vaccination could be increased by offering needle-free.

recommending a needle-free injection to friends and family.[1] In summary:

- The majority of patients (97%) were satisfied with the needle-free shot[1]
- 95% of patients responded that they would choose needle-free again next year[1]
- 95% said they were likely to recommend needle-free to friends and family.[1]

Healthcare Provider Surveys

PharmaJet has been collecting healthcare provider feedback from those administering needle-free vaccinations with Stratis® in retail and workplace health clinics for several years. The providers of needle-free influenza vaccinations have included contract nurses, pharmacists, and occupational health nurses employed full time at some organisations. For the 2016-17 workplace health clinics, six surveys were completed by healthcare providers following flu clinic events.

All (100%) of the healthcare providers surveyed were both satisfied with the ease of use of the device and all indicated that they would like to have needle-free delivery as an option in their workplace

health clinic next year. Additionally, 33% thought having a needle-free option would increase immunisation coverage in their workplace immunisation programs. Of those that responded to the immunisation coverage question, two-thirds (67%) answered needle-free could potentially increase immunisation rates in their workplace immunisation program by greater than 10%.[1]

The 2016-17 workplace health immunisation clinic results are consistent with the results obtained in previous flu clinics where the PharmaJet needle-free system was used to give influenza vaccinations. Additionally, healthcare providers that participated in vaccinations during this flu season came from similar backgrounds as the providers that performed influenza vaccinations in previous years.

Healthcare provider results from previous flu clinics are summarised below. There were 67 healthcare providers that completed the survey in total:

- 91% of healthcare providers were satisfied with Ease of Use[6]
- 87% would like the option of Needle-free next year[6]
- 82% said they would be likely to recommend Needle-free flu shots to their colleagues[6]
- 45% of respondents from previous vaccination events thought that offering a Needle-free option could increase flu vaccinations by more than 10% at their facility.[6]

The healthcare provider survey results are shown in Figure 2.

Event Co-ordinator Surveys

Event co-ordinators also completed surveys regarding their overall experience with the workplace health immunisation event, and the potential for increasing immunisation coverage for their site. Overall, 91% thought the event met the expectations for their location and 73% responded they would like to participate in an event again next year. Additionally, several respondents said that including a needle-free delivery option had the potential to increase influenza vaccinations in their workplace health programme by greater than 10% next year.[1]

CONCLUSION

There are approximately 216.5 million healthy working adults in the US aged 20-64 years.[2] However, only about 20% aged 18-49 years receive an annual influenza immunisation.[4] Only a small percentage of individuals of working age receive a flu shot each year. Based on the numbers of sick days and lost productivity reported annually, it is clear there is an unmet need for increasing vaccination rates in the workplace. Offering needle-free technology in a workplace influenza immunisation programme has the potential to help meet this need and could be beneficial to the overall health of the employees and the productivity of the organisation.

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William E Gannon Jr, MD, is a Chief Medical Officer consultant at PharmaJet, as well as Chief Scientific Officer & Medical Director for Capital City Technical Consulting (CCTC). Previously, he held positions in multinational clinical research organisations, medical device, biotech and pharmaceutical firms, most recently as Vice-President, Clinical & Medical Affairs in the biotechnology arena. Dr Gannon's experience includes a broad range of therapeutic categories, with a primary focus on therapeutic and diagnostic applications in oncology. He has managed clinical trials and operations as well as the design, corporate and regulatory strategies, regulatory submissions and execution of Phase I-IV clinical trials in the US, Europe and Asia. Dr Gannon is involved in philanthropy in the Washington DC area and currently serves on the board of directors for the Engineering World Health Organization and The Foundation for Sickle Cell Research. He received his medical training and did clinical work at Ross University (Isein, NJ, US), Case Western Reserve (Cleveland, OH, US), and George Washington University (Washington, DC, US), and also has an MBA from George Washington University.

INJECTABLE DRUG DELIVERY: DEVICES MEET NEXT-GENERATION FORMULATIONS

Although much effort has been put into making injectable drug delivery a better experience for patients, the problem remains that most devices are unable to deliver the drug to just the targeted organ and not throughout the whole body. Here, Iulia Karlsson, PhD, Regulatory Affairs Specialist at Double Bond Pharmaceutical, discusses a new technology called BeloGal which allows drugs to be delivered in high doses to the right organ and avoids the problems of low water solubility that hamper many modern formulations.

UNMET NEEDS IN DRUG DELIVERY

Today, the vast majority of the world's best-selling drugs require a drug delivery device, no matter whether they are biologics for parenteral delivery, drugs for treatment of asthma requiring an inhaler or chemotherapeutic suspensions delivered intravenously.[1]

The drug delivery industry is focussed on finding ways to enhance the injection experience, i.e. make it more pleasant for the patient, from helpful reminders, self-use devices, connecting to smartphones, making the syringes larger or smaller and containers gentler and smarter. This is a challenge to manage with the increasingly sophisticated drugs that are both unstable and difficult to administer in the right dose.

"Why is technology still more concerned with how big the syringe is, how to make it auto-inject and whether it can connect to a smartphone etc when the drug is still spreading virtually everywhere in the body and could be doing as much harm as help?"

However, the industry has largely failed to achieve one very specific and vitally important goal – to deliver the drug exactly to the organ where it is needed, so that the spread and toxicity to healthy organs and tissues is zero or close to that.

Why is technology still more concerned with how big the syringe is, how to make it auto-inject and whether it can connect to a smartphone etc when the drug is still spreading virtually everywhere in the body and could be doing as much harm as help?

Market for Drug Delivery

The global drug delivery devices market was already valued at more than US$330.0 billion in 2016,[1] and it is expected to grow further to $624.50 billion by 2021 and reach $931.1 billion by 2024, according to a new report by Grand View Research.[2] This growth is equal to CAGR of more than 11% in the forecast period though this is a lower figure compared to some other existing estimations.[3]

What is driving the development of more and more sophisticated drugs and injectable drug delivery systems on the market is a change in the following factors:

- Increased prevalence of chronic diseases such as diabetes and cancer
- Increased understanding about how drug is being taken up and metabolised in the body
- Increased understanding of the heterogeneity of patients and hence the large variety of individual requirements within each given therapy
- Increased understanding of the importance of a controlled release distribution and availability of the drug in the body.

Let us take a closer look at what drug delivery devices today can offer, what they can't and – most importantly – what can be done about it.

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ADVANTAGES & LIMITATIONS OF INJECTABLE DELIVERY DEVICES

Advancements in technological processes have resulted in the generation of improved and enhanced devices, as well as equipment that is tailor-made and specific to different categories of patient care. In addition, technological innovations like dual-injectables have further enhanced the method of drug delivery and the development of the biologics market has led to an increase in the demand for these injectables.

Classification of Injectables Delivery

Injectable drug delivery methods can be divided into two main groups – devices and formulations. Devices and formulations can be used together, so the following delivery device groups and sub-groups have been created:[4]

- Self-injection devices
- Conventional injection devices
- Needle-free injectors
- Auto-injectors
- Pen injectors
- Wearable injectors
- Auto-injector-specific selection factors
- Prefilled syringe devices
- Safety syringes
- Integrated safety syringes
- Patch injectors
- Subcutaneous infusion devices
- Other devices.

The conventional injections subcategory is further classified by material – glass and plastic, by usability – disposable and reusable and by type – fillable and prefilled syringes. The injectable are categorised as conventional drug delivery, novel drug delivery and long-acting injectables.

Advantages of Innovative Injectables

First-generation devices that are still on the market are typically mechanical – functioning only to get the drug into the body. This is still very relevant today, as even novel drugs must be properly administrated, for example, to comatose and subconsious patients. Next-generation parenteral devices are recognised more as the interface between the drug and the patient. They can also offer many features and functions which improve usability, safety, efficacy and compliance, plus many other functions beyond – such as connectivity and even diagnostics.

With the advent of self-injection devices like auto-injectors, pen-injectors and needle-free injectors, the use of injectable drug delivery (IDD) has been made relatively easy allowing patients to administer drugs at home without medical assistance. The increase in the number of diabetic patients globally has allowed the majority of the leading players in this market to launch devices for the administration of insulin with the help of self-injection devices. Thus, the homecare settings segment was the largest grosser in this market in 2015.

Limitations of Injectables

What are the main limitations of injectables? Infections and injuries caused by the needles used in syringes are a major constraint. Contamination arising from previously used injectables and needlestick injuries may cause serious complications needing further remediation and these complications often lead to further hurdles in the management of the disease.

In certain cases other drug delivery methods, such as oral administration, are often preferred over injections as they obviate toxicity implications. In addition, strict regulations can deter the use of IDD forms. Several concerns have been raised in the recent past with respect to the sterility of injectables, which has led to a decline in the number of approved production facilities that manufacture these products and hence the resultant shortage of these drugs in the market.

> "Drug delivery formulations based on liposome encapsulation can solve the bioavailability problem by giving a longer plasma circulation time and enhanced target-tissue accumulation."

Despite many constraints, the market potential for IDD is immense due to the associated advantages and its wide applicability in a range of ailments. Furthermore, the market is also fueled by many major companies that are adapting to the demand of injectables over oral dosages, as oral administration provides a much lower bioavailability compared with intravenous injection, for example, which gives 100% bioavailability with extremely rare exceptions[5,6] (Table 1).

Route	Bioavailability	Characteristics
Intravenous injection (infusion)	100%	Most rapid
Intramuscular injection	75≤100%	Large volume may be injected but painful method
Subcutaneous injection	75≤100%	Smaller volume than IM, may be painful
Oral administration	5≤100%	Convenient, first pass metabolism occurs
Rectal administration	30<100%	Less first pass metabolism than oral route
Inhalation	5<100%	Rapid onset
Transdermal (patch)	80≤100%	Usually slow absorption, lack of first pass metabolism and prolonged duration of action

Table 1: Bioavailability of drugs administered using different routes. (Source: howmed.net)

The next generation of injection devices offer therefore a broad range of upgrades in drug delivery – everything from self-administered injection devices with dose-limiting functions, very ergonomic user-friendly designed wearables to professional systems for instant mix and delivery of complex components allowing for less fluctuations in pharmaceutical ingredient concentration throughout the injection, such as dual-release formulations.

However, they all still have zero ability to restrict the uptake of the drug into healthy organs. The good news is that certain types of formulations can successfully solve this and other problems.

NEXT-GENERATION DRUG DELIVERY FORMULATIONS

New formulations of drugs that are not very water soluble are becoming more prevalent.[7] It has been estimated that 40% of drugs with market approval and nearly 90% of molecules in the pipeline of drug discovery programmes are poorly soluble in aqueous media and/or have very low permeability to allow for their adequate and reproducible absorption from the gastrointestinal tract (GIT) following oral administration.[8]

Various properties which contribute to the poor solubility of drugs include:

- Complex structure
- Size
- High molecular weight
- High lipophilicity
- Compound H-bonding to solvent
- Intramolecular H-bonding
- Intermolecular H-bonding (crystal packing)
- Crystallinity
- Polymorphic forms
- Ionic charge status
- pH
- Salt form.[9]

Formulation scientists try therefore to adopt various strategies to enhance the absorption of the drug molecules.

What Can Formulations Do?

The majority of drug delivery formulations focus on dissolving water-insoluble active pharmaceutical ingredients (APIs) in different ways to improve the drug's solubility, bioavailability in the body and increase loading capacity. Moreover, when an API has a low bioavailability – as is very usual in the case of oral administration – the only way to make the drugs bioavailable in the body is through an intravenous administration. Here, the advantages and breakthroughs in drug delivery devices for intravenous injection are all welcome, but really the absorption and solubility problem must be solved.

Poorly absorbed drugs pose a challenge to formulation scientists to develop suitable dosage forms that can enhance their bioavailability. There are several ways to improve the absorption of the active substance – including lipidic formulations, crystalline solid formulations and amorphous formulations.

One of the most efficient ways for improving the solubility of an API is a micelle formation.[10] Let's take a closer look at what difference it can make in terms of loading capacity using the example of the water-insoluble anticancer paclitaxel, and its three different formulations:

a. Taxol – a mixture of aqueous ethanol and non-ionic surfactant Cremophor-EL – used for dissolving of paclitaxel. Disadvantages in delivery of this drug here is low loading capacity (1:80) and high toxicity of Cremophor-EL.
b. Abraxane – based on use of albumin (HSA) as surfactant. Disadvantages in delivery: medium loading capacity (1:9) and use of HSA (gives risk for cross-infection).
c. Paclical – a semi-natural, non-toxic surfactant is used, finally giving a good loading capacity 1:3.3. Paclical is indicated against ovarian cancer.

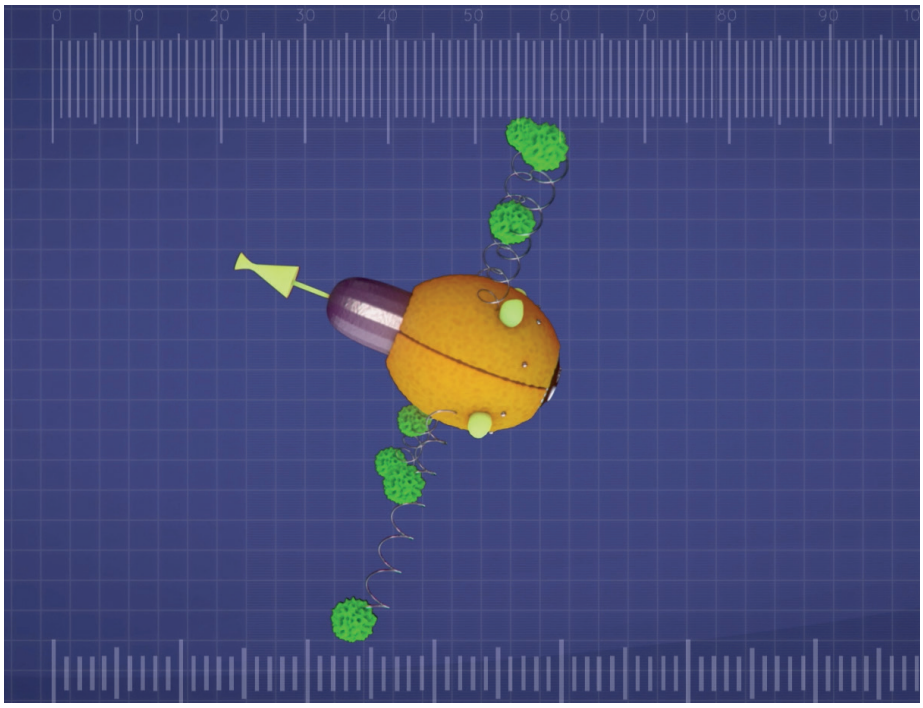

Figure 1: Schematic model of BeloGal formulation package of a water-insoluble API.

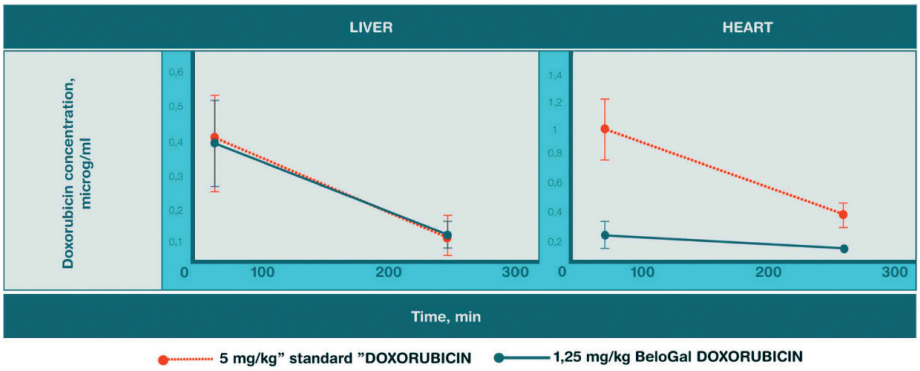

Figure 2: Biodistribution of BeloGal-formulated doxorubicin programmed to target liver specifically: equally high concentrations in the liver (left) using only ¼ of the original dose, and simultaneously 10 times lower concentration in the heart (right) compared with original API (doxorubicin) in rabbit.

Drug delivery formulations based on liposome encapsulation can solve the bioavailability problem by giving a longer plasma circulation time and enhanced target-tissue accumulation. Different APIs are currently being used in this type of formulation: doxorubicin, daunorubicin, cisplatin and vincristine. The main challenge with liposome encapsulation, however, is technical – difficulties of pharmaceutical manufacturing, including quality assurance and cost, in addition to not very pronounced tissue targeting.[11]

BeloGal technology

A very promising solution to virtually all formulation problems of this kind is a new technology called BeloGal. It encapsulates the insoluble API into a biomimetic chemical polymer-based cover[12] (Figure 1) and provides organ-specific targeting of the API to either the liver or lung, avoiding other organs such as the heart (Figure 2). Moreover, the manufacturing process is much simpler compared with other formulation methods and does not involve high costs.

The technology combines the advantages of specific tissue perfusion parameters for the liver or lung with the simplicity of intravenous administration. Furthermore, organ/tissue targeting by the use of self-navigating BeloGal particles significantly widens a therapeutic window, allowing higher doses of the drug to be achieved in the right organ while substantially lowering the spread of the API to healthy organs (Figure 2).

One of the technical advantages of this method is also an easily achieved high-loading capacity. Currently the platform is being used with doxorubicin, and the first drug candidate in the pipeline employing BeloGal technology is SA-033 – indicated against liver cancer and entering clinical trials this year.

It is also possible to use the technology to formulate other APIs to decrease their toxicity and ensure their high therapeutic effects in selected organs. For instance, doxycycline – a well-known antibiotic, can be successfully formulated using BeloGal to be delivered to the lung to combat lung infections.

CONCLUSION

After successful clinical development of the first BeloGal-based drug, the technology is expected to become a gold standard for intravenous delivery of drugs to liver and lung, allowing for an entirely new level of innovation and clinical benefit for both drug delivery and organ-targeting, self-navigating drug formulations.

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Iulia Karlsson holds a PhD in Medical Biochemistry with a background in human and animal physiology, immunology and infection biology. Iulia is currently working as Regulatory Affairs Specialist and in business development at Double Bond Pharmaceutical in Uppsala, Sweden.

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AUTO-INJECTOR DESIGN: MANAGING DRUG TEMPERATURE VARIATIONS

In this article, Jake Cowperthwaite, Partner and Senior Electrical Engineer, Key Tech, Inc, examines the impact of environmental and drug temperature variation on auto-injector performance and describes techniques for managing this variation on modern auto-injectors.

With the increasing prevalence of auto-injection devices, we're entering an age of do-it-yourself therapy and lifesaving. A self-administered drug injection to the thigh, abdomen, or other subcutaneous site (Figure 1) allows patients around the world to take control of their quality of life as well as receive life-saving medications, such as epinephrine.

Injectors may rely on mechanical (spring), electrical (battery) or other (e.g. compressed air) power sources. However, the fundamental architecture and design considerations are common to all injectors.

In recent years, the breadth of features and variety of drugs administered via auto-injectors has grown as pharma companies develop novel drugs, often biologics, which are not suitable for oral administration. This broader spectrum of drugs magnifies traditional auto-injector design challenges and introduces new obstacles. For example, the designer is now faced with managing a wider range of drug viscosities, dose volumes, dispense profiles, and use scenarios.

> "For spring-powered injectors, applying more power to compensate for cold temperature is not an option because the pre-loaded spring has a nominal force profile intended to cover all injection temperatures. This design architecture inherently results in a longer dispense duration for colder drugs."

UNIQUE TEMPERATURE CHALLENGES

Drug temperature has always been an important consideration in auto-injector design. Figure 2 shows a typical correlation between drug temperature and viscosity, where it is evident that viscosity increases exponentially as temperature is reduced.

Higher viscosity drugs require more energy to dispense when compared with the same configuration at room temperature. As temperature is reduced, either more power must be applied during the injection to maintain the same speed or the dispense duration must be allowed to increase.

Increased Power

For spring-powered injectors, applying more power to compensate for cold temperature is not an option because the pre-loaded spring has a nominal force profile intended to cover all injection temperatures. This design architecture inherently results in a longer dispense duration for colder drugs.

With an electronic injector, applying more power is an option. However, it will increase the size of the battery pack, motor, and gearbox, resulting in a larger device. The size of an auto-injector battery pack is typically based on peak amperage (as opposed to capacity) because injections are relatively short in most cases, making run-time less of a concern. The motor and gearbox must be designed to handle worst case torque conditions in order to avoid stalling or permanent damage. If the expectation is that users will normally inject the drug at room temperature, then this approach results in a larger than desired form factor simply to accommodate a rare use scenario. This is far from ideal in a product space oriented toward compact, portable devices.

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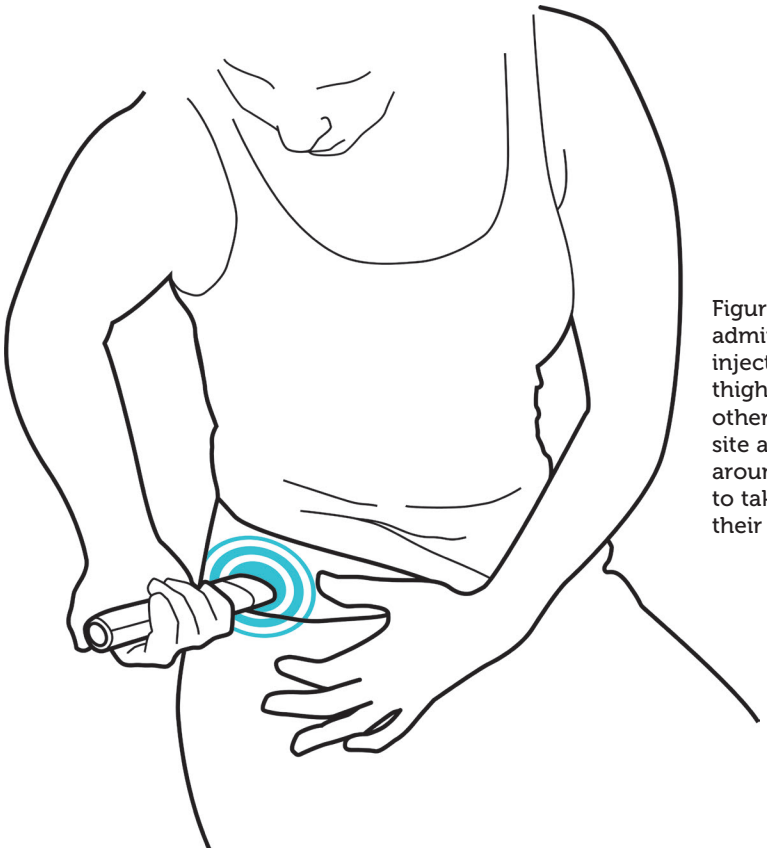

Figure 1: A self-administered drug injection to the thigh, abdomen, or other subcutaneous site allows patients around the world to take control of their quality of life.

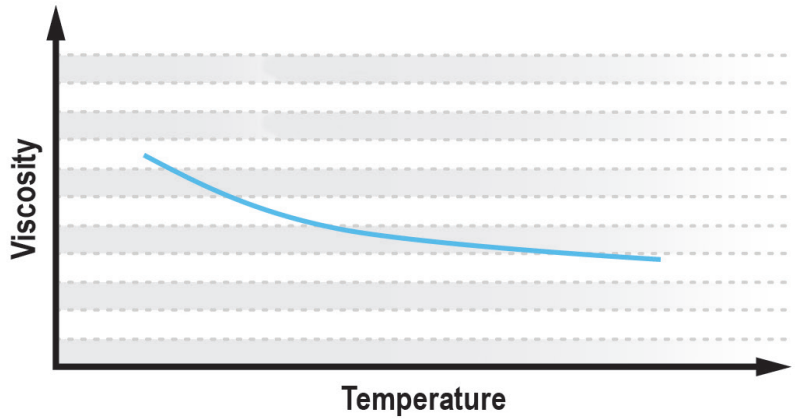

Figure 2: Typical correlation between drug temperature and viscosity.

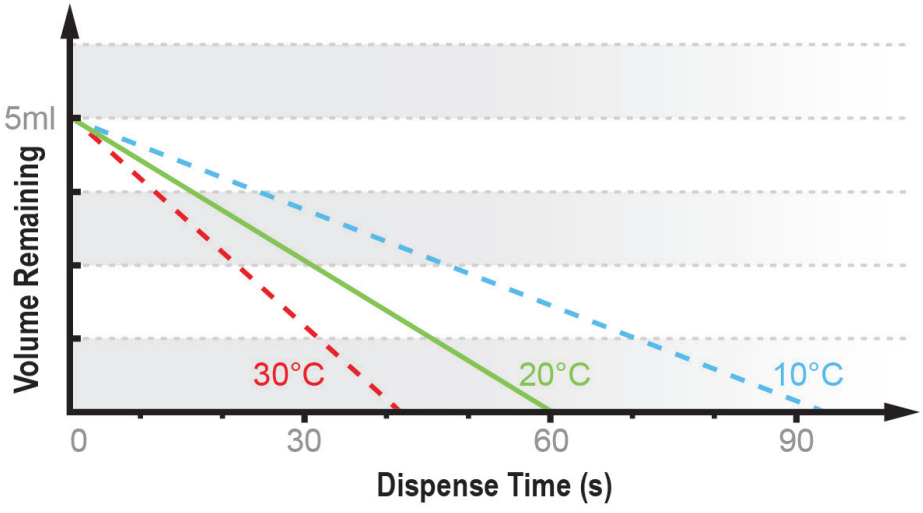

Figure 3: Examples of how dispense time could vary over temperature if the force remains constant.

Longer Injections

Increasing the dispense duration to compensate for cold drugs is also an option with electronic injectors if "smarts" exist to identify the condition. This may include either directly sensing the drug temperature or sensing the drive force and reducing speed to compensate for the increased force. The downside, in addition to longer injections, is that the device must include relatively complex sensors that add size and cost to the device. Figure 3 provides an example of how dipense time could vary over temperature if the force remains constant.

Longer injections can also introduce usability challenges. The user might not notice if a small dispense takes 50% longer because the timescale is very short, but as dose volumes become larger this impact can be significant. For example, a room temperature 1 mL dose that is normally delivered in five seconds might take seven seconds for a cold drug, which would not cause concern. However, auto-injectors designed to handle larger dose volumes with higher viscosity drugs might normally inject for five minutes or more. In these scenarios, the injection time could increase on the order of minutes, causing user confusion and potentially resulting in the needle being pulled away before the dose completes.

When designing for relatively long injections, it makes sense to consider a wearable injector to alleviate the burden of holding the device during administration and mitigate against partial dosing due to user distractions.

> "Global sales of drugs requiring cold chain storage is growing at a rate nearly double those that do not require cold storage."

Patient Discomfort

An additional challenge with dispensing cold drugs is user comfort. Evidence suggests that injecting a cold drug may cause more discomfort than a drug at room temperature, presumably because the absorption rate is reduced and the delivered drug has a tendency to pool in the subcutaneous site.

Design Solutions

The obvious solution is to prevent drugs from becoming cold but the reality is that many drugs must be stored between 2-8°C (e.g. in a refrigerator) to maintain efficacy. In fact global sales of drugs requiring cold change storage is growing at a rate nearly double those that do not require cold storage.

Temperature Interlocks

Electronic devices can include interlocks to prevent injecting cold drugs, although sensing drug temperature can be challenging. Electronic injectors are often re-usable and the drug cassette or syringe is inserted prior to use, creating a sensor interface challenge. Contact sensors (e.g thermistors) must be pressed against the exterior of the drug container and the embedded firmware may require a custom algorithm to infer when the drug has adequately warmed. An optical IR sensor can be used in a similar fashion without the need for physical contact, although at a higher cost.

Active Heating

Actively heating the drug in the device prior to injection has been considered, but is unappealing for a variety of reasons. First, rapid active heating of a biologic or other pharmaceutical solution may have unintended consequences that affect efficacy. This option would require extensive stability and pharmacokinetic studies to prove viability. Second, heating drugs requires significant power, particularly at larger volumes. Depending on the drug volume, heating time, and drug properties, the system could consume more energy during heating than for the actual drug delivery, which increases battery size. Finally, accessing the drug with a heating element is a challenge because the drug is typically encapsulated by a glass syringe, which acts as an insulator.

Over-Designing the System

A relatively common approach for managing temperature variation is to overdesign the system components so that the drug can be dispensed at the desired profile even at cold temperatures. This results in conservative design decisions and larger injectors that are capable of handling worst case forces.

Electronic injectors often include a battery "fuel gauge" for checking battery status prior to dispensing to ensure that the entire dose can be completed without interruption. If the designer is forced to assume that the drug could be cold, which requires more energy, the user may be forced to charge their device prematurely even if there is adequate charge for a room temperature dispense.

The needle gauge can also be increased to allow for dispensing higher viscosity drugs with less energy. However, this must be approached with caution because larger needles turn off many patients, resulting in compliance issues and poor product reception.

User Training

Traditional spring-based injectors have relied on the instructions for use and training to mitigate against cold drug injection. Patients are instructed to expose the auto-injector to room temperature for a defined period prior to injection. While this seems reasonable, users may not always have the time or foresight, and instead choose to inject a cold drug while bearing the increased discomfort.

One means to supplement training is to include a temperature sensitive sticker on the auto-injector or drug cassette. In this case the user is instructed to wait until the sticker turns a certain colour before performing an injection. This is a training improvement but it does not prevent users from injecting cold drugs.

> "Environmental and drug temperature variations must be considered during auto-injector design ... The effects of a cold drug can lead to more power consumption, longer injections, and patient discomfort."

SUMMARY

Environmental and drug temperature variations must be considered during auto-injector design. In particular, the effects of a cold drug temperature can lead to more power consumption, longer injections, and patient discomfort. Techniques for managing temperature variation often result in larger, more expensive devices. The design of temperature management features is crucial as more high viscosity, large dose drugs that require cold storage are developed for use with auto-injectors.

ABOUT KEY TECH

Since 1998, Key Tech has been transforming complex technologies into intuitive medical products. The company designs and develops drug delivery devices, handheld instruments, capital equipment, and consumables using new sensors, wireless, ultrasound, microfluidics, optics and robotics.

Headquartered in Baltimore, MD, US, Key Tech's uniquely personal approach attracts industry leading global companies as well as innovative start-ups. Key Tech scientists, engineers and designers take technologies into new applications, keeping their client and partner pipelines fresh.

ABOUT THE AUTHOR

Jake Cowperthwaite is a Partner and Senior Electrical Engineer who has been at Key Tech since 2004. He has managed a number of large medical and industrial multidisciplinary projects from requirements generation through commercialisation. He has a thorough regulatory understanding and is responsible for streamlining and improving work-processes at Key Tech. His engineering expertise is in the areas of mixed signal design, power electronics, automation, and sensor integration.

Mr Cowperthwaite received a BSEE from the University of Maine (Orono, ME, US) and an MSEE from the University of Maryland (College Park, MD, US) with a concentration in micro-electronics. He is also a registered professional engineer.

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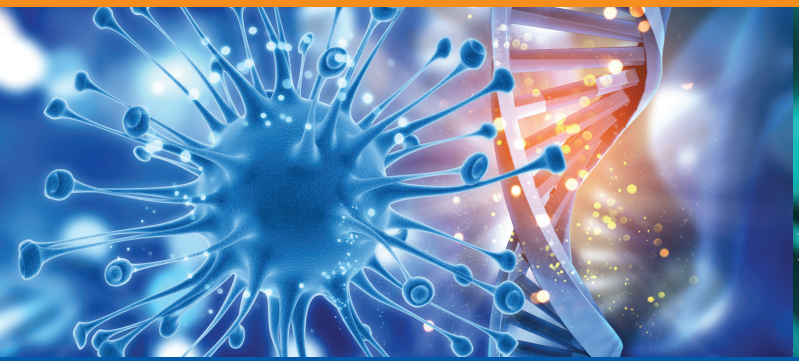

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FAST-TO-MARKET LARGE VOLUME INJECTOR FOR SELF-ADMINISTRATION

In response to a set of very specific device objectives, Bjørn Knud Andersen, MSc, Director, Front-End Innovation, Head of Technology Accelerators and IPR, and Bjarne Sørensen, BSc, ME, Director, Front-End Innovation, both of Medicom Innovation Partner, present an electronic, connected large-volume injector concept for self-administration as the ideal solution..

In supplement to the obvious everlasting need for developing safe and efficacious medicines, the ability to accompany these with patient-centric delivery devices and monitoring systems to support home-administration, plays an increasingly relevant role in securing therapeutic outcome and patient quality of life.

> "There exists an excellent opportunity for the pharmaceutical industry to assess its device strategies and evaluate its application of modern drug delivery technologies and connected health services to support patient self-administration and quality of life optimally, while satisfying healthcare providers' drive for efficacious and documented treatments."

More than three decades ago, the first commercial insulin pens were introduced to the market[1] resulting in greater accuracy, adherence and quality of life for diabetics compared to the common procedure of manually injecting using a vial and syringe. Since then, patient self-injection systems have become much more widely adopted, for example, in auto-immune disorders, blood disorders[2] and even some specific cancer-related conditions.[3] Most often, the delivery system consists of a preloaded, fixed single-dose disposable mechanical auto-injector, which provides a relatively easy solution for the isolated aspect of drug-delivery. However, in recent years, the range of solutions has diversified, i.e. in response to the need to support more complex drug preparation and/or administration procedures, which has drawn attention towards more flexible electronic delivery systems. With the focus on such higher-value re-usable devices, the possibilities for integrating additional therapy-specific patient services – such as injection reminding, site-rotation recommendation, injection adherence monitoring as well as patient-HCP communication tools – are radically expanding.

In contrast to some common general perceptions, these higher-value re-usable device solutions typically represent a lower cost per injection than the disposable mechanical drug delivery devices. This is simply because a re-usable device represents several years of use compared with one single injection. Thus, there exists an

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excellent opportunity for the pharmaceutical industry to assess its device strategies and evaluate its application of modern drug delivery technologies and connected health services to support patient self-administration and quality of life optimally, while satisfying healthcare providers' drive for efficacious and documented treatments.

Whilst the dominant enabling factor for the commercial uptake of insulin pens was associated with changing the primary packaging from a glass vial to a prefilled cartridge, similar transitions to self-administration for other therapies have been facilitated by the development of more convenient primary containers. For example a liquid drug in a vial could undergo repackaging to be presented in a prefilled syringe (e.g. for single dose delivery). More radically, a lyophilised drug in a vial could undergo repackaging to a dual-chamber syringe or reformulation to obtain a stable liquid version presented in a vial, prefilled syringe or cartridge.

Such ease-of-use improvements in primary containers are always attractive from a drug administration perspective. However, they are typically very costly and time consuming as well as being associated with inherent risk of failure. Risks might be minor for "simple" repackaging of liquids (when retaining similar materials) but they can be much steeper, particularly where clinical equivalence data may be required i.e. reformulating a lyophilised drug to a liquid.

Furthermore, for therapies dependent on dosing in line with weight or body-surface area, there can be a conflict between carrying an expensive large number of stock-keeping units to match individual dosing needs accurately, or accepting excessive amounts of waste from disposing of partial doses. Therefore, when targeting patient self-administration solutions, an effective alternative to drug repackaging and/or reformulation will often be to implement intelligent and advanced delivery system automation of central user steps to accompany the existing primary packaging as a means to secure ease of use.

So drug preparation may include a range of challenges e.g. transferring viscous medicines from primary containers, reconstituting lyophilised medicines, individualised dose-settings, as well as handling larger doses potentially pooled together from several (e.g. differently sized), primary containers.

Moving onto the drug delivery situation, there are several aspects influencing practical implementation, in particular whether the administration route is subcutaneous, intravenous or intramuscular (or another route), and how the combination of administration route and dosing volume may favour a handheld concept, or potentially some kind of body-mounted device.

Medicom has partnered in several development projects for medical injection systems based broadly on the array of both drug preparation and delivery features highlighted above. A number of these systems have already reached patients, either in terms of a full commercial launch or late-stage clinical trials.

In recent years the interest in larger volume delivery devices, for both subcutaneous and intravenous home administration, has become increasingly significant to Medicom's innovation and development focus. In response to this, Medicom is continuously strengthening its technology base to be able to implement and validate innovative concepts to address this market need quickly and efficiently with, for example, end-users and stakeholders.

The Medicom Technology Accelerators (see Figure 1) are key in providing mature building blocks, e.g. physical components, modules combined with relevant technical and regulatory expertise etc, to be combined into virtually any type of injection delivery system, thereby speeding up development execution timelines and mitigating technology and project risks.

DESIGN OBJECTIVES

The example discussed here provides a more detailed illustration of the turn-around opportunities with the Medicom Technology Accelerators, and although a few details are examples only, the complexities

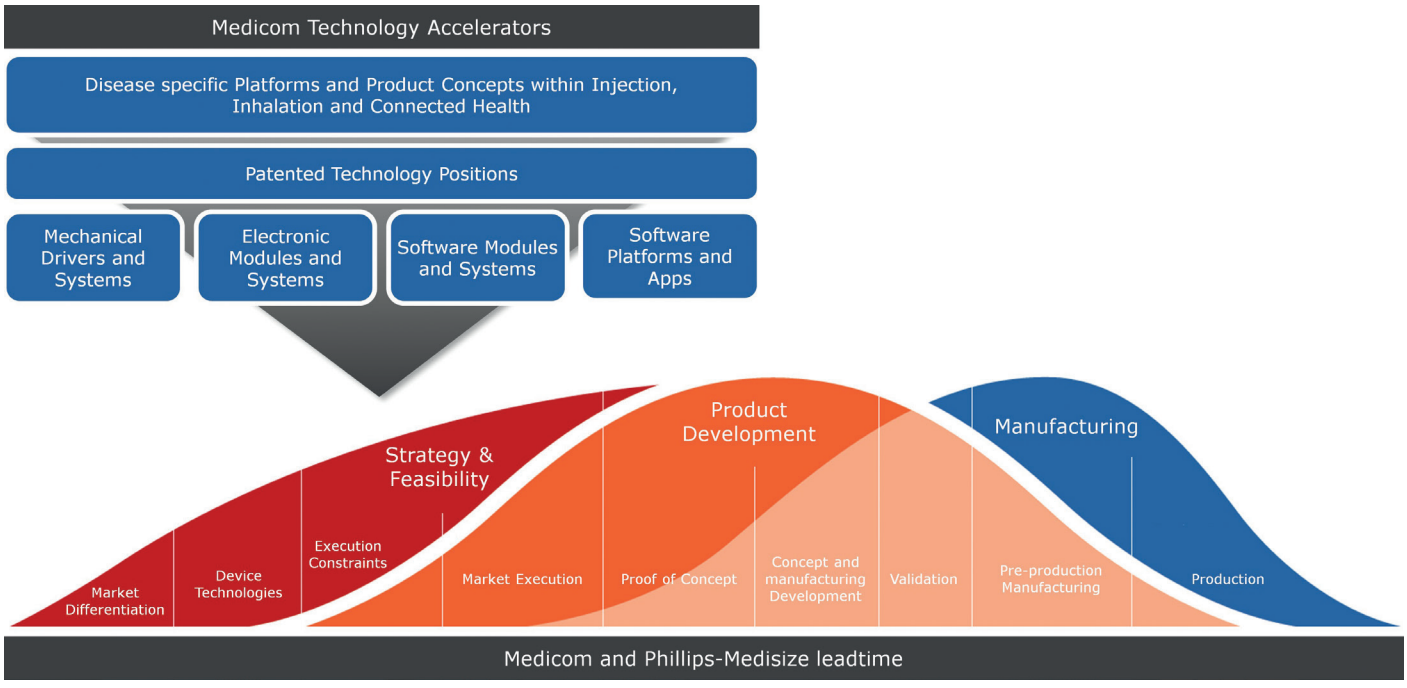

Figure 1: Medicom Technology Accelerators speed up and de-risk the development process.

"The device concept supporting all of the above requirements takes the shape of a re-usable miniature syringe pump equipped with a standard disposable subcutaneous infusion set."

draw directly upon actual implementation challenges experienced across a range of past Medicom projects.

This example explores the automation opportunities associated with preparing and administrating a large-volume, lyophilised drug provided in a glass vial together with a prefilled syringe containing diluent. The dose – typically 8-20 mL – is to be calculated based on the patient's body weight, and doses are potentially combined from two vials of medicine. When reconstituted, the drug is to be injected subcutaneously over 15-30 minutes.

Since an automated device (for cost reasons, for example) is not envisioned for all markets, the existing primary packaging should remain fundamentally unchanged.

Moving the administration procedure to the home-setting, there exist clear opportunities for simplifying the drug preparation procedure. Examples include adding automation assistance for drug reconstitution, as well as for accurate dosing preparation, this being of significant benefit to patient's ease of use. For the reconstitution process, a motorised platform may provide automation of the mixing of drug powder and diluent, reconstitution and dose withdrawal simply based on mounting the prefilled syringe and vial connected by an inline vial adaptor. During withdrawal of the final dose, the device-user interface may actively guide the patient to hold the device upright (vial septum pointing down) as well as controlling it by integrated orientation sensing.

Figure 3: Large volume injector interacting with drug vial.

In relation to accurate dose preparation, the device may be equipped to provide an integrated dose calculation based on patient's body weight. The patient could specify their weight in Kg instead of the dose in mL or, optionally, the device could have such a dose setting accessible only to the healthcare professional. The device would then automatically measure off the exact dose, based on patient weight, during withdrawal into the syringe prior to injection, and for doses combined from two vials, it will automatically guide the patient and control the amount pulled from each vial taking into account aspects of overfill and tolerances etc.

In the case of several different drug presentations, perhaps with varying dose sizes, then individual labelling of the vials combined with automatic vial detection may further guide the patient e.g. to select appropriate vials based on the required total dose. Labelling of vials could for example be done using a visual 2D barcode or colour marking, alternatively using radio frequency identification (RFID) or near-field communication (NFC) short-range wireless technologies.

LARGE-VOLUME INJECTOR

The device concept supporting all of the previously mentioned requirements takes the shape of a re-usable miniature syringe pump equipped with a standard disposable subcutaneous infusion set (see Figures 2 & 3). With this concept, the patient can initially prepare the device and dose while, for example, sitting at a desk or table, then connect and prime the infusion set and subsequently continue with injection either while still sitting at the desk or table or after having moved to a more comfortable location, a cosy armchair or a bed, all to their personal preference.

Figure 2: Industrial design example of a large volume injector.

In addition to the drug delivery device aspects, the electronic device approach also enables connectivity options from the delivery device to a patient app and onwards to a secure cloud data structure capable of facilitating data sharing between the patient, healthcare provider and other relevant stakeholders. Beyond, adherence data etc, the mobile app is able to provide guidance and assistance including patient training, thereby helping to mitigate

[Continued on Page 36...]

"The lifetime of a re-usable injector typically is set at three years (or at least 600 injection cycles) so there are also significant cost-per-dose savings from disposing only of the infusion set as opposed to partly or entirely scrapping a patch pump device at every single administration procedure."

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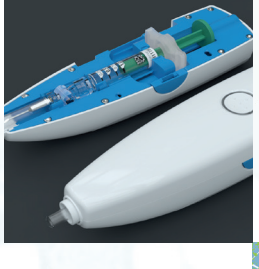
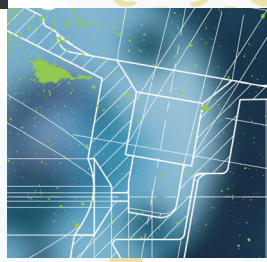
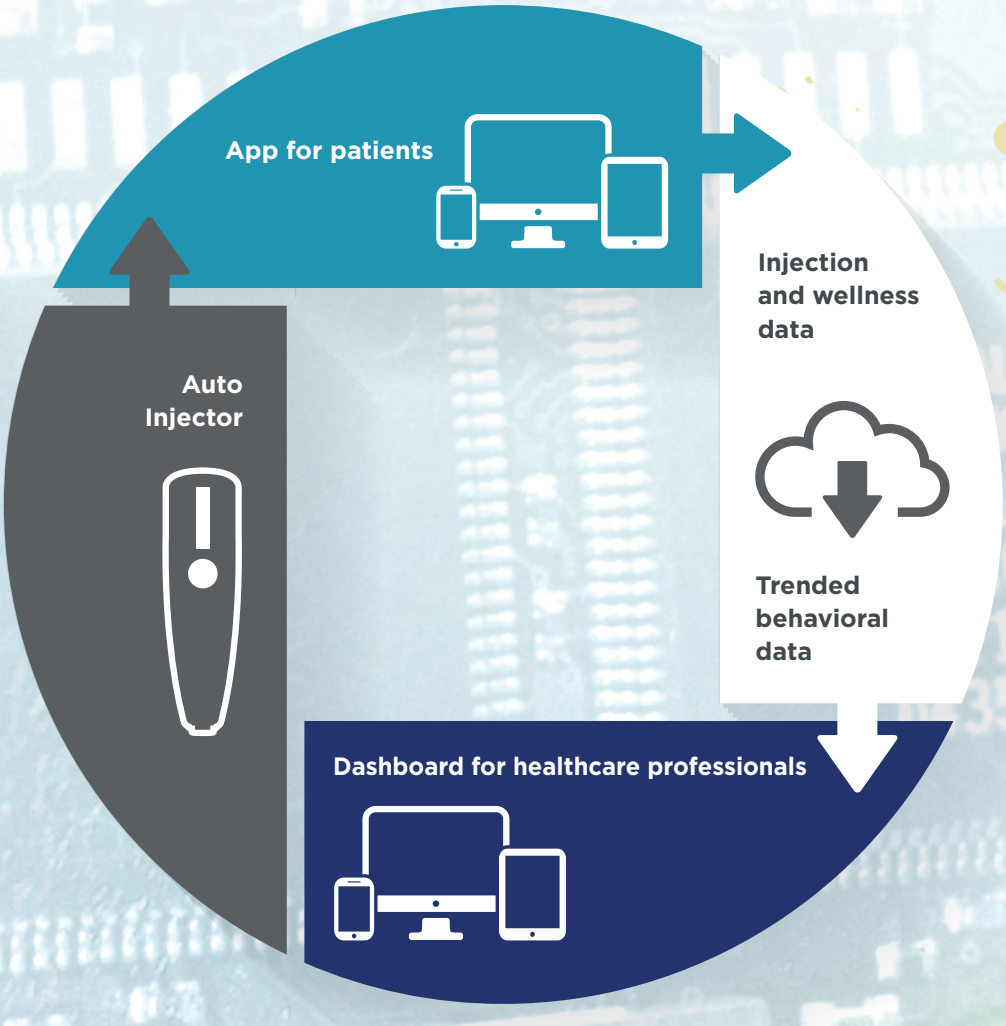




Devices
Connectivity
Connected Health Service Solutions



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remaining risks such as those associated with non-compliance.

Such interactive services in correct and compliant use of self-administration with the device, and reporting of symptoms and side effects, allow a more focused effort for healthcare professionals, allowing additional assistance and therapeutic intervention to be focused on those patients who really need it. Thus, a connected health service approach directly supports patient empowerment and hence quality of life while at the same time ensuring that patients in need will never fall below the radar.

The ability to execute an initial lifecycle-management device extension in line with this example very rapidly often overrules any potential ambitions for a more compact patch pump with, for example, integrated needle handling, especially because such further advancements could be activated at a later point in time.

However, the lifetime of a re-usable injector typically is set at three years (or at least 600 injection cycles) so there are also significant cost-per-dose savings from disposing only of the infusion set as opposed to partly or entirely scrapping a patch pump device at every single administration procedure.

CONCLUSIONS

Based on Medicom's Technology Accelerators and substantial experience, the speed of execution for the above exemplified device development could be reduced to 18-24 months, including the initial strategy and concept phase, additional detailed feasibility and development, validation etc, and including a small-scale manual-validated production line. As needed, the establishment of a scaled-up full production-volume manufacturing line is an option to be activated anytime following design validation, for example in response to further expanding capacity requirements from additional markets and/or product therapeutic indications.

Automated drug delivery solutions remain key in driving therapeutic procedures out of the clinics and into patients' homes to the benefit of patients, healthcare professionals and payers.

Historically, practical examples have often been defined by the opportunities vested in primary packaging formats but pressure for faster lifecycle-management updates due to, for example, intensified competition may be incompatible with realities such as minimum reformulation and/or repackaging timelines. Instead, the approach of applying intelligent technology to automate otherwise manual user steps may bridge needs and thus provide a fast track to market with higher-valued, re-usable device solutions while realising a lower cost-per-dose compared with conventional and unconnected, mechanical delivery devices.

ABOUT THE COMPANY

Medicom Innovation Partner (a Phillips-Medisize Company) is a leading global innovation, development and low-volume production provider focused on drug delivery devices and connected health solutions. Medicom Innovation Partner was established as a technology venture of Bang & Olufsen A/S in 1989 and the company has been a dominant player within the drug device world for more than 25 years. Medicom holds a dedicated staff of more than 90 high-calibre innovation specialists, mechanical, hardware, software, quality assurance, regulatory and production engineers based in Struer, Denmark, and Cambridge, UK. Medicom has experienced considerable growth over the last five years.

As of May 31, 2016, Medicom became part of Phillips-Medisize Corporation. Phillips-Medisize (a Molex company) is a leading global outsource provider of design and manufacturing services to the drug delivery and combination products, consumable diagnostics and medical device, and specialty commercial markets. The company has annual sales of over US$700 million with 80% of the total revenue coming from drug delivery, medical device, primary pharmaceutical packaging and diagnostic products such as disposable insulin pens, glucose meters, specialty inhalation drug delivery devices, single-use surgical devices and consumable diagnostic components.

The combined Phillips-Medisize and Medicom organisation is becoming one of the leading players within the growing drug delivery device and connected health market.

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SENSILE MEDICAL

BUILDING BRIDGES FROM DRUGS TO PATIENTS: USABILITY & HUMAN FACTORS

Sensile Medical has been conducting usability engineering for a number of years in its projects in order to consider these factors and develop appropriate solutions. Here, Nicolas Sandoz, Head of Product Management, describes Sensile Medical's approach to ensuring it takes usability and human factors into account during the development of its devices, in particular for subcutaneous delivery.

> "The shift from hospital or clinic setting delivery to home self-administration using a wearable injector needs careful consideration regarding patient safety, as well as reflection on the ease of use, comfort and, more generally, the usability of the injector unit."

With the advance in biotechnology over the last two decades, therapies using biologic drugs are becoming increasingly frequent. Very often, those biologics are large and complex molecules and cannot be administered orally. Indeed, their size and polar surface prevent them from diffusing through the epithelial layer of the intestine and stomach and they may also be damaged during their journey through the gastro-intestinal tract.

Consequently, these large molecules necessitate a different administration route and frequently parenteral delivery is appropriate. However, such administration is a more complicated and technical process than just swallowing a few pills or a few millilitres of a drug, and can result in higher therapy costs and more burden for the patients. For instance, intravenous (IV) administration requires the placement of an IV line by a nurse, and patient surveillance during delivery in case of complications.

Subcutaneous (SC) delivery provides the possibility of self-administration, for example at the patient's home, thus helping to lower therapy costs. As a result a growing number of drugs are now being reformulated for SC delivery using a wearable injector for home use. Various scenarios, where IV delivery in a hospital setting could be substituted or supplemented by SC delivery at home have been discussed in a previous issue of ONdrugDelivery.[1] They are still valid today so will not be re-visited here.

Some drug manufacturers also want to use automated delivery devices to simplify the act of administering the medication, thus diminishing the burden on patients, and giving them more flexibility.

The shift from hospital or clinic delivery to home self-administration using a wearable injector needs careful consideration regarding patient safety, as well as reflection on the ease of use, comfort and, more generally, the usability of the injector unit.

BENEFITS AND RISKS

A shift from delivery conducted in a hospital or clinic environment, where trained professionals administer the therapy,

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to self-delivery by the patient at his or her home brings a number of benefits to the patient but also a few risks.

The first obvious benefit is that self-delivery does not necessitate the presence of a healthcare professional (HCP) once the patient is trained to self-administer the drug. Furthermore, home therapy provides the patient with an environment that is personal, familiar and comfortable – clear advantages on top of the cost decrease.

Depending on the therapy, home administration gives more flexibility and freedom to the patient who may even be able to carry out other activities or work while the drug is being delivered by the device. This not only saves time but also allows the patient to be productive during the therapy, and can be beneficial to several parties, the patient, the employer and payers.

Self-administration reduces the need for regular trips by the patient to a healthcare centre and the stress related to transportation and traffic. This also brings advantages in terms of comfort, time and cost savings.

The resulting benefit is that the therapy has less impact on the daily routine of the patient, thus helping the patient to remain active and mobile, and continuing a regular social life. All these factors may contribute to better patient compliance and improve therapeutic outcome.

"Even though the benefits speak in favour of self-administration at home, the related risks are real. This is where usability engineering can play a central role to understand potential problems and develop mitigation measures."

On the risks side, a wrong manipulation of the drug or delivery device, or a misunderstanding of a setting, can lead to administration of the wrong dose, potentially resulting in an adverse effect. Absence of personnel with medical training in case of anaphylactic reaction or simple forgetfulness leading to missing or skipping one or more deliveries are also increased risks.

Such eventualities must be avoided and necessitate a thorough understanding of the therapy, its possible side effects, the environment it's being used in as well as patients' limitations, for example limitations caused by their condition.

Even though the benefits speak in favour of self-administration at home, the related risks are real. This is where usability engineering can play a central role to understand potential problems and develop mitigation measures. Issues related to device use, understanding patients and their interaction with the drug and delivery system are tested during usability studies. The results are subsequently integrated into the product design.

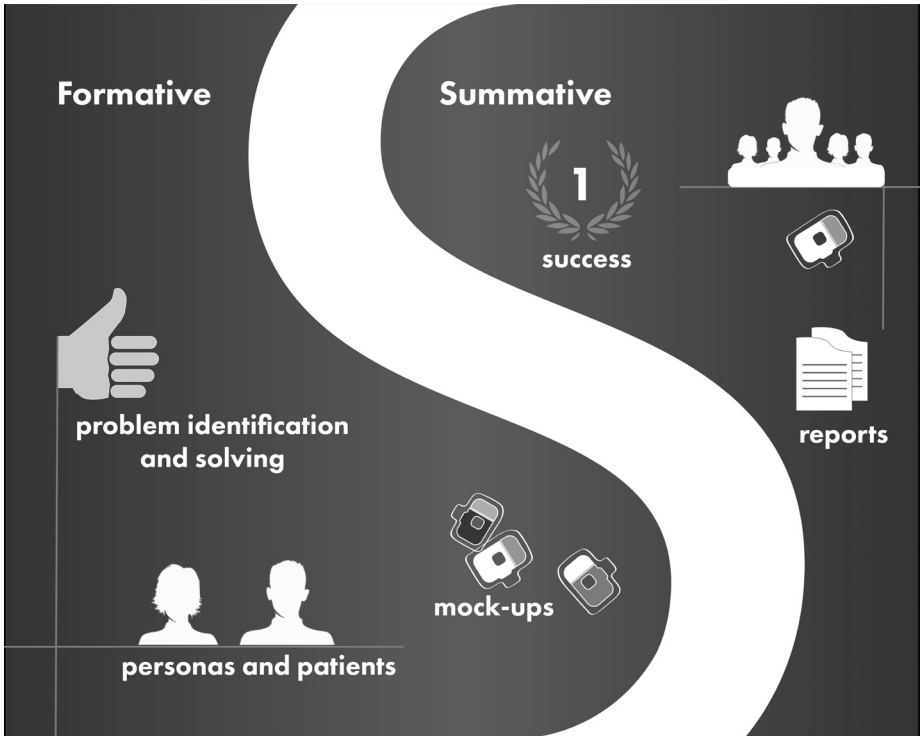

Figure 1: The purpose of using both formative and summative testing.

USABILITY ENGINEERING

Sensile Medical utilises human factors and usability studies and integrates them into their development projects as part of a usability engineering process.

Originally developed to study and optimise military equipment during the Second World War, human factors is often nowadays wrongly thought to be mainly a discipline for interactions between human and computer only. It actually applies to the development of any product interacting with human beings. For medical devices, usability engineering has evolved with US FDA Guidance[2] and the IEC 62366 standard.[3] The latter takes the patient condition and resulting limitations into consideration in order to improve the usability of the device, to make sure its user-interface is understandable and to contribute to safety.

In addition to risk mitigation, usability engineering also provides the opportunity to create and optimise the design. The look and feel of a device should address patient concerns and fears (e.g. needle phobia) and provide the best possible user experience.

The usability process at Sensile Medical consists of an iterative approach integrated into the various phases of the development project. It begins with formative studies where the preferences of patients are tested followed by further studies where various aspects of the device design are evaluated and refined. The formative studies series ends with a confirmation study testing the whole product as well as the set-up foreseen for validation. Finally, a summative study demonstrates the safe use of the design and acceptance by its users and formally provides its validation (see Figures 1 & 2).

FORMATIVE STUDIES

Preference Studies

Preference studies are formative studies usually carried out at the beginning of a development project to determine which concept is the most suitable for patients

among a choice of several alternatives. At Sensile Medical, we start with elaborating use scenarios and performing a use error analysis to identify wants and needs as well as potential risks arising from the operation of the device.

Using semi-functional mock-ups presented to a sample of patients and HCPs for them to simulate the injection process, their behaviours are observed and their opinions evaluated through a number of targeted and specific questions. These studies can address the complete unit or only a part of its functionalities. Very often elements like preparation of the unit before therapy, or interface and position of the auxiliary equipment, or type of user interface are tested during such studies.

The advantages of this formative step are: a reduction of the multiple solution possibilities at an early stage of a development; gathering information by observing the patient handling the mock-ups; and confirming whether patients' conditions may affect their use of the device. A difficulty arising at this stage is often the wide behavioural spectrum of patients and subsequent development of the corresponding mitigation measures in the next design iteration.

Concept and Design Refinement

Concept refinements also involve formative studies used to refine the product concept further. The use error analysis is further detailed based on the chosen concept and the foreseen use scenarios. This becomes part of the instrument risk analysis and enables risk-mitigation solutions to be tested with patients and HCPs. Aspects like user interface concept, warning messages and alarm signals as well as instructions for use (IFU) and training are evaluated.

Concept refinement is often an iterative process happening during the feasibility and design input phases. It may continue beyond the concept stage into the prototype stage of the design output phase to refine and finalise the product design. Depending on the stage of the development, these studies make use of semi-functional mock-ups or semi- or fully-functional prototypes.

The studies performed at this stage represent a first confirmation of product acceptability and help to adjust its design and functionalities. They also provide valuable insights for potential improvements and help identify features that may not be very useful.

Formative vs. summative tests
What's the difference?

Formative Studies	Summative Studies
Purpose: to guide the whole design process	**Purpose: to formalize the outcome of the formative process**
• From the beginning of and during the development • Shaping the design iteratively • Testing/improving with sketches, mock-ups, prototypes or similar • Problem identification and solving • Gain valuable insights – to reach user goals	• At the end of development phase • Formal documentation of the usability of a product, its user interface and inst-ruction for use • Testing with series product • Using metrics (task durations, success rates, satisfaction scores) • Generate data to support marketing claims about usability
Output: • ***Qualitative as well as (semi-)quantitati-ve results with respect to usability of the future product*** • ***Participant comments and questions (attitudes, sources of confusion, rea-sons for actions...)*** • ***Photographs/Videos*** • ***Usability problems and suggested solutions***	***Output:*** • ***Statistical measures of usability (success rate, average time to complete a task, number of assists...)*** • ***Formal validation reports***

Figure 2: The differences between formative and summative tests.

Confirmation of Design

Towards the end of the design output phase we test the full product as planned as part of a pre-validation step. This helps confirm that the system works as foreseen and can be used by patients and HCPs as planned before transferring the design into commercial series production. This step also enables testing the validation set-up for the summative studies. At this stage, the product and its IFU are tested along with packaging, training materials and training procedures.

During patient interviews, it is useful to test error states to make sure the users can resolve potential problems with the information that would be available to them in real use conditions.

This step is comparable with the final rehearsal before the premiere of a show. It is the last confirmation that everything runs smoothly. The size of the patient and HCP sample need not to be as large as for the validation but big enough to be representative.

SUMMATIVE STUDIES

Summative studies are carried out to validate the usability of the device. They confirm that the training materials and procedures are effective, and that the IFU is understandable. The usability of the device is tested under normal use conditions. Tests of error state and troubleshooting procedures make sure that the interpretation of warnings or error signals are correct and that the patients can resolve problems on their own.

LEARNINGS

The use of techniques and tools like personas, patient journey and use cases have been found very helpful at various stages of development. Elaborated during the requirement elicitation phase, they help to illustrate and understand the role, environment of use and condition, as well as limitations of users of the product. They are particularly helpful in usability engineering to determine the focus and content of the handling studies, as well as to elaborate a choice of design alternatives for the product.

Collaborating with companies specialised in human factors studies has proven very useful. Sensile Medical partners with them not only for the logistics aspects such as providing appropriate location and facilities for the studies but also for them to

manage patient recruitment, and conduct the testing and interviews. These firms also develop interview protocols based on the goals and content that Sensile Medical provides.

Another important factor that such partnerships bring is a neutral position with respect to design alternatives during the interviews, thus preventing an influence on the results by the interviewer. Indeed, an interview by someone involved in the device design could involuntarily bias the outcome of the study.

Interview facilities are usually equipped with filming capabilities. Videos of the tests are recorded with user consent. This provides useful material that can be examined to re-confirm the observations and understand the context in which they happened.

CONCLUSION

The advance of biotechnology has led to an increase of large biologic molecules requiring parenteral administration for various indications. SC delivery through self-administration by patients using advanced drug delivery systems is an opportunity to improve therapies and decrease costs, as well as provide patients with more flexibility and comfort.

However, self-administration may bring a number of challenges with it regarding the safe and effective use of these devices. Most of these challenges can be addressed with a usability engineering approach. Sensile Medical recognised the importance of this discipline long ago, and has integrated it into its development projects with positive results.

In addition to the benefits this discipline can bring to patient safety, satisfaction and compliance with the therapy, the iterative nature of Sensile Medical's approach of usability engineering provides an early indication of product acceptance on the market.

ABOUT SENSILE MEDICAL

Sensile Medical is a leading company in the area of advanced micro pump technology developing a broad range of customer-specific delivery and dosing solutions. Sensile Medical is a full-service provider of pump-based drug delivery solutions, with in-house specialists for engineering, electromechanics, software development and more. Our partners include well-known pharmaceutical companies and research organisations.

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CONTINUOUS GROWTH & INNOVATION IN COMBINATION PRODUCT MARKET PRESENTS CHALLENGES & OPPORTUNITIES

In the context of the fast-growing biologics market fuelling a rapid rise in the number of patients self-injecting chronic therapies at home, Paul Sullivan, Associate Director of Business Development, Noble, describes market research that underlines the importance of appropriate training and its impact on adherence and compliance, and shows how, amongst available training techniques, smart training devices that are true to the form and function of the actual device, with error-detecting technologies, deliver the most promising results.

The pharmaceutical industry is evolving as more companies are shifting focus from small-molecule drugs to biological medicines requiring drug delivery systems, with more than 60% of recent patent filings from the industry's top ten companies being for biologics.[1]

> "Device manufacturers and stakeholders, including biopharma companies, healthcare providers, payers and patients, have realised the benefits and importance of training prior to initial self-injections, continuous training and onboarding throughout disease management to counteract administration training decay, and ultimately the role of training and onboarding to help improve adherence and health outcomes."

It could be said the combination product market is booming with biopharmaceuticals having an annual growth rate of more than 8% – comprising 20% of the pharma market and growing – due to biologics' and biosimilars' ability to treat and manage chronic conditions effectively.[2] Complementing the growth of the biologics market is the drug delivery device market with the auto-injector being one of the top preferred injectable delivery systems due to the device being self-contained and convenient injection method for the growing number of patients who self-administer medications.

Auto-injectors are expected to continue to remain a preferred delivery device with chronic disease management being a life-long process, and as life expectancy continues to grow. Auto-injectors were designed to improve administration by reducing the complexity of user steps required for injection, taking into account human factors including psychological considerations as well as dexterity and mobility impairments. Other integrations included tactile feedback such as auditory and visual signals indicating the beginning and conclusion of administration.[3]

While auto-injectors have helped self-injecting patient populations with administering treatment there are still

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challenges as patients continue to make administration errors based upon factors including anxiety and confidence, memory retention and recall, device familiarity, changes in viscosities and volumes requiring longer injection times, and other issues.

These errors and low adherence rates correlate with the emergence of drug delivery training devices. Device manufacturers and stakeholders, including biopharma companies, healthcare providers, payers and patients, have realised the benefits and importance of training prior to initial self-injections, continuous training and onboarding throughout disease management to counteract administration training decay, and ultimately the role of training and onboarding to help improve adherence and health outcomes.

One example of how the growth of combination therapies has an effect on stakeholders can be found with healthcare professionals who receive training on proper administration technique for multiple drug delivery devices. These trainings could include a variety of different devices, and could result in confusion when correctly recalling the operational sequences and functionalities for a particular device. The resulting confusion could be detrimental for a newly diagnosed, device-naïve patient receiving in-office training.

Even if the healthcare professional correctly demonstrates proper administration technique, patients may still not understand how to self-inject. Try putting yourself into a patient's shoes: you have just been diagnosed with a condition, which could be painful or debilitating, and you'll have to manage it by self-injection for the rest of your life. You might be distracted due to possibly being in shock, frightened, sad or be confused due to misunderstanding technical language.[4] The gravity of the situation may hinder information retention and create a difficult learning and training environment. For the information received, findings suggest 40-80% of medical information provided by healthcare providers to patients is forgotten immediately.[5]

Another example of how the growth of combination therapies has an impact on stakeholders is through continuous industry innovation with formulations and new biologics providing patients with improved therapies and longer periods between injections. While there are many advantages these innovations provide to patients, including normalcy of not being reminded of their condition and added convenience of gaps between self-injection, there are also some disadvantages when it comes to the patient successfully onboarding and remaining adherent.

The first 30-, 60-, 90-days and beyond (with some treatments self-injected once a quarter) are commonly referred to as onboarding and are the most important times regarding patient adherence. Longer periods between injections could contribute to lower adherence since a patient will most often perform their injections alone outside of healthcare provider supervision (see Figure 1). Factors such as training decay resulting from transience and diminished memory recall of self-administration technique, forgetfulness of treatment dosing schedule, incorrect training due to message erosion and continual patient support could lead to patients receiving sub-optimal treatment, adverse events and even discontinuation of treatment.

Ultimately, patient non-adherence is a major issue that not only affects health outcomes, but costs the healthcare industry billions of dollars each year.[6] To address stakeholder challenges Noble works closely with biopharmaceutical and original equipment manufacturer (OEM) companies specialising in the design, development and manufacturing of advanced drug delivery systems to develop innovative solutions.

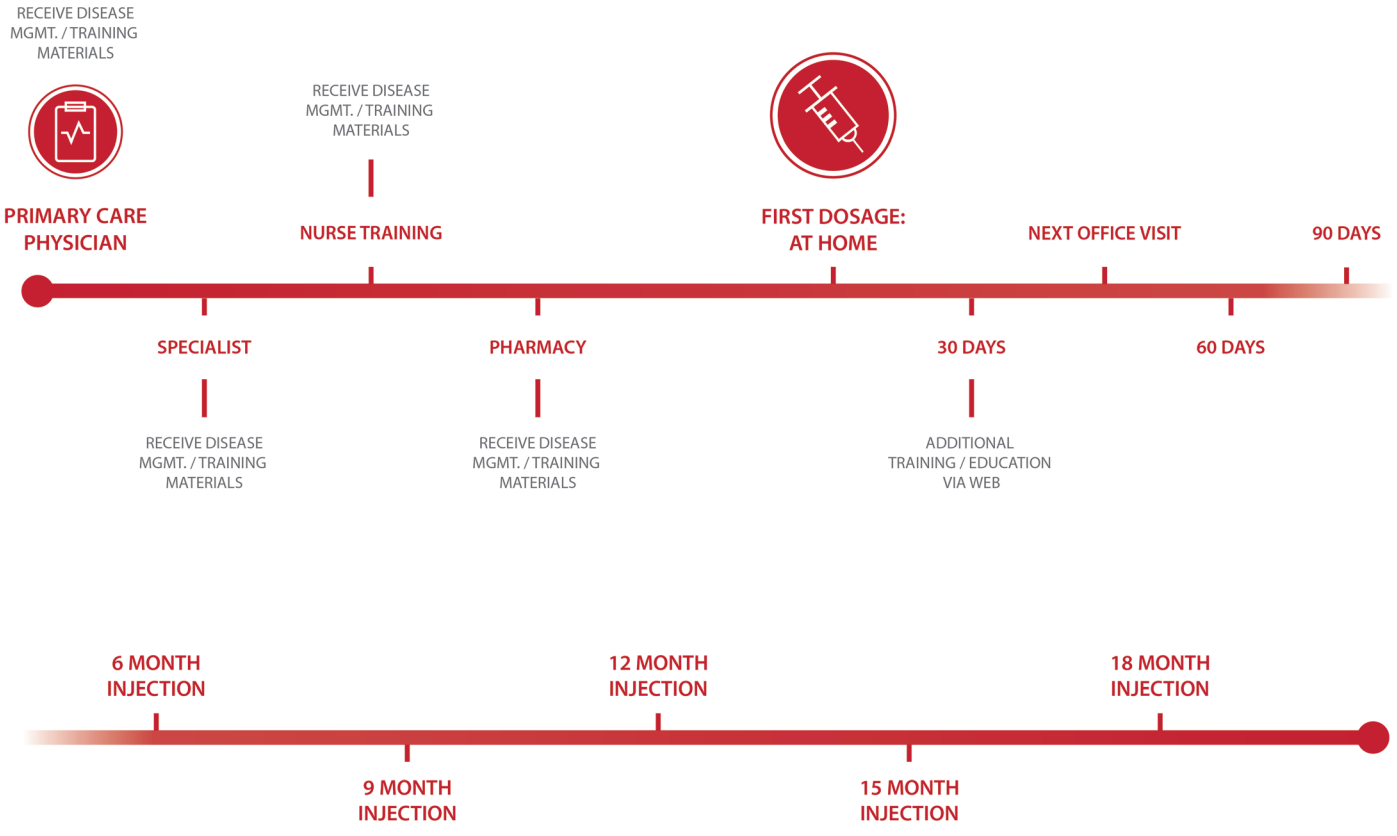

Figure 1: Timeline showing onboarding including initial and subsequent injections at different dosing frequencies.

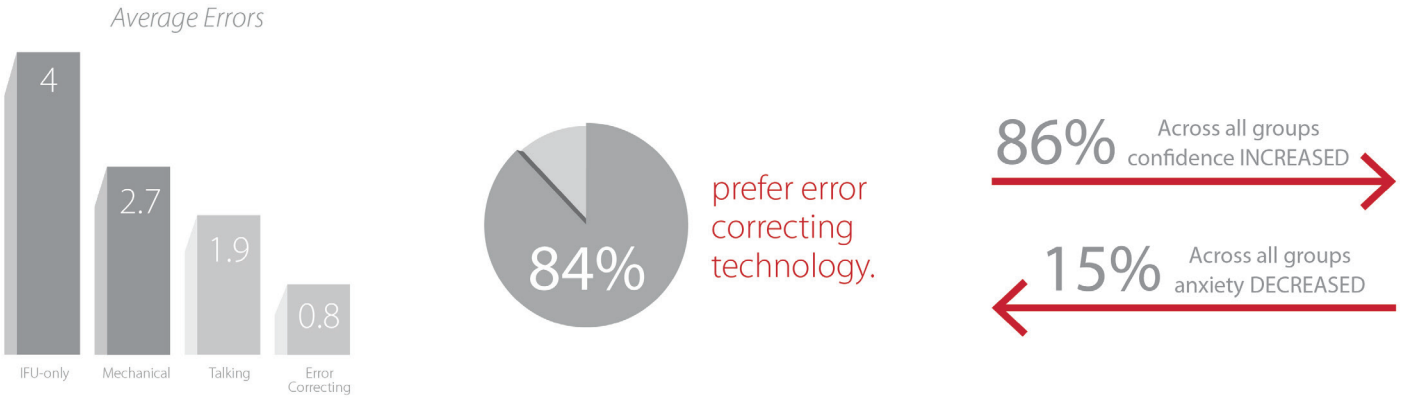

Figure 2: Patient confidence and anxiety are factors impacting compliance and patient adherence and were included as elements of the device preference market study.

Together, Noble and these innovative players are leveraging collaborative research efforts, understanding of human behaviours, and design best practices to carry out a shared mission of offering patients a complete solution of best-in-class molecules, drug delivery devices and training and onboarding programs to assist them with better management of self-administered therapies.

Noble's in-depth market research found that nearly two-thirds of patients do not thoroughly read instructions for use (IFU) documents prior to treatment.[7] Additionally, 73% of patients report increased anxiety regarding injection therapies when relying on an IFU as their only form of training.[8] Research also suggests that 45% of patients skip or avoid injections during onboarding due to anxiety or fear.[9]

To counteract some of the cognitive, psychological and emotional factors patients experience, Noble has developed robust patient-centred training and onboarding platforms ranging from mechanical trainers to smart error-correcting devices, training IFUs, quick-tips and more. In doing so, these complete solutions provide value to commercial teams, helping brands strengthen pre-launch, transition and post-launch strategies and maintain positive patient engagement.

Providing patients with a training device that is true to form and function as the actual drug delivery device, means they become familiar with all facets of a device's operation through a simulated injection. Thus, the patient builds confidence, muscle memory and has a reduction in anxiety, thereby minimising risk of engaging in avoidance behaviours.

Just as the combination product industry has been developing innovative products, Noble also continues to develop improvements to the training and onboarding process for auto-injector and other drug delivery devices.

DEVICE PREFERENCE MARKET STUDY

A device preference market study was conducted to reveal the impact different types of device trainers have on the patient experience. During the study, 55 participants were placed into four groups that received a different combination of training tools and devices to learn a 15-step drug delivery process. Each group was monitored for the number of errors made while practicing the injection treatment with a training tool:

- Group 1 used IFU only for their training and made four errors
- Group 2 used IFU and Mechanical Trainer (tactile and visual feedback only) and made 2.7 errors
- Group 3 used IFU and Talking Trainer (tactile, visual and audio feedback) and made 1.9 errors
- Group 4 used IFU and Error Correcting Trainer (tactile, visual and audio feedback with error correcting technology) and made 0.8 errors.

> "These complete solutions provide value to commercial teams, helping brands strengthen pre-launch, transition and post-launch strategies and maintain positive patient engagement."

As stated previously, patient confidence and anxiety are factors impacting compliance and patient adherence and were included as elements of the device preference market study. As shown in Figure 2, based on participant feedback, 84% of users prefer error detection technologies to overcome anxiety when onboarding to device-delivered therapies. Patient anxiety decreased by 15% across all training methods evaluated during this study. Smart training devices with error-detecting technologies are preferred methods in overcoming anxiety and preventing errors.

COLLABORATION PROVIDES PATIENTS BEST-IN-CLASS EXPERIENCE

The biopharmaceutical industry is undergoing a renaissance as many innovative combination products continue to be conceived, refined and brought to fruition to provide patients with better quality of life.

Collaboration has contributed to the growth of combination therapies with companies now forming strategic partnerships by leveraging expertise and finding synergies to develop innovative new drugs. This evolution in the biopharma business model has made it possible for new drugs to go to market faster and at a lower cost creating opportunities for companies to address diseases affecting both large smaller patient populations alike.[10]

As part of the sharing of knowledge and resources between biopharma companies to develop an innovative pharmaceutical product there's also the design, development and manufacturing of the drug delivery device. Formulation, device and commercial teams are collaborating earlier in the development process with an emphasis on using a human-centred approach to gather product needs and user needs to ensure the drug and device integration is optimised for performance and user experience.

Similar to innovations in the biopharma industry, training technology is allowing the engineering and capabilities of these devices to continue to advance. These advancements are imperative as they will allow patients to become more confident, overcome treatment barriers, and ultimately lead healthier lives.

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ADJUSTING & CONTROLLING INJECTION SPEED BY DESIGN: IMPACT ON PAIN PERCEPTION

In this article, Isabell Delcroix, Strategy Director, and Pascal Dugand, Technology Product Manager, Device Development, both of Nemera, describe a study of the multi-award-winning Safelia® auto-injector platform, which investigated the impact of varying the injection speed on pain perception and showed how slowing injection speed, particularly at the beginning and end of the injection process, could reduce pain perception.

Nemera's generation of two-step auto-injectors, Safelia® (Figure 1), has been designed to ease the patient self-injection experience and to deliver a variety of drug products in glass syringes. These range from more fluid formulations to the most challenging drugs such as viscous, sustained-released, concentrated formulations, products for subcutaneous and intramuscular injection, and including larger volumes.

The Safelia® auto-injector:

- Administers a large range of formulations and injection volumes; the platform can adapt by design to handle both fluid and highly viscous formulations, taking care specifically of biologics, sustained-released formulations and sheer-sensitive molecules, of up to 2.25 mL injection volumes
- Improves the patient experience, with the possibility to reduce needle gauge, reduce injection time, and slow down the needle penetration inside the body tissues, and gives the possibility of a delayed retraction for viscous injections especially.

PAIN PERCEPTION

Subcutaneous injection is a common route for self-administration using syringes, prefilled syringes and auto-injectors. Subcutaneous injections are typically 1 mL. However, increasingly treatments tend to require up to 2 mL injections.

Factors leading to a perception of pain are well known:

- Injection site choice
- Needle gauge (large diameter needles)
- Formulation active ingredients, temperature, viscosity, pH
- Dose volume
- Injection speed

It is observed that larger dose volume (2 mL *versus* 1 mL) and faster injection could lead to higher stress in the tissues at the site of injection, and consequently higher pain perception. It is usually

> "Diminishing the initial injection speed will lower the injection force and could lower pain perception. At end of injection, dose volume is at its maximum, whilst tissues are saturated. Diminishing end of injection speed will lower injection force, favouring drug absorption. The resulting pressure drop in the tissues could help also to reduce pain perception."

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Figure 1: 1 mL and 2.25 mL versions of the Safelia® auto-injector.

Expected benefits	Standard Auto-Injector	Safelia	Safelia Features
Creating possibilities for viscous injections with the same AI platform as for standard glass syringes	x	✓	Injects fluid and viscous drugs up to 1000 cP
Risk of syringe breakage eliminated Possibility of using all (or no) syringe flanges	x	✓	No stress on syringe flanges
Enables increased spring force and use of small gauge needles (less patient pain) without risk of glass breakage	x	✓	No stress on syringe flanges
Reduction of pain at needle insertion	x	✓	Adjust needle insertion speed
Reduction of pain during injection	x	✓	No initial injection peak
Drug is delivered at the right depth	x	✓	Needle insertion disconnected from injection

Table 1: Summary of design features and benefits of the Safelia® platform.

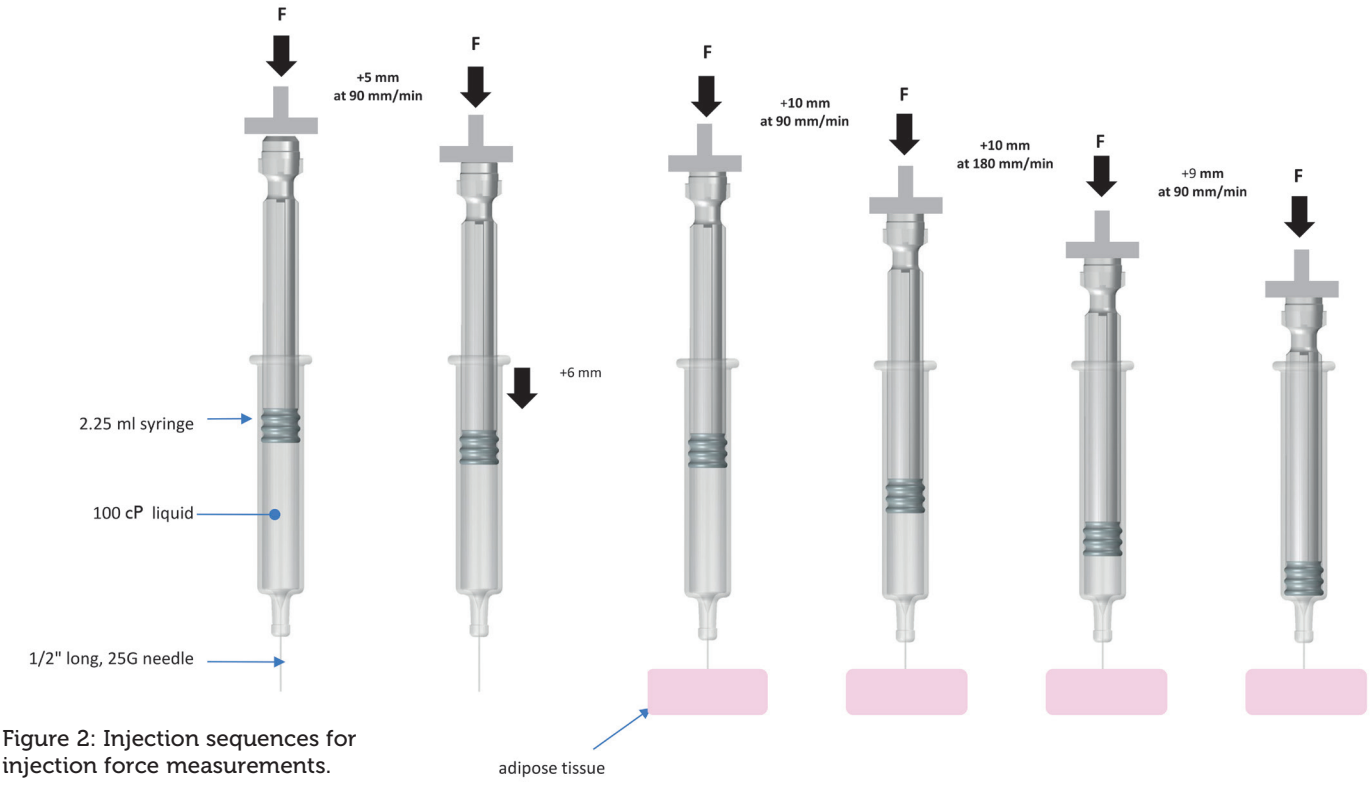

Figure 2: Injection sequences for injection force measurements.

considered that a practical injection time should not exceed 10 seconds, which leads to 0.2 mL/sec injection flow rates in the case of 2 mL injected volumes. As a result, compared with 1 mL syringes, it can be anticipated that the increased injection speed, could cause a higher perception of pain to patients.

Design features and benefits of the Safelia® device are summarised in Table 1.

STUDY OBJECTIVES

Nemera has conducted a study investigating how adjusting and controlling injection speed could impact on pain perception, in particular for viscous and large-volume injections.

The primary objective of this study was to estimate injection force increase in porcine adipose tissue in the case of high viscous formulations (100 cP) and large dose volume (2 mL). The final aim was to propose a way to optimise injection devices to minimise the perception of pain by patients.

METHOD

In a first step, injection forces were performed at different speeds in air and in tissues. In a second step, the impact of injected dose on injection force was measured. Syringes of 2.25 mL, with 25G, ½" long needles were prefilled with a

100 cP Newtonian liquid. Injection force in tissue was measured consecutively for injection in air and in tissue:

1. Injection in air was performed to determine injection force without tissue back force.
2. Injection in porcine adipose tissues was then performed (injection depth 6 mm, simulating subcutaneous injection).

Tests were performed at three different speeds (90 mm/min, 135 mm/min and 180 mm/min).

The sequence is shown in Figure 2.

RESULTS

The Injection force in porcine adipose tissue increases with injection speed. Injections at a flow-rate of 0.09 mL/s generated a maximum back force of 20 N. (Note that it was also confirmed that injecting at a 0.09 mL/s flow-rate after injections at 0.18 mL/s generated a maximum back force of 20N, i.e. 60 N minus 40 N.)

Injection forces in air and injection forces in porcine adipose tissue (Figure 3) can be considered to estimate the injection pressure in the tissue. By subtracting the injection force in air to injection force in tissue, the tissue back force can be evaluated (Figure 4).

As anticipated, a higher injection speed is associated to a higher tissue back force. It has been also observed that the injection force smoothly increases with increasing dose volume, leads to a back force increase of 8 N (see Figure 5). It has been also observed that injection forces in porcine adipose tissue presents large variations. (Note that injection at 0.18 mL/s flow-rate generated a maximum back force of 32 N.)

CONCLUSIONS

Injection force increase in porcine adipose tissue in the case of highly viscous formulations (100cP) at high speed and large dose volume (2 mL) have been observed. These measurements allowed a skin back force estimation. This information is very useful for auto-injector development.

For Safelia® auto-injector, we have developed a mathematical model allowing injection time prediction including back force. This model enables us to anticipate

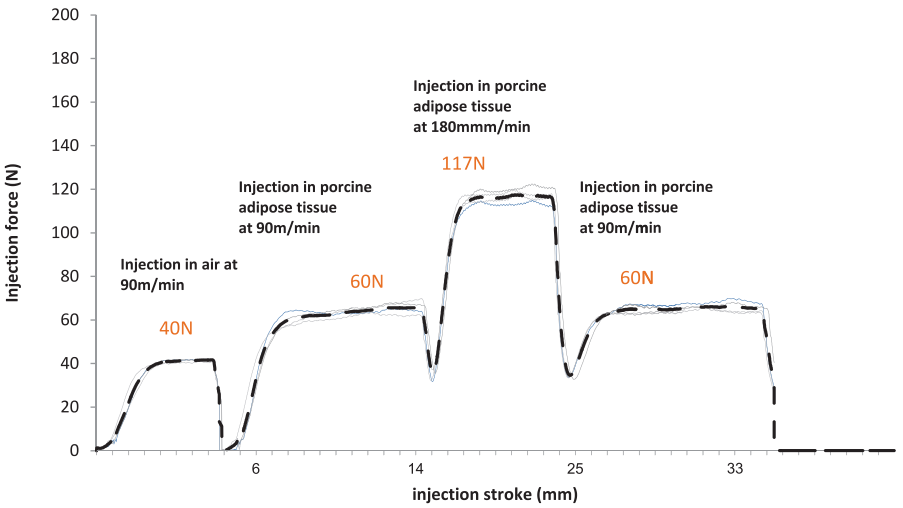

Figure 3: Relation between injection force and injection speed in porcine adipose tissue.

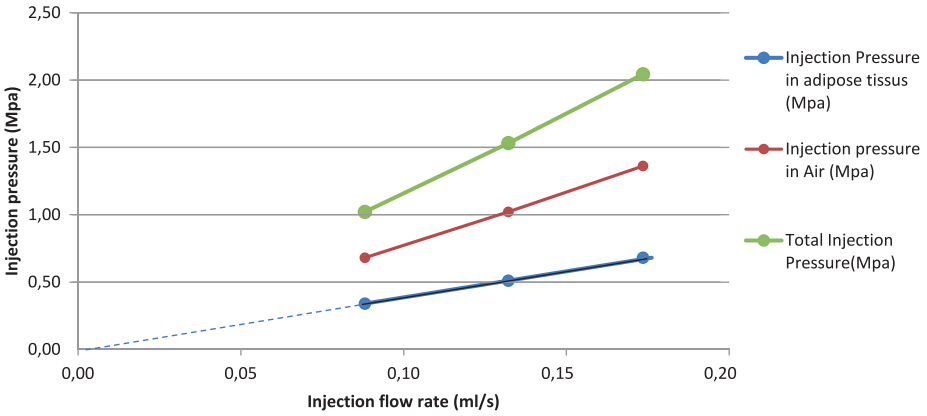

Figure 4: Injection forces measurements in air and in porcine adipose tissue.

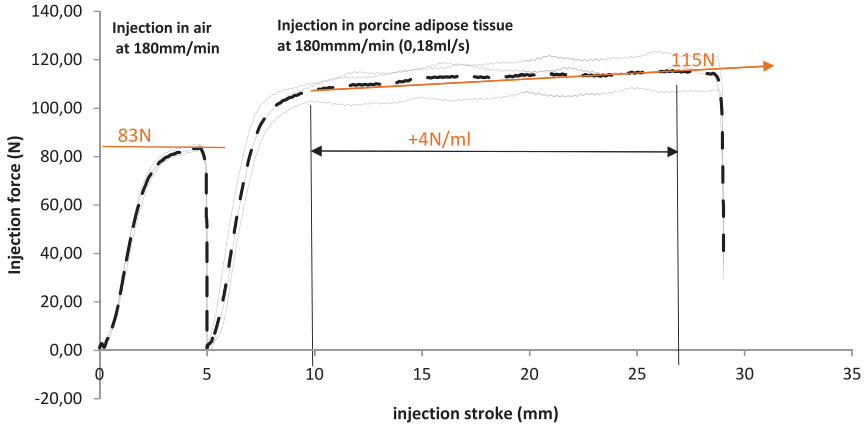

Figure 5: Relation between injection force measurements and dose volume in porcine adipose tissue.

auto-injector design at an early stage. Considering our example, with a 100 cP Newtonian liquid, 2.25 mL syringe with 25G needle and a 100 N spring force, the injection time in porcine adipose tissue is 10 seconds greater than injection in air (see Figure 6).

Increasing auto-injector energy could allow the dose to be delivered within the expected delivery time; but different studies have shown that the higher injection speed and dose volume limit dose absorption by the tissues and induce greater pain.

There are generally two critical times in the injection cycle: start of injection and end

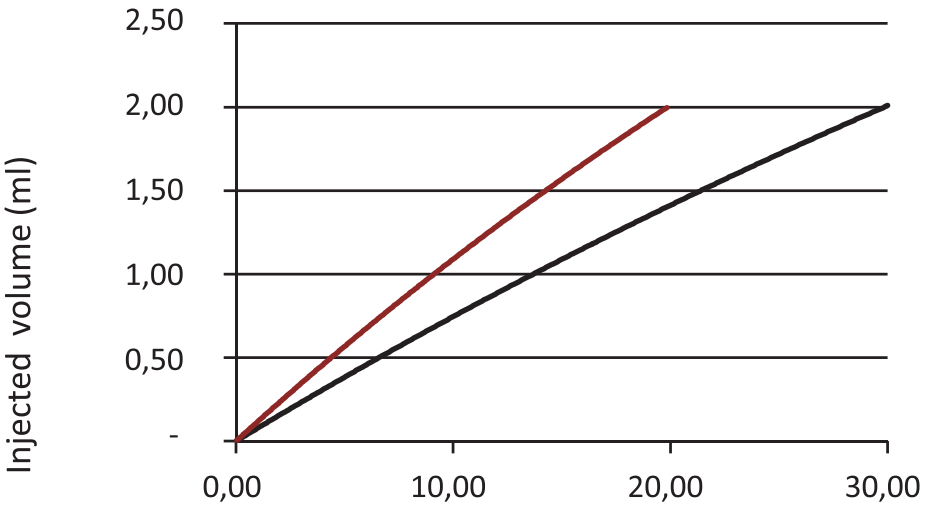

Figure 6: Injection time prediction in air and in porcine adipose tissue.

of injection. At start of injection, injection speed is at its maximum (maximum energy). Diminishing the initial injection speed will lower the injection force and could lower pain perception.

At end of injection, dose volume is at its maximum, whilst tissues are saturated. Diminishing end of injection speed will lower injection force, favouring drug absorption. The resulting pressure drop in the tissues could help also to reduce pain perception.

By design, the injection speed profile of Safelia® can be tailored to minimise injection forces. This injection force control should prevent the initial injection peak force, and allow a better drug absorption, and could lead to less pain perception.

New generation auto-injectors have to deliver highly viscous formulation, in larger volumes.

Injection should be painless, and comfortable for users. Controlling injection speed is a way to achieve less painful injections.

ABOUT NEMERA

More than five million diabetics rely everyday on parenteral devices manufactured by Nemera.

With more than 1,300 people and four plants across two continents, Nemera is a world leader in the design, development and manufacturing of drug delivery solutions for pharmaceutical, biotechnology & generics industries. Nemera's expertise covers several modes of delivery: Parenteral, Nasal, Buccal, Auricular, Ophthalmic, Pulmonary, Dermal and Transdermal.

Nemera leverages decades of manufacturing and development experience in the parenteral devices segment (passive safety devices auto-injectors, pens, and implanters), from full development to pure contract manufacturing, through customised solutions. Nemera applies the same quality-oriented process to the development of proprietary devices and to customised solutions under contract with laboratories.

ABOUT THE AUTHORS

Pascal Dugand, Technology Product Manager, Nemera, graduated as a polymer engineer from EAHP in Strasbourg, France. He holds a Masters in polymer mechanics and joined Plastic Omnium in 1990 where he started to work in development and innovation. In 2004, the medical division of Plastic Omnium was acquired by Rexam and more recently the four drug delivery devices plants, including the Innovation Centre, became Nemera. Today, Mr Dugand is an experienced medical device developer engineer specialised in the development of parenteral delivery devices. He developed for Nemera own IP products including Safe'n'Sound and Safelia auoinjector as well as working on several customer injectable product development projects.

Isabelle Delcroix holds an MSc in Neuropharmacology from Tokyo University, Japan. She is Strategy Director at Nemera and she is in charge of parenteral range of proprietary products including Safelia®, and the passive safety device, Safe'n'Sound, for prefilled syringes. Isabelle joined Nemera (previously named Rexam Healthcare Devices) nine years ago as Marketing Director for the Devices Business Unit. In her previous career she worked for AirLiquide Santé HomeCare Division and as a consultant specialised in strategy for innovation.

SAFELIA®: AN AWARD WINNING DEVICE PLATFORM

Nemera has already won two major industry awards for Safelia® in 2017.

In February, during the award ceremony at Pharmapack Europe in Paris, France, Safelia®, was celebrated as a best-in-class innovation displayed at the show for "Patient Centricity & Customisation".

In March, at the International Pharmaceutical Expo (INTERPHEX) in New York, NY, US, show organisers together with a team of industry experts selected Nemera as Winning Exhibitor and Editor's Choice, for its Safelia® device.

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READY-TO-USE COMPONENTS

Here, Joël Cotten, Business Development Director, Aptar Pharma, highlights the importance of sterile transfer in parenteral combination product manufacturing, and describes Aptar Pharma's portfolio of ready-to-use delivery device components that are suitable for gamma sterilisation.

"Ready-to-use elastomeric closure solutions present many advantages. One of the main benefits of ready-to-use solutions is to accelerate the time-to-market and delivery of the first industrial batch of final products."

We have observed a strong trend for turn-key solutions in the very conservative pharmaceutical manufacturing field. This trend affects not only the development of drugs with ready-to-use incubators but also fill-and-finish operations, with a large number of newly installed isolators using ready-to-use components. Likewise the trend affects not only legacy glass primary containers (such as vials, bottles, cartridges and prefilled syringes) but also plastic primary containers using ready-to-use sterile closures.

Ready-to-use elastomeric closure solutions present many advantages. One of the main benefits of ready-to-use solutions is to accelerate the time-to-market and delivery of the first industrial batch of final products. Indeed, most of the validation part has been done by the producer of ready-to-use components. Formulation of the elastomer, as well as the validation of the manufacturing operations, including the washing and the sterilisation of the components, are monitored and an access to the Drug Master File (DMF) in the US (or licenses in, for example, China) is established to facilitate registration of the combination drug and primary packaging later on.

Several billion ready-to-use components are produced each year. These components are packaged in a variety of bags (examples shown in Figure 1) that could accommodate the needs of R&D laboratories, medium-sized or large injectable drug producers.

Ready-to-use components have to be processed in a clean environment with a gentle process to ensure an ultra-low level of particle contamination.

Ready-to-use components are sterilised prior to shipping to the pharmaceutical industry. Many accepted sterilisation methods exist, like ethylene oxide (EtO) sterilisation, steam sterilisation or gamma radio-sterilisation. The latter offers the advantage of being performed in leak-free

"Aptar's RTU Gamma products are sterilised via radio sterilisation as this provides the highest level of sterility assurance. In addition, custom packaging has been designed to provide evidence of product integrity prior to its immediate use in sterile products manufacturing."

Joël Cotten
Business Development Director

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Figure 1: DPTE bags for the aseptic transfer of combination product components. (Image courtesy of Getinge La Calhène)

bags along with a controlled dose of gamma radiation, ensuring 100% sterility and a parametric release of the components.

Obviously each sterilisation method generates a slight stress on the components, and the compatibility of the final components with the drug itself has to be checked by the drug manufacturers. All of the methods are available on the market; steam is still the predominant method of sterilisation.

APTAR PHARMA'S GAMMA STERILISATION AND RTU

Aptar's RTU Gamma products are sterilised via radio sterilisation as this provides the highest level of sterility assurance. In addition, custom packaging has been designed to provide evidence of product integrity prior to its immediate use in sterile products manufacturing.

The large choice of plungers and stoppers available, in addition to the many packaging systems, ensures compatibility with most of the fill-and-finish line equipment that exists on the market, whether standard, restricted access barrier system (RABS) or isolator based.

The data and documentation supporting the RTU Gamma product facilitates its qualification and filing in conjunction with production line optimisation, new line installations and time-sensitive product developments. RTU Gamma is documented, validated and filed with key regulatory agencies to meet the highest quality, compliance and filing needs.

ABOUT THE COMPANY

Aptar Pharma is part of AptarGroup, Inc (NYSE: ATR) a leading global supplier of a broad range of innovative dispensing and sealing solutions for the beauty, personal care, home care, prescription drug, consumer health care, injectables, food and beverage markets. AptarGroup is headquartered in Crystal Lake, IL, US, with manufacturing facilities in North America, Europe, Asia and South America.

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YPSODOSE WEARABLE DEVICE FOR THE LARGE-VOLUME INJECTION OF BIOLOGICS

In this article Ian Thompson, Vice-President Business Development at Ypsomed, describes self-injection device trends for larger injection volumes and introduces YpsoDose, a new prefilled large-volume wearable injector being developed by Ypsomed Delivery Systems.

Worldwide, pharmaceutical companies are focusing on biologic therapeutics, many based on monoclonal antibodies. Due to their molecular characteristics they are usually administered parenterally and, when self-injected, subcutaneously. Injections are infrequent – typically weekly, biweekly or monthly and there is a demand for less frequent injections e.g. every two, three or six months. The trend to fewer injections, ranging from traditional peptides/hormones to antibody therapies, means that larger doses and thus larger injection volumes are required.

These larger volume injections are mainly being considered for treating autoimmune diseases such as rheumatoid arthritis, psoriasis and IBD/Crohn's, but also for new therapeutics such as the PCSK-9s recently launched for the treatment of hyperlipidaemia. Looking into the future the potential for new drugs for treating Alzheimer's, and immuno-oncology therapies to control already treated cancers, will further increase demand for larger volume infrequent self-injections.

> "There are a number of wearable device concepts available and in development covering a broad range of specifications... It is clear that there will be a range of devices required to cover different drug and patient needs."

TRADITIONAL 1 ML AUTOINJECTORS & NEW 2.25 ML AUTOINJECTORS

Since the introduction of prefilled syringe (PFS)-based disposable autoinjectors around a decade ago, the majority of devices have been based on the 1 mL-long PFS and there are now over 10 different devices on the market. For a number of years there was a general acceptance that 1 mL was the maximum volume that could comfortably be delivered by an autoinjector. With the increased need for higher payloads and following clinical testing this no longer holds true and the 2.25 mL PFS is now accepted as the standard primary container for injection volumes in the 1-2 mL range.

Based on the demand for less frequent injections, the interest in 2.25 mL prefilled syringe-based autoinjectors is growing significantly. The injections are often for slightly viscous drugs with injection times in the 10-15 second range.

Ypsomed is covering this demand with the YpsoMate 2.25, which serves patients with an easy and convenient two-step automatic injection. While the standard YpsoMate 1 mL version has been industrialised and is being customised for over 15 customers, the new YpsoMate 2.25 mL version has been adopted by first customers and is in development for clinical studies (Figure 1).

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Figure 1: YpsoMate® 1 mL and YpsoMate® 2.25 mL two-step customisable autoinjectors cover injection volumes up to 1 mL and 1-2 mL.

THE WEARABLE INJECTOR FOR VOLUMES ABOVE 2 ML

For volumes above 2 mL, which require longer injection times, there is a need for large-volume wearable injectors. This implies a disposable injection device that is worn and connected to the body with an infusion set or ideally attached directly to the skin with an integrated fluid path and needle system. Compared to an infusion pump, which performs drug infusions over hours or days, the large-volume wearable injector is intended to administer 2-10 mL or an even greater volume of drug typically within 2-15 minutes.

In the large-volume injector field there are a number of wearable device concepts available and in development covering a broad range of specifications including: prefilled but not assembled; fillable; prefilled and preassembled; mechanical; electromechanical; cartridge-based and collapsible container-based systems. It is clear that there will be a range of devices required to cover different drug and patient needs. Learning from both previously developed and current offerings, it is also clear that the key focus in the area of biologics is in the 2-10 mL injectable volume space requiring prefilled and preassembled, electromechanical, cartridge-based, connected wearable injectors.

> "Ypsomed has changed the rules in the market and accelerated customer projects by developing platforms, by engineering them, by patent protecting them and – this is key – also industrialising them."

AUTOINJECTOR OR WEARABLE INJECTOR?

For drugs with longer pharmacokinetic half-lives, pharma companies need to weigh up the pros and cons between more frequent injections from an autoinjector and less frequent injections from a wearable injector. Whether an autoinjector or wearable injector is selected for a particular therapy depends on a number of factors. Autoinjector technologies are established and proven and the prefilled syringe drug reservoir is typically also available for use by healthcare professionals (HCPs) or patients, in the form of a bare syringe or in combination with a safety syringe system. While an autoinjector typically contains a prefilled syringe, a skin-worn wearable injector requires a different drug reservoir – typically a cartridge, combined with a sterile fluid path and needle system.

Many more questions are being asked. For example, what is preferred by patients, four 10-second autoinjections per month or one 5-minute injection with a wearable device? Does a pharmaceutical company want to invest in a bespoke drug reservoir/fluid path system that can only be injected with the aid of a bespoke device? How much added value, convenience or differentiation does the wearable device add to the therapy regime compared with the autoinjector?

These questions can only be answered by extensive research into the way new therapies are provided to patients and a thorough understanding of patient preferences. But, it is clear that the wearable injector market will grow significantly over the coming years and establish itself as a third device class to complement the already well developed markets for pens and autoinjectors.

WEARABLE INJECTOR NEEDS

Ideally, a wearable injector should be as easy to use as a disposable autoinjector (or easier) based on less frequent injections, which means it must incorporate the following key technical features:

- Prefilled and fully disposable to remove any need to assemble the drug reservoir and device
- Easy adherence to the skin during injection; and easy to remove after injection
- Automatic insertion and retraction of the needle at the start and end of the injection process.

In order to be truly versatile, the device also needs to be able to deal with the following aspects:

- Recognise that the device is ready to inject when attached to the skin
- Cover a range of fill volumes and viscosities and provide a reproducible injection time per drug
- Communicate via audio and visual signals clearly with the patient before, during and after the injection
- Ideally, have a wireless connection to allow patient monitoring.

All of these requirements mean that the wearable injector is a significantly more complex device than a disposable

Figure 2: YpsoDose®, the prefilled, preassembled, electromechanical wearable injector for injection volumes in the 2-5 mL range.

autoinjector but, in cost terms, this may well be compensated by the lower number of devices required compared with an equivalent therapy provided by an autoinjector.

YPSODOSE WEARABLE INJECTOR DEVELOPMENT

The development and manufacture of a wearable injector system brings with it a number of challenges to fulfil the device needs described above. Ypsomed has a proven track record of working on complex injection devices with in-house engineering expertise, combined with a high level of technological integration for manufacturing pens, autoinjectors, pen needles, insulin pumps and infusion sets under clean and cleanroom conditions. All these competencies are key in developing the subsystems required by YpsoDose (Figure 2).

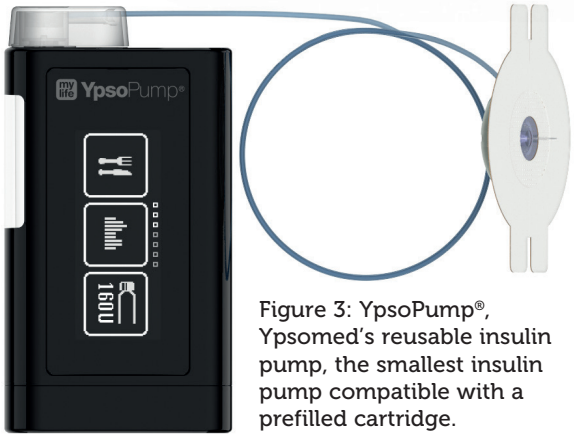

Figure 3: YpsoPump®, Ypsomed's reusable insulin pump, the smallest insulin pump compatible with a prefilled cartridge.

The subsystem development for YpsoDose focuses on the drug reservoir/fluid path, needle mechanism, drive mechanism, adhesive patch and electronic interface. With such a complex project the close proximity of development and manufacturing within the company and access to an existing supplier network in the heart of Europe help to simplify the development and industrialisation process.

Ypsomed has changed the rules in the market and accelerated customer projects by developing platforms, by engineering them, by patent protecting them and – this is key – also industrialising them. YpsoDose is no exception and the device is now moving from innovation into the realisation phase based on the following device features:

- Conventional cartridge technology for the primary drug container
- Proprietary integrated sterile needle unit and needle mechanism to complete the fluid path and insert the needle
- Low noise proprietary electromechanical drive programmable to accommodate different injection flow rates
- Electronics to provide patient feedback and connectivity
- A technical design that allows the pharma company or contract filler to easily assemble the device subassemblies with the drug cartridge.

CUSTOM PRODUCT APPROACH AND THE PATIENT JOURNEY

Implementing the Ypsomed Custom Product platform approach for the YpsoDose wearable injector is a clear aim of the project. This involves significant investment in resources and infrastructure for fully automated manufacturing of the needle unit under cleanroom conditions and assembly of the device subassemblies. Streamlining the device technology and manufacturing processes is important in order to achieve a scalable and cost-efficient device. At the same time, customers demand the ability to customise the device for different drugs and patient groups. This is why Ypsomed is investing heavily in modular product design and human factors engineering for multiple user groups.

There is a parallel between YpsoDose and the significant development and manufacturing investments that have been made for YpsoPump, Ypsomed's reusable insulin pump, the smallest insulin pump compatible with a prefilled cartridge (Figure 3). At half the size of existing pumps, with an intuitive icon-based touch screen, it is a prefilled solution that avoids cumbersome manual filling of insulin. This pump, weighing only 83 g, includes sophisticated electronics and has an integrated Bluetooth connection module.

For YpsoDose, the journey is at the realisation phase and the results of the most recent design studies were presented

at the recent PDA *Universe of Prefilled Syringes & Injection Devices* conference in Huntington Beach, CA, US, October 17-18, 2016. The dialogue with pharma customers is now intensifying as YpsoDose moves through the realisation phase towards the clinical phase.

ABOUT YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed is the leading independent developer and manufacturer of innovative autoinjector and pen injector systems for self-administration. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pens that include automated injection mechanisms and easy-to-use injection devices for drugs in dual-chamber cartridges such as lyophilised drugs. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio. Ypsomed provides its partners with excellent technological expertise and full regulatory support for the device-relevant aspects of the registration process.

The injection systems are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and current Good Manufacturing Practice (cGMP) guidelines with operational quality assurancce (QA/QC) experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are successfully inspected on a regular basis by both pharma customers and regulatory agencies (including FDA) and supply devices for global markets including US, Europe, Japan and China. Ypsomed has more than 30 years' experience and well-established working relationships with numerous leading pharma and biotech companies. Ypsomed Delivery Systems continues to focus on the development and manufacture of next generation pen, autoinjector, wearable and connected injector technologies.

ABOUT THE AUTHOR

Ian Thompson has been with Ypsomed AG, formerly Disetronic AG, since 1995 in a number of roles in key account management and business development working with pharma companies to develop and bring to market innovative self-injection systems.
He studied biochemistry and biotechnology in the UK from 1979-1983, working initially in commercial roles for fermentation technology. He has worked in medical device companies since moving to Switzerland in 1990.
Since 2003 his main focus has been business development and new product innovation leading to the successful development and launch of a range of new pen and autoinjector Custom Products for Ypsomed Delivery Systems.


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