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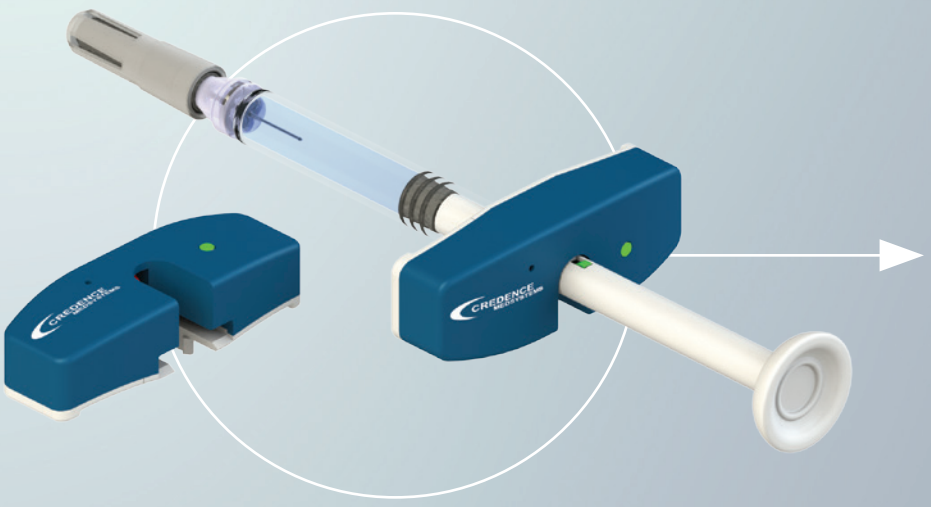

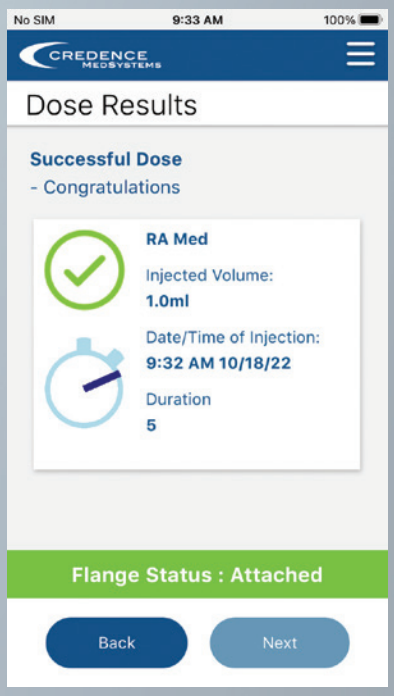

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ONdrugDelivery Issue N° 141, December 14th, 2022

CONNECTING DRUG DELIVERY

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

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Mar/Apr	Skin Drug Delivery: Dermal, Transdermal & Microneedles
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Dec/Jan	Skin Drug Delivery: Dermal, Transdermal & Microneedles

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2023 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
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OWEN MUMFORD
Pharmaceutical Services

AREAS TO WATCH IN CONNECTED DRUG DELIVERY DEVICE DEVELOPMENT

In this article, Michael Earl, Director, Pharmaceutical Services, at Owen Mumford, identifies areas of development in the field of connected drug delivery devices, providing an insight into what can be expected in the coming years. He draws on Owen Mumford's own research, as well as discussions with industry experts and counterparts.

The market for parenteral drug device combination products has evolved rapidly over the last 15-20 years. In particular, there is a growing focus on connected devices that enable capture of a variety of data relating to drug administration. These devices are already enabling remote patient monitoring, producing many benefits for the healthcare ecosystem, such as promoting treatment adherence. However, there remains a whole host of potential benefits that are not yet available, but that are likely to emerge as the industry continues to innovate.

FLEXIBLE, MODULAR PLATFORMS

With connected drug delivery devices evolving rapidly, there are now multiple configurations to choose from. The debate tends to revolve around single-use versus reusable devices, and integrated versus add-on connectivity. Although reusable drug delivery products are more desirable in terms of cost and environmental impact, decisions between single-use and reusable autoinjectors, for example, depend on the therapy regimen, target market and specific patient needs.

Regarding connectivity features, opinions on the optimal choice are continually changing with enhancements in wireless technology and the performance of electronic components. Likewise, as regulations evolve, the commercial arguments and trade-offs for pharmaceutical companies may shift, meaning they need to keep their options open. Geographical differences on the route to market, regulatory approvals and environmental standards should be factored in, as commercialisation strategies suitable for one area may not work in another.

As a result, pharmaceutical companies are looking for flexible drug device platforms that can be adapted to different markets, therapies, drug formulations and/or patient groups. Platform devices that have the option of added connectivity allow relevant stakeholders to make a choice flexibly based on preference, cost and reimbursement considerations whilst maintaining the essential device functionality. Adding connectivity to existing combination products is another option, where possible, and can extend product lifecycle and potentially patent life.

THE ISSUE OF INTEROPERABILITY

Currently, healthcare systems are lacking adequate data integration and interoperability – the ability of different information systems, devices and applications to connect and share data

"Currently, healthcare systems are lacking adequate data integration and interoperability."

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"New standards are needed to streamline communication protocols."

in a co-ordinated manner.[1] Data captured from connected devices are often siloed and not combined with other data sources, such as electronic patient health records. This makes it difficult for healthcare stakeholders to make decisions based on available data and access it in real time. As the focus on remote patient monitoring grows, tackling interoperability challenges becomes increasingly important.

New standards are needed to streamline communication protocols. One challenge is that healthcare systems themselves, and the way in which they approach data integration, vary significantly across the globe. In Europe, for instance, data is highly fragmented, with different privacy laws at national and regional levels, creating challenges for pharmaceutical companies wanting to launch connected products into multiple markets.

Limited data access and interoperability is also hindering healthcare providers' aspirations to create new services and business models based on data generated from connected devices. One example is the US, where payers are placing increasing emphasis on adherence monitoring to deliver improved patient outcomes and strengthen population heath.

A NEW PLACE FOR CONSUMER DEVICES

Meanwhile, there is a wealth of new data being captured by smart consumer devices, which could have interesting implications for drug delivery – and healthcare as a whole. Smart devices that are able to monitor both physiological data, such as blood pressure and heart rate, and broader "lifestyle" data, such as sleep and exercise patterns, could be harnessed to tailor treatment to a patient and their environment (Figure 1). For example, asthma patients could be advised to increase their daily dose of inhaled corticosteroid when in areas of high air pollution. Smart use of these devices helps to create populations more aware of their health.

THE CHANGING ROLE OF APPS

Smartphone apps play a central role in the connected device ecosystem as they provide both a means for data upload and a user interface for patients to track and manage their therapy. In the future, it is likely that there will be more stand-alone digital health apps as new payer regulations allow healthcare professionals to prescribe apps. For example, in Germany digital apps have been eligible for prescription via the statutory health insurance system since 2020.

However, advancements in technology mean the role of apps is changing. With the emergence of 5G and edge computing, future devices will be able to send data directly to the cloud without the need for a secondary app or device. Apps may still play a role, with cloud data transmitted back to the app, but will become secondary in importance. This real-time data transfer will make tracking and monitoring device usage even easier for users as they won't need to install an app and pair their device. Real-time updates may also give pharma companies a commercial and competitive advantage.

Figure 1: Smart consumer devices are able to capture a wealth of health and lifestyle data.

"An optimised user experience is critical to driving continued product use, which in turn supports better treatment adherence."

ENHANCED USER EXPERIENCE

An optimised user experience is critical to driving continued product use, which in turn supports better treatment adherence. With connected devices, patients can manage their condition while receiving immediate feedback to guide them through each step of using the device. Rather than manually recording data themselves, they can effortlessly capture key information such as injection date and time, dose and injection site through automated features. In addition, notifications can help remind patients when their next dose is due, as well as alert them to missed doses.

However, to reassure patients worried about data privacy and security, and to prevent unauthorised use, manufacturers may consider adding medication and user authentication. There needs to be a balance though; multiple authentication steps can increase the difficulty of setting up devices and discourage adoption for those patients who are less familiar with the technology.

Patient feedback is another area where balance is required. While some feedback can be useful and reassuring for patients, it can also add complexity if the device is difficult to navigate ergonomically or cognitively. As it is, a significant proportion of the older, less tech-savvy population may struggle to embrace connected products. Direct-to-cloud solutions, as described above, can limit the amount of user interaction needed during the set-up stage and help to solve this issue.

IMPROVED TRAINING AND SUPPORT

The rise in self-administration means the delivery device itself has a greater role in supporting the patient through the injection process. To ensure patients properly understand how to use their products, manufacturers are increasingly deploying training devices. With options of added enhanced sensors and data capture, they can offer more specific guidance to patients who are using a new device or beginning a treatment for the first time.

Sensory feedback from devices can confirm that they are being handled and used correctly. For instance, visual feedback can help patients to rotate their injection sites, and audible clicks or beeps can indicate the beginning and end of a dose and guide patients on device hold times. These features are especially important as pharmaceutical companies continue to innovate with drug formulations.

Some newer drugs come in larger volumes, extending injection time but allowing a reduction in frequency. In some instances, treatment only needs to be administered biannually or quarterly. One example of this is Skyrizi (risankizumab-rzaa – Abbvie, IL, US),[2] which is used for the treatment of plaque psoriasis, psoriatic arthritis and Crohn's disease. Intuitive products facilitate administration even after long periods.

DATA TO IMPROVE DEVICES

Finally, data from connected devices can be used to enhance the performance of the device itself. Prior to product launch, data about how patients are holding a device and the amount of force or pressure applied during injection can be gathered during clinical trials. This data is invaluable for human factors studies and, with usability regulations becoming ever stricter, it can be used to prove devices are being used as intended during testing and that any user risks have been adequately addressed. Following product launch, new data can allow pharmaceutical companies to track complaints and concerns, and determine their root causes. They can then relay this information to the device manufacturers, enabling ongoing improvement of the product.

> "Data from connected devices can be used to enhance the performance of the device itself."

A THOUGHTFUL APPROACH

The development of connected drug delivery devices holds great potential and new developments are constantly in the pipeline. However, introducing connectivity is a complex issue as digital tools need to be cost effective and user centric, as well as needing to provide real value. Some challenges, such as the need to streamline data capture and storage, may need the involvement of multiple players. Connectivity strategies therefore need to be approached thoughtfully and holistically. Many potential benefits are on offer. Intelligent digital solutions can provide a differentiating factor for pharma companies, improve the patient experience, assist clinicians in their daily work and help payers to reduce healthcare costs.

ABOUT THE COMPANY

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

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ABOUT THE AUTHOR

Michael Earl joined Owen Mumford as Director of Pharmaceutical Services in November 2020. He was previously the Commercial Vice-President at Bespak (now part of Recipharm), leading the commercial team there to drive growth in their substantial medical devices business. Prior to that, he worked for a number of pharma, biotech and device companies. In a career spanning more than 35 years, Mr Earl has been responsible for all aspects and stages of drug and device development and commercialisation. He has also completed a substantial number of commercial, licensing and mergers and acquisitions transactions.

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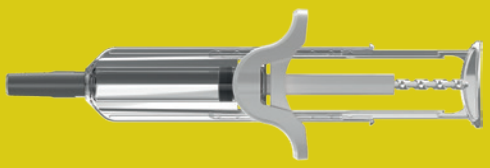

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DESIGNING EFFECTIVE AND ENGAGING DIGITAL SOLUTIONS TO DRIVE ADHERENCE

In this article, Florian Krummenacher, Therapy Management Lead, and Philippe Müller, Digital Health Solutions Manager, both at Ypsomed, discuss the effectiveness of combining connected injection devices with digital solutions to drive therapy outcomes.

Laura sits at home in the heat of summer. Her friends are at the local pool, but Laura has not joined them today. In fact, she hasn't joined them all summer. Her skin itches and her rashes are visible; this makes her feel ashamed and she doesn't want anyone to see it. All the while, the anti-inflammatory injectable drug she was prescribed to treat her condition sits unused in her fridge. Laura doesn't like to inject herself and doesn't even want to think about having to do it. She knows that the medication will probably help, and that not taking her medication will only make things worse, but she can't help it. Her fear and hesitancy take over and dictate her inaction.

While a fictitious example, this situation is all too often the reality for people living with chronic skin diseases such as atopic dermatitis (AD) and psoriasis. AD is a chronic inflammatory skin disease that affects about one in every ten people worldwide and up to one in five children.[1] It is thought to be caused by a combination of genetic and environmental factors, causing the immune system to overreact, leaving the skin dry and prone to rashes. While the disease typically begins in early childhood, it can become a lifelong burden with flare-ups well into adulthood. The condition can be highly distressing for sufferers and is often stigmatised. It can also have a significant negative impact on day-to-day life, both personal and professional, as sufferers may find it difficult to wear certain clothing and are often affected by itching, which can lead to insomnia, anxiety and depression.[2]

> "Adherence to treatment regimens can be a challenge for AD patients."

NEED FOR A MULTIFACETED APPROACH

Depending on the severity of the disease, the current standard of care may range from behavioural changes to tailored medication. The latter includes both topical steroids and biologics, such as anti-inflammatory drugs, which are often injected subcutaneously by the patients themselves. Besides medication, lifestyle choices can have a big impact on the severity of symptoms and disease progression, affecting the patient's experience. Avoiding certain situations that might trigger a flare-up of the disease is one of the measures that can help to manage the disease. Ensuring that the skin is appropriately hydrated can also help to reduce symptoms. Eating a healthy diet, limiting stress and maintaining good sleep hygiene are other important factors.

As with many chronic conditions, adherence to treatment regimens can be a challenge for patients, who can often feel isolated and unsupported in their disease journey. The reasons for these feelings are often varied, as outlined in the example above, and this can have an adverse effect on the patient's health outcomes.[3]

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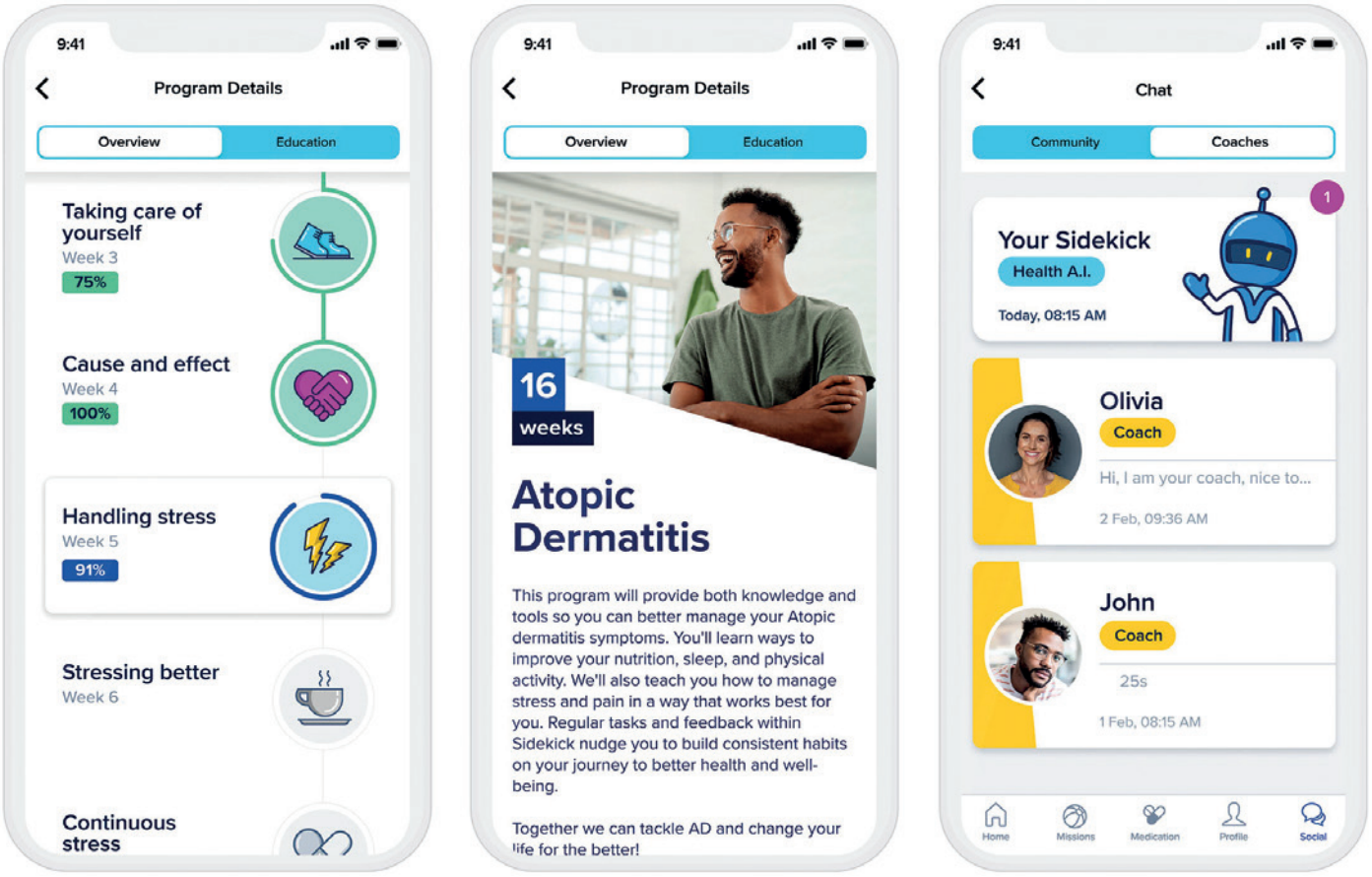

Figure 1: The Sidekick app offers comprehensive support for AD patients.

Injection device manufacturer Ypsomed supports patients by making self-medication with injectable biologics as simple as possible using pens and autoinjectors. To better embed self-injection in broader therapy management, Ypsomed has joined forces with digital therapeutics developer Sidekick Health (Reykjavík, Iceland). The two companies are jointly developing a module on self-injection that will be part of Sidekick's existing digital therapeutics platform, which is already available for AD patients in several countries, including the UK, Belgium and Finland (Figure 1).

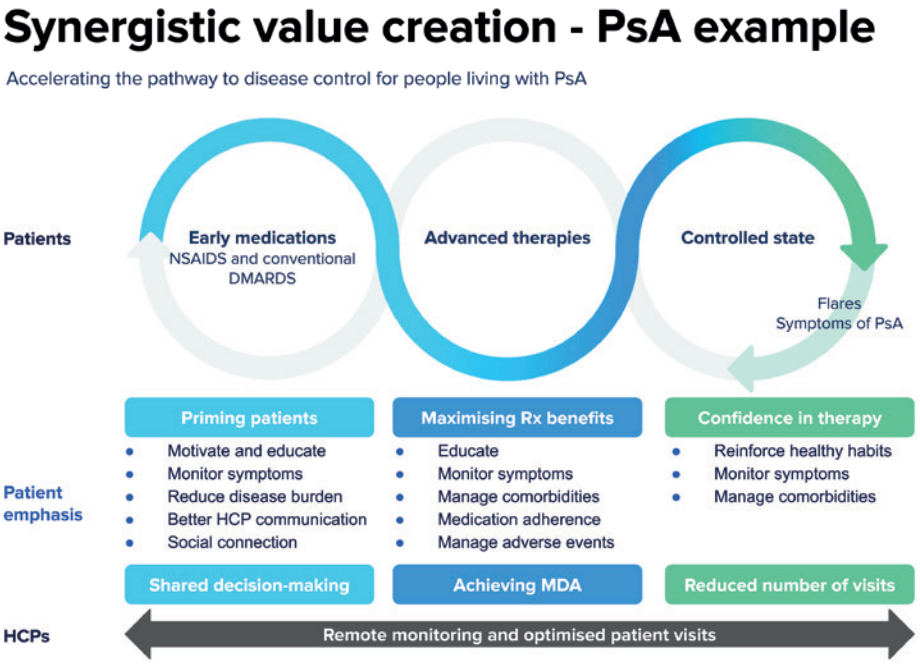

Figure 2: The patient journey for psoriatic arthritis (PsA) patients.

EFFICACY OF A DIGITAL SOLUTION

Living with AD and managing the therapy is a complex challenge and requires a lot of active engagement, know-how and resilience from patients. Digital solutions that complement the pharmaceutical drug have shown to provide significant value to patients, caregivers and healthcare professionals by improving medication adherence, quality of life and therapy outcomes. There are several modes of action for a digital therapeutics solution – for example, using neurobehavioural techniques to improve patients' self-management capabilities, personalised disease-specific knowledge, simplifying treatment scheduling and management of symptoms and side effects, tracking medication intakes and supporting the adoption of a healthier lifestyle (Figure 2).

In a recently published study in the Dermatology and Therapy Journal, Sidekick evaluated the clinical efficacy of its digital therapeutics programme in patients with AD. For patients enrolled in the six-week digital programme, it reported an average reduction in AD severity of 46%, higher medication adherence and improved quality of life.[4] The programme included the following key functionalities provided to

> "A key success factor of the app lies in its ability to be personalised to the individual patient."

the users as support tools or missions – patient education, medication reminders, symptom tracking, stress reduction and sleep improvement to overall facilitate behaviour change toward self-efficacy.

Besides the improvements in therapy outcomes, Sidekick found strong engagement and retention results in the study. Patient retention to the digital therapeutics programme was 95.3% at completion of the six-week study, with a user engagement rate of 6.5 days per week and an average of 8.9 missions completed per day. According to the clinicians, a key success factor of the app lies in its ability to be personalised to the individual patient, and having a holistic approach to therapy management beyond medication intake by considering the psychological and lifestyle factors that strongly influence the condition. Overall, the study findings showed that digital solutions can significantly improve adherence and therapy outcomes for patients with AD through interventions to promote behavioural modifications toward higher disease awareness, treatment adherence and self-efficacy.[4]

HOW DIGITAL SOLUTIONS CAN DRIVE ADHERENCE FOR SELF-INJECTION THERAPIES

For patients prescribed an injectable drug for at-home treatment, device and injection training, management of injection-related stress and the establishment of an injection routine are key factors for successful treatment initiation and continuation. Most patients are left to execute their medication-taking schedule on their own. Additionally, some patients may also experience anxiety around self-injection and express concerns around spillage, pain or fear of needles.[5]

To address these challenges, digital therapy management applications for self-injection therapies should include an injection-specific experience, including features that purposefully engage with these challenges. By including important information about device characteristics, instructions for use, educational content and coaching about self-injections and self-management, a digital injection module can provide great support to the user in their ability to self-inject and manage their treatment journey. The following sections describe in more detail selected use cases of the digital injection module being developed by Sidekick and Ypsomed.

Injection Training and Coaching

During the treatment initiation phase, patients require self-injection training to be confident in the use of their injection device to overcome any concerns regarding the safe delivery of the drug. However, in practice, many patients report a lack of injection training and onboarding to the device.[6] Video-based injection training embedded into the therapy management application, in addition to a demonstration by a nurse, has shown to be effective and appreciated by patients.[5] Combining this with a connected injection device that provides follow-up guidance can further enhance the patient experience.

Accordingly, educational materials in video format, interactive images, text or quizzes around how to prepare for the injection, the injection process itself and management of injection site reactions are key elements of a digital injection module with the aim of reducing use errors and early therapy drop-offs and improving adherence. To optimise the benefits to the patient and cover individual needs and questions, digital tools should be complemented with human coaching. In this way, the patient can get the best of both worlds. Many questions and challenges will be covered by the digital educational materials, allowing the human coaches to support many more patients than without a digital injection module.

> "Management of injection-related stress and the establishment of an injection routine are key factors for successful treatment initiation and continuation."

Reminders and Habit Building

Many patients prescribed an injectable drug suffer from comorbidities, which makes therapy management even more complex and challenging. Accordingly, a digital therapeutic should be capable of personalisation to the individual patient's experience and cover several comorbidities within the same application. Easily configurable reminders and tips on how to set up an injection routine are helpful tools to manage the treatment schedule.

In addition, the integration with connected injection devices allows automatic tracking

of injections and summarises them in a medication logbook within the app. First, this simplifies users' lives as it takes away the cumbersome task of logging injections manually. Second, studies have shown that tracking medication intake has a significant effect on medication adherence.[7] Showing progress, tracking flares and providing treatment goals powered by altruistic rewards can increase users' motivation and engagement. Over time, establishing an injection routine can further simplify the injection journey by significantly reducing the cognitive effort required by the patient to plan and perform the injections.

Management of Injection-Related Stress and Anxiety

Another key area where a digital injection support module can provide significant value to the patient is the management of injection-related stress and anxiety. Despite the advantages in convenience and usability, at-home administration undeniably places a significant burden of responsibility on patients. Accordingly, there is a range of emotional aspects related to self-injection, such as concerns about incorrect technique, anxiety from needles and pain, lack of self-confidence and frustration with illness and treatment.[8]

A digital injection module can address these challenges by providing useful stress management and relaxation techniques before and after injections. Sidekick's digital health platform is designed to address these factors through cognitive-behavioural tasks that promote stress management and thought restructuring. In addition, patients are educated in dealing with negative feelings and stigma and are given the tools to cope with their condition. Last but not least, personal rituals before and/or after self-injection have been shown to be effective measures to reduce the cognitive load and injection-related anxiety.[8]

SUMMARY AND CONCLUSION

Living with a chronic disease, such as AD, poses a huge burden on a patient's life. Adherence to treatment, as well as adjusting habits, are of great importance. Using a digital application to support this and complement the medication-based treatment has proven to be effective, as Sidekick Health has shown in a recent study.

Self-medication for diseases like AD offers great advantages to patients and the healthcare system at large. However, there are also several challenges associated with it, from adherence issues to the lack of support patients receive. Together with Sidekick, Ypsomed aims to resolve these challenges by offering a digital module supporting self-injection within Sidekick's existing product. Combining connected injection devices with digital solutions is seen as an effective way to drive therapy outcomes (Figure 3).

Figure 3: Ypsomed's connected devices and therapy management solution with Sidekick.

> "Combining connected injection devices with digital solutions is seen as an effective way to drive therapy outcomes."

Combining digital and device solutions is set to be a winning formula to deliver substantial value for the pharmaceutical industry, patients and the entire healthcare system.

ABOUT THE COMPANY

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

With over 35 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases and integrating these insights with digital therapy management ecosystems.

The company leverages its in-house capabilities in electronics, software and connectivity for the development of new devices and digital product systems. Ypsomed is ISO 13485 certified and all its processes comply with design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's FDA-registered manufacturing facilities are regularly inspected by pharma

customers and regulatory agencies to supply devices for global markets, including the US, Europe, Japan, China and India.

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Florian Krummenacher leads Ypsomed Delivery Systems' digital therapy management efforts, driving the company's transformation to become a provider of integrated healthcare services. Prior to his current role, Mr Krummenacher worked at a large pharmaceutical company in several different positions, most recently within a global product strategy organisation working on digital tools for patients and healthcare providers. His background is in business administration and finance, and he holds an MA from the University of St Gallen (Switzerland).

Philippe Müller is a Digital Health Solutions Manager at Ypsomed Delivery Systems. He leads the development of new digital therapy management solutions and works closely with the company's partners in the digital health industry. Prior to his current role, Mr Müller was actively involved in the design and development of YpsoMate On – Ypsomed's prefilled connected autoinjector. He holds an MSc in Applied Economic Analysis from the University of Bern (Switzerland).

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DIGITAL HEALTH: ADDRESSING MODERN HEALTHCARE CHALLENGES WITH SENSORS

In this article, Haykel Ben Jamaa, PhD, Key Account Manager Medical at Sensirion, explores why modern society needs digital health and how it is organised and implemented, with a focus on sensing technologies empowering digital health technologies.

Digital technology is playing an increasingly critical role in modern healthcare. As society faces new healthcare challenges – including a rise in chronic diseases and an ageing population – public health services will increasingly benefit from the growing role of digital technology. The WHO defines digital health as "the field of knowledge and practice associated with the development and use of digital technologies to improve health".[1] The term has far-reaching implications and encapsulates a wide range of digital technologies, from software solutions, which enable better management of patient data and provide easier access to patient support services, to new diagnostic tools and smart drug delivery devices.

ARE MODERN HEALTH CHALLENGES A DRIVER FOR DIGITAL HEALTH?

Globally, healthcare providers are dealing with an increase in the incidence of noncommunicable diseases, such as cardiovascular diseases, cancers, diabetes and chronic respiratory diseases – primarily chronic obstructive pulmonary disease (COPD) and asthma. On the one hand, this is a result of a reduced number of deaths from infectious diseases, such as tuberculosis. Nevertheless, as noted by the WHO, noncommunicable diseases pose devastating health consequences and socioeconomic effects, which make their control a major challenge that needs to be addressed.[2]

The occurrence of such diseases is increasing in line with the world's ageing population. As birth rates decline and healthcare improves in many regions, the WHO estimates that the proportion of the world's population over the age of 60 will almost double by 2050. Dealing with the healthcare consequences of the ageing population requires health, activity and medication monitoring. Hospital stays are costly and increase the risk of infections, so drug delivery in a homecare setting, perhaps with remote monitoring, is expected to reduce healthcare costs and improve outcomes.[3]

> "Dealing with the healthcare consequences of the ageing population requires health, activity and medication monitoring."

At the same time, environmental conditions are also amplifying the incidence of some of these diseases. The increase of ultrafine particles in the air due to urban traffic, industrial processes, pollution and the increasing frequency of wildfires are worsening environmental conditions for patients with asthma and COPD, as well as being linked to increased rates of diseases such as cancer and even dementia.

Digital health plays a vital role in helping healthcare systems evolve to meet these challenges. Digital health already plays an undeniable role in modern healthcare, from online appointment booking through continuous glucose monitors to digitising patient records. Many of these provisions – such as virtual platforms and video call appointments – were expedited by the response to the covid-19 pandemic, as necessity pushed through years' worth of reforms in the space of just a few months.[4] Following this recent push, the

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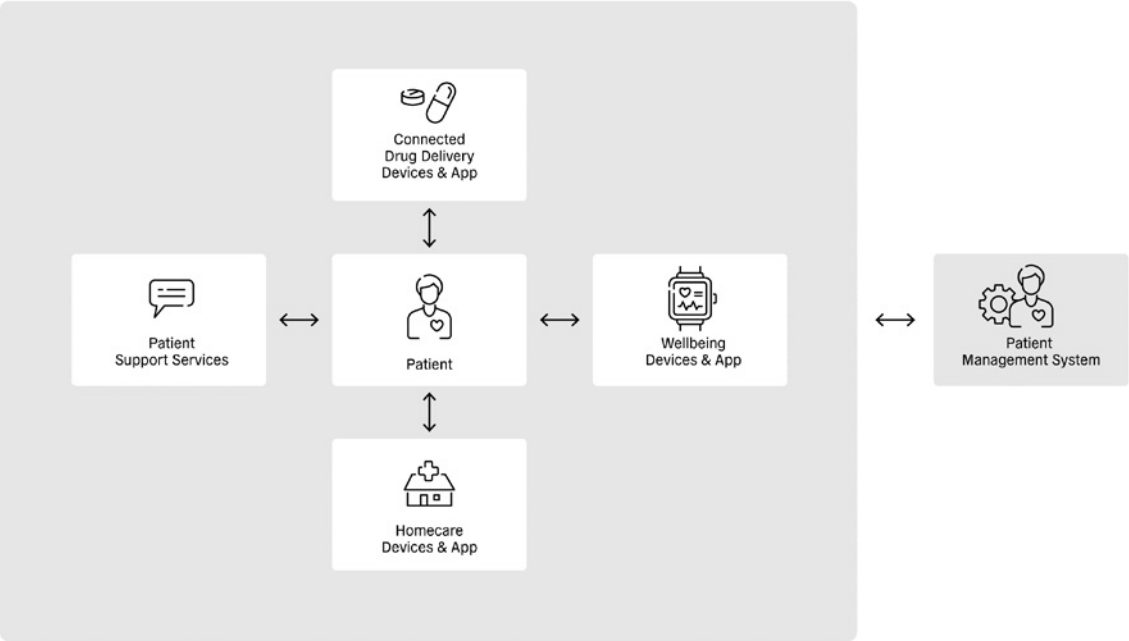

Figure 1: Relationship between the patient, different healthcare apps, patient support services and the patient management system.

infrastructure of digital health is now being defined and consolidated by governments, healthcare providers and industrial partners.

HOW IS DIGITAL HEALTH ORGANISED AND IMPLEMENTED?

"Digital health" is a broad, all-encompassing term for the application of digital technology to healthcare. Organisation of healthcare services, such as real-time digital patient data management, medical act management and billing tools, is one of the key ways in which digital health is currently implemented. However, digital health means more than just this.

Arising applications of digital health include new types of medical devices, such as smart injection devices, that implement new monitoring and diagnostic functions. These medical devices are used in direct proximity to the patient, often as wearable or hand-held devices, such as insulin pumps or smart inhalers, respectively. Moreover, new consumer wellbeing devices, such as smart watches, sleep monitors and breath analysers, provide the public with additional health-related information.

At the patient level, digital health enables health-related information to be shared directly between the patient and connected drug delivery devices, wellbeing devices, homecare devices and patient support services (Figure 1). In turn, these devices, services and apps can transfer patient information to service providers, where it can be stored and analysed. Sharing this information with healthcare providers enables diagnoses, treatments and disease-management procedures to be assessed, which can, in turn, be relayed to patient management systems and shared with payors (Figure 2).

The increased availability of health-related patient data can play an important role in drug development, enabling the realisation of personalised therapies or drugs on a large and practical scale. Moving further along the healthcare value chain, connected medical devices make it easier for patients and caregivers to monitor healthcare and manage the therapies.

Furthermore, clinical trials and research studies have highlighted the potential of digital health technologies to reduce non-

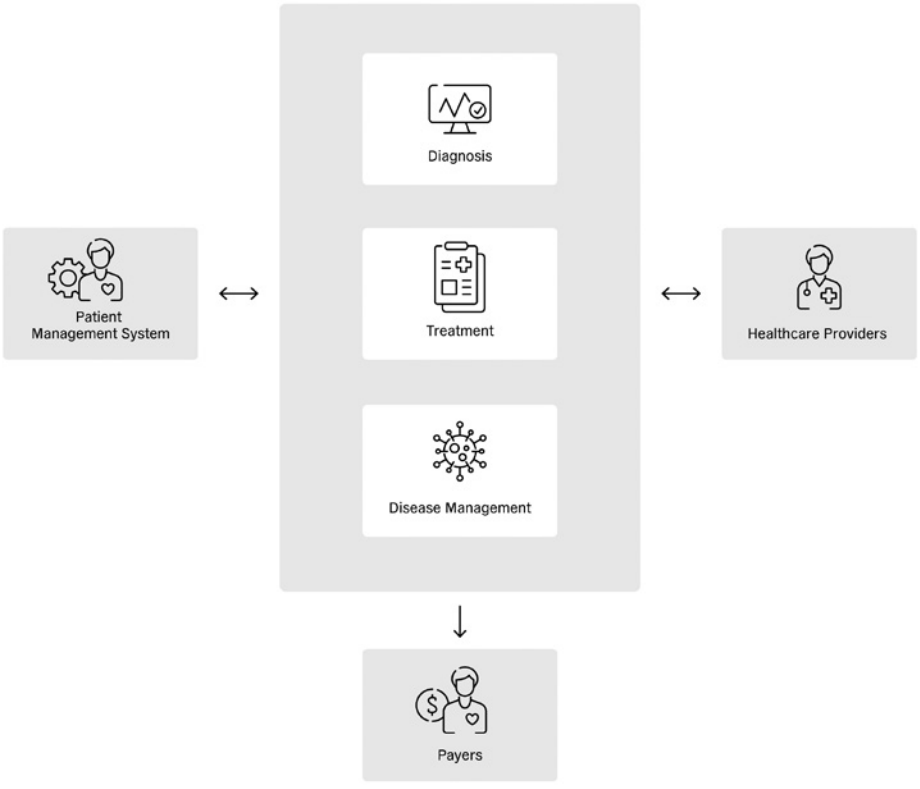

Figure 2: Reciprocal influence between patient management system, therapy and healthcare providers.

adherence.[5] Non-adherence to asthma treatment is a major issue that causes disease exacerbation, hospitalisations and high financial costs. However, patients using the next generation of smart inhalers can monitor the quality of their inhalation, obtain feedback on the drug delivery efficiency and even on the course of the disease. The adherence of these patients could be significantly improved, leading to improved outcomes and lower healthcare costs.

Given the high value for the patient, partnerships are forming between pharma companies and technology companies around the world, resulting in the development of a spectrum of new drug delivery devices.[6] For example, GSK recently partnered with Propeller Health (WI, US) to develop a digital inhaler and AstraZeneca has partnered with Adherium (CA, US) to bring an adherence monitor to market to support AstraZeneca's Turbuhaler (budesonide and formoterol) medication.[7,8]

The implementation of digital health is also being supported by governments. New legislation, such as the DiGA in Germany and Article 51 in France, is laying the foundation for digital health by supporting new care pathways, such as the prescription of digital health apps by healthcare professionals.[9,10] The extended definition of remote patient monitoring in the US with additional Current Procedural Terminology codes since 2022 is also further advancing the use of connected devices.[11] These devices enable monitoring of non-physiological information to help assess patient adherence to a prescribed therapy, such as by determining whether patients are following their care regimen and how effectively the therapy is working. This can help identify the likelihood of potential failures of patient adherence and enable healthcare providers to make the appropriate adjustments.

The successful implementation of new digital health technologies, such as connected drug delivery systems and smart inhalers, relies not only on software solutions but also on developing new measurement and feedback solutions. Such new solutions are most powerful if they can interact with the patient by collecting data, analysing it and providing feedback to the patient and their healthcare provider. This is where the right sensors provide a strong value proposition by collecting usage, safety and diagnostic data.

> "Choosing an optimal sensor solution can be challenging from a design perspective, as it must fulfil its intended function and seamlessly integrate into the patient's user experience."

SENSING SOLUTIONS – WHAT ARE THE BENEFITS FOR THE PATIENT?

The nature of the interaction between a patient and a connected device comes down to the sensor. Choosing an optimal sensor solution can be challenging from a design perspective, as it must fulfil its intended function and seamlessly integrate into the patient's user experience. On its path towards digital health, Sensirion has thus far developed multiple different sensing technologies. In the following sections, this article will focus on three of them.

Airflow Sensing

Smart inhaler add-ons are medical devices that bring additional functionality to regular inhalers by gathering information about inhaler usage. This information can easily be transmitted to a smartphone app and provide patients and healthcare providers with insights into inhaler usage. This information can contain details on the patient's adherence to their therapy and how the inhaler is being used, such as exhaled volume, inhaled volume and a detailed inhalation flow profile containing inhaled flow rate over time, including the timing of inhaler actuation.

This feedback can allow a healthcare professional to recognise patients who adhere poorly to their therapy, or who urgently require additional training on correct inhaler use. The significance of non-adherence is highlighted by countless studies. For example, one study on *in vitro* lung deposition reported that patients make at least one mistake when using an inhaler as often as 70%–90% of the time, resulting in only 7%–40% of the full dose being delivered to the lung.[12] Providing feedback to patients that they are using their inhaler correctly can be motivational and affirmative. Additionally, it can ease the worried minds of parents about whether or not their children are getting the correct dose delivered to the lungs.

Recording physiological data with every use of the inhaler and without interfering with the patient's user experience is a powerful tool – recent studies have demonstrated that data relating to peak inspiratory flow or inhaled volume already provide an information base for assessing the course of the disease, enabling healthcare providers to improve its control and prevent exacerbations and hospitalisations.[13] Gathering accurate physiological data on every inhalation will help to unlock many more insights and generally improve inhaler-based therapies in the future.

Airflow sensors are an essential part of smart inhalers. Sensirion's SDP3x line of differential pressure sensors is optimised for airflow sensing in smart inhalers, allowing for sensitive and accurate measurement of airflow rates while offering other benefits for healthcare applications:

- Immediate feedback on the inhalation procedure due to direct and fast measurement.
- Meaningful feedback and improved patient confidence by accurate inhalation-to-inhalation and breath-profile comparisons, enabled by high accuracy and time resolution.
- Monitoring of the course of the disease over time to help predict and prevent exacerbations by measuring lung function parameters from the recorded breath profiles.
- Seamless user experience by allowing small form factors due to the small size of the sensor and the low power consumption of its coin cell battery.
- Robust and unsusceptible to environmental conditions and user errors due to the two-port design and use of a coin cell battery.
- Enables breath-triggered drug release by providing fast response time and high sensitivity for even the smallest airflows.

Drug-Flow Sensing

Large-volume injectors (LVI) – also known as on-body delivery systems, patch pumps or wearable drug delivery devices – have been replacing conventional intravenous infusion for the delivery of large-volume doses of injectable drugs.[14] These enable patients to receive precisely controlled drug dosages automatically, continuously and with minimal disruption to their day-to-day lives.

"Red biotechnology" approaches use biological materials, such as proteins and large molecules, to treat disease targets more effectively than existing pharmaceuticals and with fewer side effects. Typically, these therapeutics are expensive, viscous and highly concentrated formulations, often requiring lyophilisation and reconstitution prior to use. This means that they generally cannot be administered orally, instead requiring subcutaneous or intravenous administration in volumes of up to 50 mL. LVIs provide a simple, versatile platform for the administration of these emerging therapeutics.

In addition, LVIs have the potential to play a vital role in the delivery of precision medicine for predictive, preventative, personalised and participatory patient care. With prices and reimbursement levels based on evidence-based criteria, such therapies will likely depend on proof of patient compliance. LVIs provide a straightforward and measurable approach to ensuring adherence, thus maximising the efficacy of personalised therapies.

Controlling the drug flow rate and closely monitoring for failures is critical in automatic drug delivery systems. Sensirion's LD20 liquid flow platform of single-use flow rate sensors offers a dedicated solution for LVIs:

- Precise measurement of the delivered drug with high accuracy is essential when a precise dosage is critical, such as with specific painkillers or chemotherapy drugs. It is also desirable with expensive, viscous or highly concentrated formulations. Accurately measuring drug flow with the LD20 technology platform enables a reliable assessment of the remaining drug inside the cartridge and can become more important as prices and reimbursement levels start to be determined by evidence-based criteria, such as proof of correct drug delivery and patient compliance.
- Detection of failure mechanisms, such as open flow and occlusion, is another valuable feature. For example, occlusion may occur for various reasons, such as tissue growth or clotting of the cannula outlet. In some cases, the patient may make a mistake with assembly of the LVI or the reconstitution of the drug, leading to an open flow condition. The remote detection of such failures assists the patient, maximises the benefits of the therapy and helps save costs by enabling remote drug administration.

> "In future, digital health will also empower patients to monitor their health from their own homes, administer their drugs without a healthcare provider present and obtain feedback on drug delivery and the course of their disease."

- Flow range, size and interfaces are adjustable for very compact integration into the LVI due to the modularity of the LD20 technology platform. This is an essential feature to enable versatility for the drug delivery system so that it can be optimally configured to the drug type, concentration and viscosity while keeping it as compact as possible.
- Sensor compatibility with different drugs is essential, enabling the use of a single device platform for different drugs and for the reconstitution of lyophilised drugs. This feature is enabled by Sensirion's in-house sensor calibration for one or more drugs, taking their different viscosities and properties into account.

Breath Analysis

Breath analysis provides a non-invasive insight into the human body, allowing for fast, pain-free and low-cost diagnostics. Today this mainly covers gases, such as CO_2, O_2 and NO. Sensirion's STC31 platform allows for the measurement of CO_2 concentration in human breath, enabling entirely new applications with its low-cost technology structure, in contrast to the optical sensors that are often used in capnography applications, which are often in the lower four-digit price range. Applications in both the medical and consumer sectors can offer value to the user by providing measurement-based insight into their metabolism or fitness. The STC31 is:

- Compact and easy to fit into handheld or wearable medical devices, allowing for discrete and portable products that can be used in all environments, such as at home, outdoors or in the gym.
- A highly robust and reliable sensing solution, as there are no moving parts or sensitive optics involved.
- Manufactured without any complex assembly or alignment, further helping to save on cost and reduce form factor.
- New applications and use cases in compact and discrete portable devices that only require small batteries and allow for longer run times without the need for charging.

CONCLUSION

The 21st century has brought a number of completely new healthcare challenges – increasing numbers of chronic diseases, including cancer, COPD, asthma and diabetes; an ageing population; and broad changes to both the environment and lifestyle that amplify the occurrence, consequences and cost of such diseases. Digital health infrastructure has recently received a major push to address the healthcare challenges, automating the sharing of patient data, accessing sites of care and simplifying the payment flow.

In future, digital health will also empower patients to monitor their health from their own homes, administer their drugs without a healthcare provider present and obtain feedback on drug delivery and the course of their disease. Such functions will be implemented and enabled by portable, wearable and interactive devices that use sensors to monitor the patient. Sensirion is actively supporting this developing ecosystem with sensors built to address these needs, measuring patient airflow, drug flow and breath CO_2 levels. As this journey has only just begun, Sensirion is working to improve and expand the technologies and sensors available to digital health technologies.

ABOUT THE COMPANY

Sensirion is one of the world's leading developers and manufacturers of sensors and sensor solutions that improve efficiency, health, safety and comfort. Founded in 1998, the company now employs over 1,000 people at their headquarters in Stäfa, Switzerland, and in numerous international subsidiaries. Sensirion supplies globally operating customers with off-the-shelf and customised sensor solutions for a wide range of applications. In the medical field, the company's temperature, humidity, liquid flow, gas flow and gas concentration sensors enable safe and reliable devices for medical ventilation, anaesthesia,

drug delivery, diagnostics and digital health applications. Sensirion's aim is to make the world smarter with pioneering sensor technology.

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ADVANCEMENTS IN MONITORING ADHERENCE – A SMART MESH NEBULISER

Here, Edgar Hernan Cuevas Brun, Business Development Manager & Scientist, Aerosol Drug Delivery, and Yuan-Ming Hsu, PhD, Research and Development Director, both at HCmed Innovations, consider patient adherence and the role the company's AdheResp mesh nebuliser plays in monitoring adherence.

Patient adherence for people who suffer from respiratory conditions is essential to improve and/or stabilise medical conditions and symptoms, especially with chronic diseases such as asthma and allergic rhinitis.[1] Moreover, patient adherence has been investigated in a group of interventional studies that revealed its benefits for several conditions, including chronic obstructive pulmonary disease (COPD) and cystic fibrosis.[2]

It has been identified that, with respiratory diseases, adherence can be considered as an approach to reduce cost by keeping patients' conditions under control. To enhance adherence and compliance, advancements in technology over the past decade have vastly contributed to the development of mobile apps and smart devices that can be effective tools to facilitate monitoring and tracking patients' behaviour and support their treatment adherence.

As an extension of the advancements, in 2018 during the 71st World Health Assembly, the World Health Organization stated that mobile health (mHealth) apps are an essential part of digital health and that access to mobile wireless technologies could provide significant health service resources as its use is far-reaching.[3] In the same year, it was also reported that several mobile apps focused on the management of chronic respiratory conditions were available in the two major mobile app distribution platforms: Apple App Store and Google Play. Among the apps, most were intended for asthma management but also included COPD, rhinitis and rhinosinusitis. Their scope centred around three areas: self-monitoring, personalised feedback and user education.[4] These areas are fundamental to the support of patient adherence.

> "Digital approaches have advanced to the extent that some of the services that were effective in the pandemic remain in use today and are expected to last in the post-pandemic world."

During the covid-19 pandemic, digital healthcare undoubtedly became one of the solutions to provide healthcare services, accelerating its spread and adoption. Digital approaches have advanced to the extent that some of the services that were effective in the pandemic remain in use today and are expected to last in the post-pandemic world.[5] This situation has further advanced the use of smart devices and mHealth apps in all fields, including adherence monitoring in the respiratory field.

DIGITAL TECHNOLOGIES FOR INHALATION THERAPY

Several smart cap accessories for inhalers have been developed in the last few years, with some already being marketed as tools to monitor patient adherence. Many of these

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devices are designed to be incorporated into pressurised metered dose inhalers, offering visual, acoustic or haptic feedback during the treatment intake and recording the number of dosages being taken and the time of administration. Their use is commonly involved in the delivery of bronchodilators and inhaled corticosteroids.

Data from the smart caps is mostly transmitted to a mobile device that can be synchronised later to a health cloud, which allows medical practitioners and patients to access the information as needed.

From a large number of available smart inhalers and mHealth apps for asthma treatment, one study identified six apps, with two being used in seven studies. The results of the studies showed that the interventions moderately improved inhaler adherence; however, there were no significant improvements in asthma control test results.[6]

Connectivity via Bluetooth has been incorporated in some nebulisers to monitor adherence for treatments involving antibiotics and vasodilators. Data transmission of time stamps and personalised treatment reminders are some of the key features in these devices to improve patient adherence and allow a more reliable source to collect treatment history data for medical evaluation and the prognosis following treatment. An increase in the number of nebulisers of this type is expected in the coming years as digital approaches continue to tap into the inhalation therapy field.

A NEW SMART BREATH-ACTUATED NEBULISER

The AdheResp smart breath-actuated mesh nebuliser has been designed and developed by HCmed Innovations to be used in combination with formulations that require a high level of delivery efficiency while reducing fugitive aerosol emission.

"Relying on the detection of pressure change during a breathing cycle, the AdheResp nebuliser can trigger aerosol generation during a specific section of the inhalation phase."

"To demonstrate the capabilities of the connectivity feature, HCmed is developing a demonstration mHealth app that uses the transferable data from the AdheResp nebuliser."

Relying on the detection of pressure change during a breathing cycle, the AdheResp nebuliser can trigger aerosol generation during a specific section of the inhalation phase. This feature is particularly useful when aerosolising formulations, such as antibiotics and biologics, which require reducing drug waste during treatment to improve efficiency and, at the same time, protect bystanders from inhaling fugitive aerosol.

Besides breath actuation, another major feature of the AdheResp nebuliser is Bluetooth connectivity, which has been developed to offer an effective vehicle as an adherence monitoring platform for different diseases. The AdheResp nebuliser has a Bluetooth module integrated into the main unit of the device and allows the transfer of three sets of data: time stamp, pressure reading and battery level. The data is continuously shared from the nebuliser to a mobile device that acts as a receiver to display information for the patient and/or medical practitioner. Connection to a healthcare cloud could be further achieved with the implementation of a function from mHealth apps.

AdheResp: Data Transmission

To demonstrate the capabilities of the connectivity feature, HCmed is developing a demonstration mHealth app that uses the transferable data from the AdheResp nebuliser. The types of data that can be transferred to a mobile device are described as follows:

Time Stamp

The total treatment length – and times at the beginning and end of each treatment – can be displayed from the time stamps collected during nebulisation. As well as benefiting the patients themselves, these values are useful for clinicians and medical practitioners to monitor patient adherence.

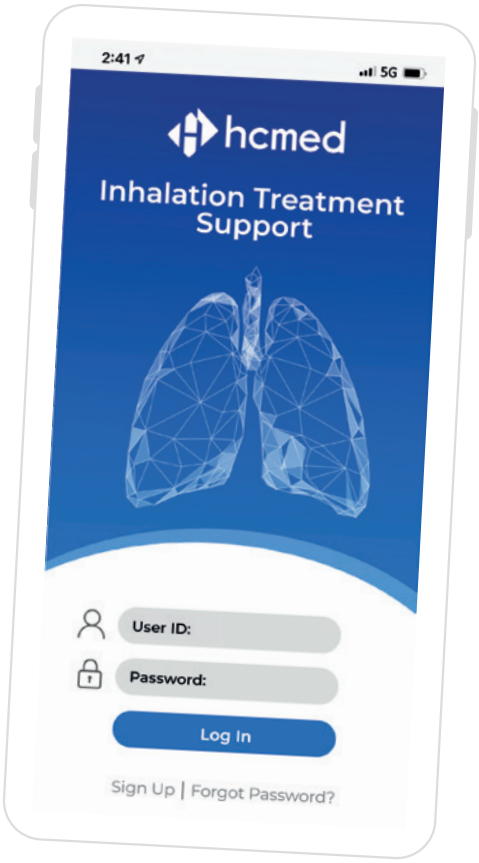


Figure 1: AdheResp – demonstration mobile app sign-up/log-in page.

Pressure Reading

The pressure readings throughout the treatment are transmitted from the device to the mobile device. The data can be used to profile the pressure change created by the breathing pattern of a patient with wave graphs.

Battery Level

Levels of battery power are transmitted when the device is first connected to allow patients to have a better understanding of the battery status.

mHealth Demo: Interface

The demonstration mobile app for the AdheResp nebuliser has been designed to provide an overview of a standard interface, rather than focusing on a specific indication. As AdheResp is a nebuliser for the development of combination products, each indication is expected to make use of the transferable data in different ways; therefore, a simpler approach was used for the demonstration mobile app.

The initial page requires users to sign up upon first use to complete the registration process or log in (Figure 1). Basic personal information has to be input at this stage to create an account with its corresponding password to secure patients' data.

A total of four pages can be navigated through in the AdheResp demonstration app: AdheResp, Treatment, Knowledge and Settings. Each one of the pages displays essential information for the user to self-educate, operate the device and monitor their treatment by means of the collected data.

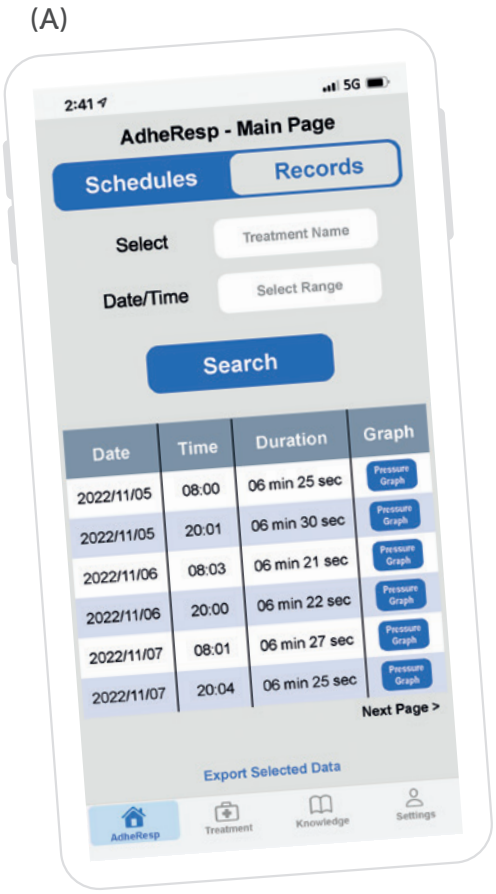
AdheResp: Main Page

Once registration is complete, the user will be directed to the AdheResp main page section where the scheduled treatments and reminders are shown. This section also allows users to schedule new treatments (Figure 2). Furthermore, main page offers the option of accessing records from previous treatment for which the treatment and timeframe can be first selected to obtain information about the date and time of treatment, duration and pressure profile (Figure 3A). This last feature provides an extended graph of the changes in pressure during the treatment that follows the breathing pattern of the patient, providing valuable data for posterior evaluations (Figure 3B).

Treatment

The Treatment page offers three options for the user to select: start treatment, transfer data and healthcare cloud. The start treatment option guides the patient to prepare for treatment, from the medication loading to Bluetooth pairing and the nebulisation process (Figure 4). While nebulising, a graphics interchange format guides the user to inhale and exhale at a specific rhythm to enhance aerosol intake. Data are continuously transferred to the mobile app during this process until the treatment is completed. At this point, the AdheResp nebuliser will automatically switch off and the mobile app will be delinked.

Transferring data from previous treatments when the nebuliser was not connected to a mobile device is possible with the second option of the Treatment page, called transfer data. The AdheResp nebuliser is able to store data for up to 30 treatments, before overwriting previous ones. This function can be used when the patient is charging the nebuliser and the Bluetooth function is in pairing mode. At this moment, the patient can press the icon to transfer data, and all the sets of data that had not been transferred from the nebuliser previously will be sent at pairing.



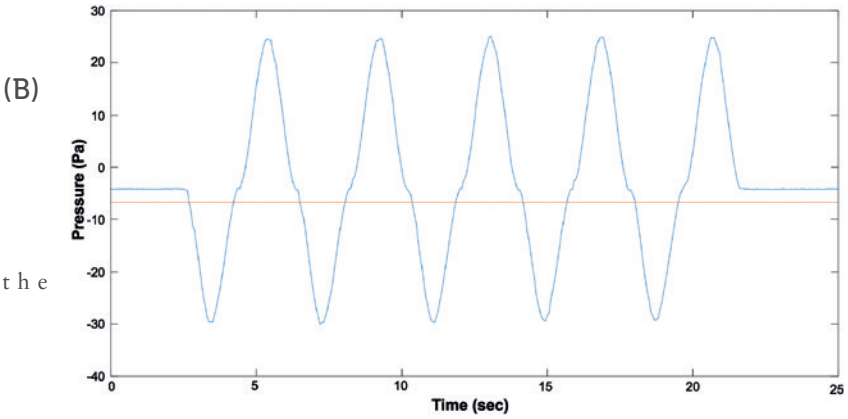


Figure 3: (A) Mobile app main page – records. (B) Pressure change graph generated from a breathing pattern.

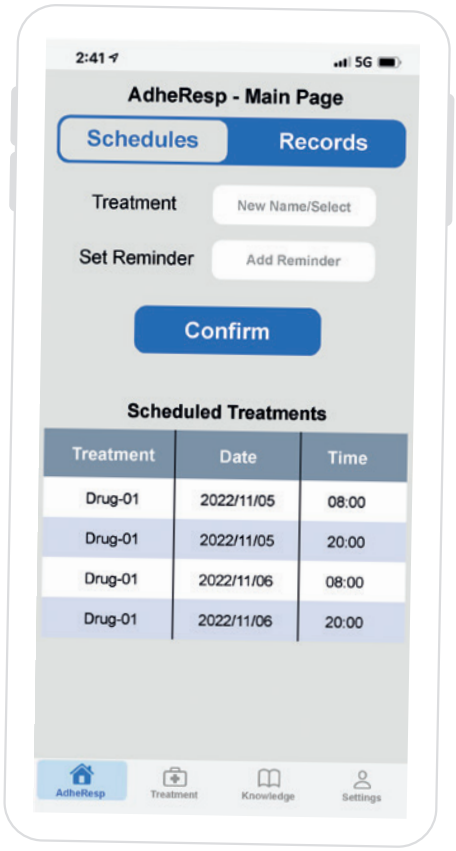


Figure 2: Mobile app main page – schedules.

Last but not least, the healthcare cloud offers the option to upload data stored in the mobile device to a secure cloud. The cloud access could then be configured to give access to healthcare practitioners and caregivers to observe and monitor the treatment data of the patient, who should give consent prior to data collection.

Knowledge

The Knowledge page presents a space for users to learn about the basic use and maintenance of the product. It is currently being built to combine text, images and videos that can describe the correct handling of the AdheResp nebuliser to ensure optimal performance. The section also includes a troubleshooting area and a space for information about the drug expected to be administered and the indication being treated by the combination product to provide educational information to patients about their condition and special care.

Settings

Modifications and updates to personal information and passwords are available in the Settings page. This page is also expected to offer functions such as printing

treatment summary reports, clearing stored data and even scheduling future appointments with a clinician to follow up treatment progress.

For combination development, data gathered by HCmed has pointed to the conclusion that most pharmaceutical companies prefer to develop their own mHealth app as each indication may require some customised interfaces, features and parameters. Considering this, the development of the demonstration app showcases the key functions that can be created around the transferable data capabilities of the AdheResp nebuliser, providing a solid reference for other potential developments.

Future Challenges in mHealth

Although it is undeniable to say that the future of healthcare may be in the hands of digital healthcare and connectivity, there are still several aspects to be further refined, such as data safety, efficacy and patient privacy. Different countries and regions have adopted their particular approaches on how to regulate connected devices and mHealth apps. The US FDA has updated the Device Software Functions Including Mobile Medical Applications guidance to encourage and regulate mHealth apps, while the Health Information Technology for Economic and Clinical Health Act and the Health Insurance Portability and Accountability Act are in place to protect patient information for data transmitted from medical devices. On the other hand, the EU has also played its part with the European Data Protection Board, which ensures the safeguarding of users' data according to the General Data Protection Regulation applicable to mHealth Apps.[7]

With the continuous evolution of digital healthcare, addressing existing issues related to cybersecurity and personal data information is crucial to build trust from users and speed up the spread of connected devices and mHealth apps. These two have the potential to be highly beneficial for adherence monitoring of respiratory diseases, such as asthma, COPD, pulmonary arterial hypertension and others. The incorporation of these solutions in combination products, using nebulisers like the AdheResp device, could open up several new possibilities for future treatments, providing better outcomes and cementing the adoption of digital health. Moreover, pharmaceutical companies,

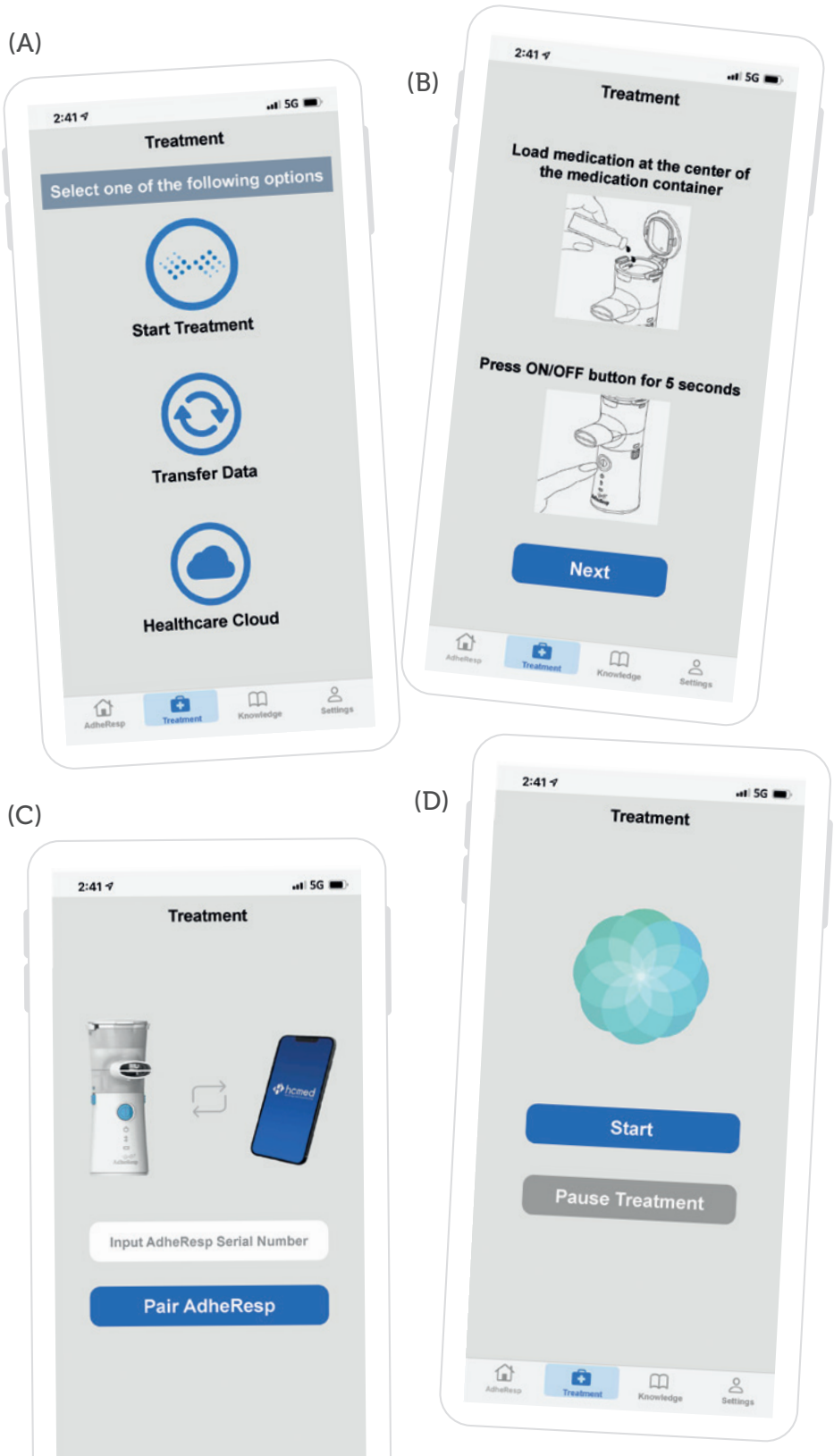


Figure 4: (A) Start treatment interface: (B) treatment preparation, (C) Bluetooth pairing and (D) treatment in progress.

"Different countries and regions have adopted their particular approaches on how to regulate connected devices and mHealth apps."

which are allowed to own and analyse the patient adherence database, could also benefit from the user preference to adjust existing and new medication regimes.

ABOUT THE COMPANY

Founded in 2014, HCmed Innovations is a contract development and manufacturing organisation that provides high-quality and cost-effective vibrating mesh nebuliser technology and services to support global pharmaceutical partners in the development of drug-nebuliser combination products for inhalation therapy. HCmed offers mature customisable mesh nebuliser platforms to enhance drug delivery. This technology enables efficient and reliable nebulisation of different types of medication, ranging from small-molecule synthetics to large-molecule biologics, as either solutions, suspensions or even difficult-to-deliver high-viscosity drugs. The latest platform includes the incorporation of breath-actuation and connectivity features to enhance drug delivery and monitor patience adherence.

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CONNECTED DRUG DELIVERY – IS THE NEAR-TERM OPPORTUNITY IN CLINICAL DEVELOPMENT?

– AN INTERVIEW WITH OLIVER EDEN, JABIL HEALTHCARE

Oliver Eden discusses at the factors influencing the return on investment metrics in clinical development and introduces Jabil's autoinjector platform Qfinity™ and its connected version, Qfinity+™.

DR OLIVER EDEN,
BUSINESS UNIT DIRECTOR,
JABIL HEALTHCARE

Oliver Eden, PhD, is focused on the development and commercialisation of drug delivery devices for the division's pharmaceutical delivery systems business. Operating from the UK, Dr Eden earned his Master's in Mechanical Engineering and PhD in Biomaterials Engineering from the University of Exeter (UK).

Q To begin, can you give us an overview of the challenges facing pharma with respect to return on investment?

A An urgent challenge across the healthcare ecosystem is how to accelerate the development of safe, efficacious medicines that improve health outcomes for patients. For every one asset in Phase I trials that becomes an approved medicine, there are nine that will not. Costs for developing a new molecular entity can run into the billions. Although return on investment metrics depends upon a variety of factors, improving patient engagement is a primary concern for pharma within clinical development. Connected health helps to mitigate challenges with patient retention and adherence to study protocols, thereby supporting accelerated timelines, but in order for these benefits to be fully realised, connectivity must be executed with a patient-centric mindset and, critically, at a price point that is not a barrier to adoption.

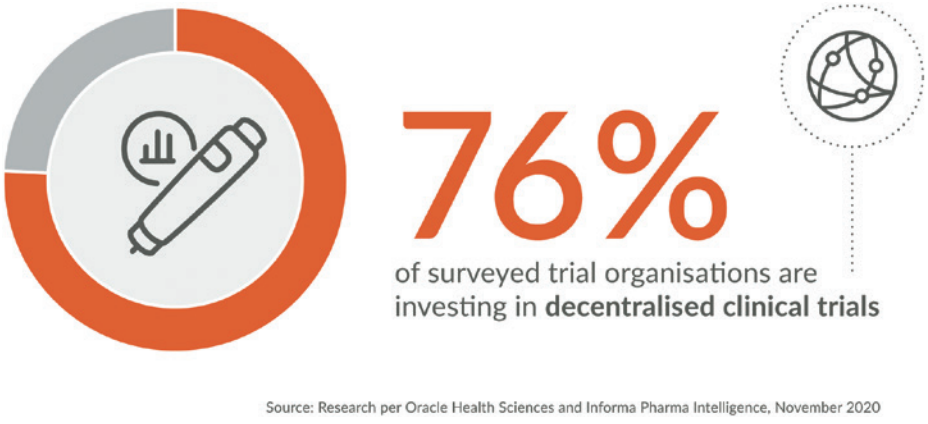

Figure 1: There has been a shift in clinical trials towards a more virtual and decentralised structure.

Q What are the macro trends or other considerations driving development of autoinjector platform solutions?

A Potentially significant tailwinds are in play for pharma customers aligning their drug development strategies with the following two emerging industry macro trends. Firstly, there is an increasing orientation within pharma pipelines towards biologics, which must be administered via a drug delivery device, such as an autoinjector. And secondly, there is a shift in clinical trials, particularly in the post-covid-19 landscape, towards a more virtual and decentralised structure, which is driving greater reliance upon connected technology solutions (Figure 1). Together, these trends are driving growth in self-administered subcutaneous drug delivery via an autoinjector and an increase in the use of connected solutions.

Q Do you see the role of digital health solutions increasing in clinical development?

A Yes, absolutely. As a contract manufacturer to major healthcare brands across the industry, Jabil's engineers and technicians work on the industry's transformation to digital healthcare every day. In fact, about 50% of the healthcare products Jabil manufactures have a digital component, and this is rising by around 10% each year. So, to offer a product that meets current and future market demand, especially for the dynamic decentralised clinical trials (DCTs) market, we must consider how it will collect, connect and deliver.

"Improving patient engagement is critical for reducing study delays and accelerating product-development cycle time."

Q What is the outlook for digital solutions in clinical development and commercial supply?

A The near-term opportunity for digital health solutions in clinical development is particularly compelling. Pharma research and development programmes continue to face sub-optimal recruitment and retention performance, along with other study management challenges, opening a line of sight to the value proposition for what digital can provide.

Viewed through a monetisation lens, connectivity's value in clinical trials is demonstrable and quantifiable, delivering improved patient engagement and retention. This leads to shorter and/or smaller studies, while also supporting more informed decision making regarding programme advancement or termination.

The valuation model for connectivity in commercial supply is also attractive but hinges on less transparently quantifiable adherence, compliance and persistence performance metrics, as well as challenges in defining digital health's impact on healthcare outcomes and total healthcare costs. If deploying connected solutions in clinical development can be demonstrated to improve patient engagement – delivering the value proposition described – it will become easier to quantify the impacts upon patient behaviour that would drive value in commercial supply.

Q How does a connected autoinjector deliver value in clinical development?

A Based on participation surveys and studies reviewed from the Tufts Center for the Study of Drug Development (MA, US) and research from GlobalData (London, UK), approximately 80% of studies are delayed by as much as six months, and 20% of clinical trials fail due to insufficient patient enrolment. These shortfalls are costly. Improving patient engagement is therefore critical for reducing study delays and accelerating product-development cycle time.

Incorporating a connected autoinjector in clinical studies provides investigators with a valuable tool for capturing patient insights, enabling them to manage study participants more effectively to adhere to the protocol. When study investigators are freed up to focus their efforts primarily upon those study participants who – for a variety of reasons – are struggling to follow the study protocol, it helps improve retention metrics and other key performance indicators.

Figure 2: The Qfinity platform offers the market an autoinjector with an option for a connected version in the same form factor and with the same user operation steps.

"Connected devices facilitate real-time data collection, providing sponsors with increased actionable information earlier in a trial regarding which assets should be progressed or terminated."

Q Can you quantify the potential opportunity provided by connectivity?

A With reference again to the Tufts studies and other research that projects costs for developing a new molecule at circa US$2.6 billion (£2.3 billion) with only a 12% probability of success. Improving the odds by just 1% through the improved decision made possible by a connected autoinjector's adherence/compliance data would equate to saving around $120 million.

Connected devices facilitate real-time data collection, providing sponsors with increased actionable information earlier in a trial regarding which assets should be progressed or terminated. There is significant value in optimising how these decisions are made.

Additionally, consider how connectivity's improvement of patient engagement supports both smaller studies and shorter study timelines. Patient recruitment and retention accounts for nearly 24% of a study's total cost, so for an asset with peak sales of $1 billion per annum, shortening the development process projects to an increase in total sales of approximately $85 million per month.

Q What does Jabil Healthcare's connected platform autoinjector measure?

A Qfinity+ captures adherence, compliance and persistence data. In other words, connectivity provides critical insight into how well or easily a participant can execute the clinical study per protocol. Additionally, Qfinity+ measures injection duration, confirming whether a full dose is delivered.

Integrating these data with additional connected sources, such as data from wearables, can provide a broader set of values for assessing safety signals around

a dosing event, such as heart rate and longitudinal measurement of activity or sleep, which may be associated with efficacy.

Q Why did you develop both connected and non-connected versions of the autoinjector platform?

A The intention with the Qfinity platform solutions is to offer the market an autoinjector, with an option for a connected version, in the same form factor and with the same user operation steps (Figure 2). The connectivity feature benefit in Qfinity+ is seamless, recording dosing events and transmitting the data without any additional user steps (or training requirement) versus the non-connected version, Qfinity.

Ease-of-use for patients and caregivers has been Jabil's goal throughout the development of these platforms. Providing a more sustainable solution has also been intentional, which is why Jabil chose to develop Qfinity and Qfinity+ as reusable autoinjector platforms. Incorporating electronics into the reusable injector unit delivers connectivity for Qfinity+ that does not impose additional patient burden, and at a cost that is comparable with an unconnected, disposable autoinjector.

Q Why do the connected and non-connected autoinjectors look and feel identical?

A From the outset of the development process, Jabil focused on finding the best way to ensure that Qfinity+'s additional feature benefit – connectivity – does not impose any additional burden on patients or caregivers. The company intentionally designed Qfinity+ with the electronics integrated within the same form factor as the non-connected version. For the user, this minimises patient burden because they follow the same steps and grip function without requiring additional training.

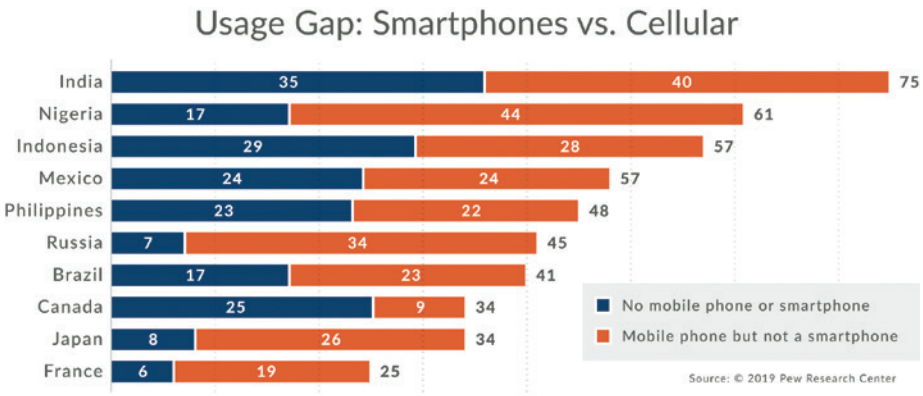

Figure 3: Smartphone penetration varies by geography, demographics and socio-economic status.

Q Was consideration given to potential user transitions between connected and non-connected versions?

A Absolutely. Even though today's shift towards more virtual, decentralised or hybrid clinical studies drives greater reliance upon connected technology solutions, it is important to realise that connectivity may not always be required when that product comes to market.

The design challenge then becomes how to ensure minimal impact in terms of user experience for participants transitioning between versions of the autoinjector without the need for retraining. This solution, informed throughout by patient-centricity, simplifies the user experience and allows for much greater ease moving between versions.

For example, it would be possible to conduct a DCT with Qfinity+ and then launch the product commercially with Qfinity because the user steps are the same. Similarly, the two platforms' shared design enables the transition of a trial participant from Qfinity to Qfinity+ allowing healthcare providers the opportunity, as needed, to engage more effectively with those patients who may be struggling to adhere/comply with their treatment plan.

Q What is the connection protocol – how does the connected autoinjector transmit data?

A Many market-leading autoinjector platforms require smartphones for data transmission. While seemingly convenient, smartphone penetration varies significantly by geography, demographics and socio-economic status (Figure 3). Even in an advanced country like the US, smartphone penetration in those over 65 years old – a key healthcare market – is

Figure 4: The benefits of a cellular home hub.

> "The evidence is already compelling and will continue to build: connected technology is a key component for enabling decentralised trials."

only 61%. Throughout the developed and developing world, coverage gaps exist and must be considered.

Therefore, integrated cellular communication was chosen for the Qfinity+ platform. It is the most inclusive connectivity solution providing more than 95% coverage worldwide. This feature also supports the broader strategic objective of pharma companies and regulators to recruit more representative patient populations for trials.

Q How is the Qfinity+ platform more inclusive and accessible?

A The Qfinity+ platform does not require a smartphone or wi-fi and connectivity is enabled without touchscreens, apps or other interfaces. The only difference for the user is the addition of a home-hub base. When the user places the Qfinity+ drive unit into the home hub, that action seamlessly transfers the data to the cloud while simultaneously charging and safely storing the device for the next use, meaning that both these critical requirements of a digital healthcare device's performance are accomplished with a single step (Figure 4).

Q Do participants require any additional training for the connectivity feature?

A No. The dosing event ends when the patient places the autoinjector into the home hub. This is a very simple and intuitive solution for patients and caregivers, in contrast with some market-leading single-use autoinjectors that use a reusable electronic sleeve. The downside of an add-on sleeve solution, particularly in clinical studies, is the potential it has for changing the user experience with training, user steps and grip function as well as, possibly more importantly, the way it signals to participants that they are being monitored.

Likewise, some solutions require study participants to interact with an external app to push data to a smartphone. These user-engaging steps serve as overt triggers and can potentially influence behaviour.

Q How do you see patients and caregivers responding to your product choices?

A The attributes Jabil set out to include have been validated through a series of formative human factors studies. The Qfinity platform compared favourably in a compromised patient population (rheumatoid arthritis), with reference to two market-leading disposable single-use autoinjectors.

Q Any additional comments on the opportunities in today's market for a connected autoinjector?

A Recently, the Tufts Center for the Study of Drug Development and Medable (CA, US) have been collaborating on a comprehensive return on investment analysis for conducting DCTs. The initial narrative calls attention to the dramatic reduction in cycle times and cost savings for sponsors using DCT technology as part of their protocols. The evidence is already compelling and will continue to build – connected technology is a key component for enabling decentralised trials.

Jabil understands that there are choices and options for pharma customers seeking to meet challenging objectives. Solutions, ideally, need to work for all stakeholders, and they also need to work in the real world. This is where the company started its work – the prospect of aligning form with function for a more seamless and inclusive patient journey, greater value for pharma customers and better health outcomes for the patients they serve.

ABOUT THE COMPANY

Jabil is comprised of over 260,000 people in more than 100 facilities in 28 countries working every day to be the most technologically advanced and trusted manufacturing solutions provider in the world. Within the Pharmaceutical Delivery Systems sector, Jabil works with healthcare's leading global brands to design, develop and manufacture some of the most complex and innovative drug delivery devices in the market.

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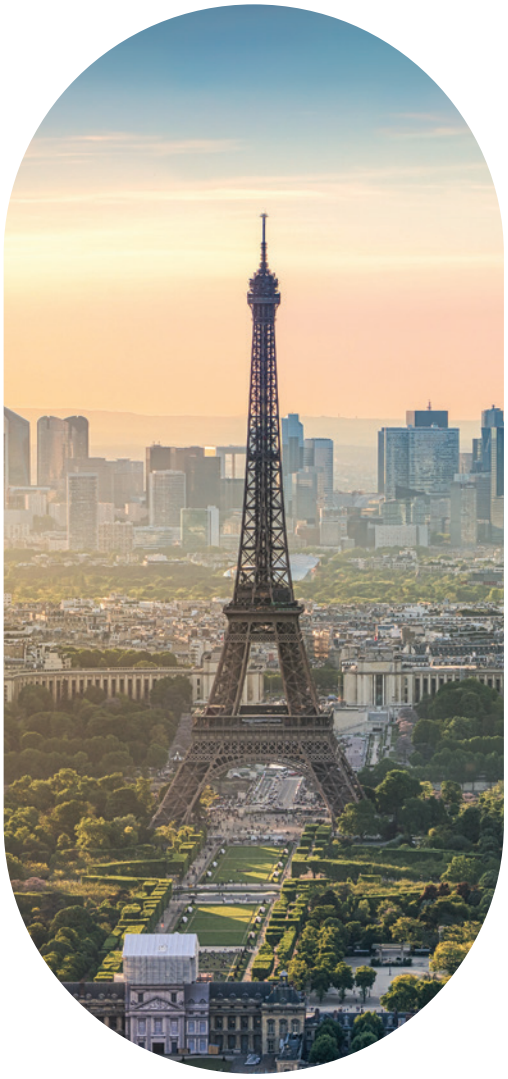

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BUILDING DIGITAL SOLUTIONS TO MEET THE UNIQUE THERAPEUTIC NEEDS OF PATIENTS

In this article, Benjamin D'hont, Director of Strategic Marketing at Aptar Digital Health, and Joe Reynolds, Senior Manager, Strategy and Patient Insights, at Noble, an Aptar Pharma company, discuss how the key to maturing the digital health market and increasing user retention of digital health apps is integrating agile app development from the beginning of a therapeutic's development cycle.

Across the healthcare and life sciences industries, adoption of patient-facing digital health solutions is notoriously low. The US Office of the National Coordinator for Health IT has reported that only 40% of patients use the portals connected to their providers' electronic health record (EHR) systems.[1] Researchers from the University of California San Francisco have found that only 10% of patients view, download or transmit their EHRs.[2] Meanwhile, the UK's National Institute for Health and Care Research has estimated that 70% of patients abandon assistive technologies, ranging from digital health tools to memory and mobility aids to remote monitoring devices.[3]

Many factors explain this lack of adoption. Some patients may feel uneasy about relying on technology to help manage their health, while others may feel they are healthy enough that they would not benefit from assistance. However, the most significant obstacle to adoption is poor design. Difficulties with registration and setup, low-quality feedback, poor usability, questionable reliability, unnecessary features and limited impact on behaviour can all cause patients to stop using a product.[4]

All too often, this happens because the digital solution has been an afterthought in the product development process. Pharma companies remain steadfast in their focus on developing safe and effective therapies that will gain the necessary regulatory approvals, and rightfully so. However, waiting until the later phases of product development to consider the role of a digital solution in supporting a therapeutic will only result in creating a solution that fails to deliver tangible outcomes.

> "To create digital solutions that solve usability problems, pharma companies need to incorporate patient engagement from the very beginning of product development."

To create digital solutions that solve usability problems, pharma companies need to incorporate patient engagement from the very beginning of product development. Only then will they be able to understand and accommodate the needs, wants and preferences of patients to provide a value-added solution. Aptar Digital Health and Noble, an Aptar Pharma company, have been working extensively with patients to optimise the design and development of digital solutions and maximise adoption by enhancing patient experiences, which ultimately lead to more positive health outcomes.

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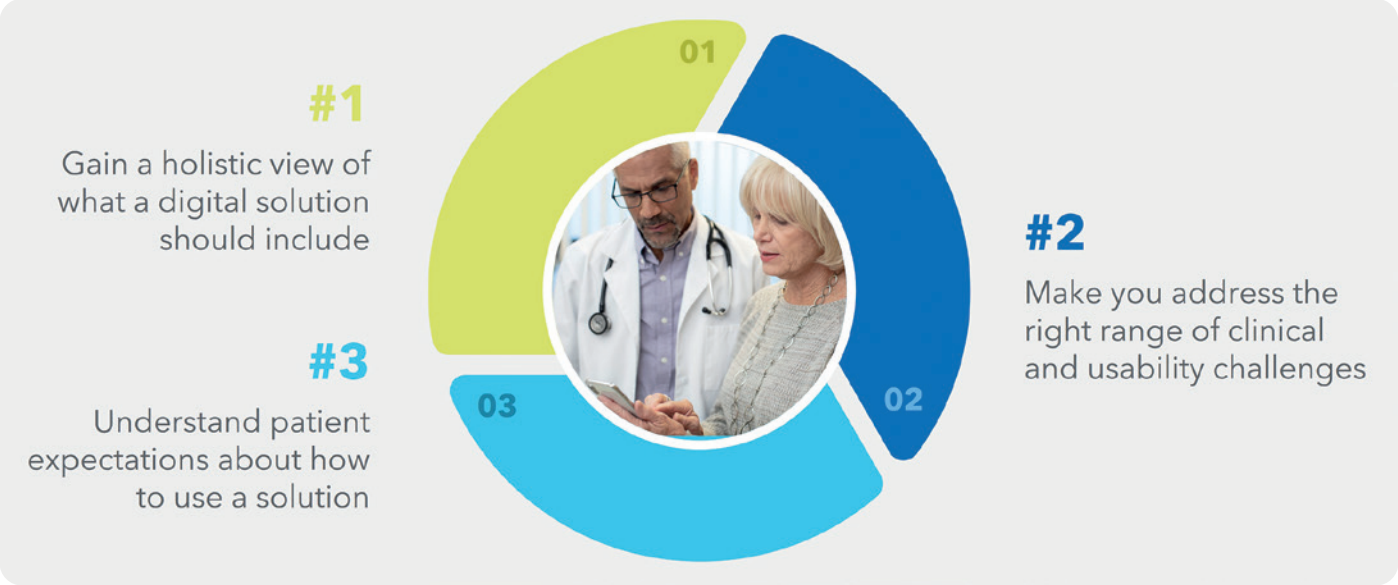

Figure 1: The value of patient feedback.

PATIENT FEEDBACK MATTERS FOR DIGITAL SOLUTIONS

Any pharma product manager understands the importance of obtaining patient feedback at the right moment in the development cycle. If patient feedback during a Phase III trial indicates that the button on an injectable device is not the right size or should be located in a different spot, it is much too late for that issue to be robustly addressed via a design mitigation solution before market launch. Such discussions need to happen long before the clinical trial phase.

Similarly, product managers know the value of obtaining patient feedback first-hand. While real-world evidence and previous clinical studies both demonstrate the market need for a new product and strengthen the regulatory application submission, product teams must recognise that these are secondary sources of information. Direct patient feedback around efficacy, side effects, ease of use and outcomes provides a much clearer picture as to how a therapeutic will perform once it is on the market.

These same strategies for developing a therapy should be applied to developing the digital health solution that accompanies it, with patient involvement right from the very beginning and feedback gathered throughout the development cycle. Adopting this approach has three clear benefits (Figure 1).

The first benefit is gaining a holistic view of what a digital solution should include. Adopting a piecemeal approach midway through product development increases the likelihood that a solution will focus on an individual pain point, such as patient anxiety around self-injection or poor long-term adherence. By looking at the big picture, product managers can collect more patient data and gain better insight and perspective into the overall needs of patients.

The second benefit is striking a balance between an n = 1 and an n = all digital solution. The former may be highly customisable, but can be difficult to scale, while the latter may be too general-purpose to meet specific needs. For example, frequent reminders to encourage adherence may alienate patients who are already fully compliant. Gathering feedback throughout product development ensures that the digital solution is designed to address the right range of clinical challenges faced by patients and to address them in the right context.

> "The goal of patient involvement throughout the digital health development cycle is to understand patient needs, wants and preferences for using the solution alongside their therapy."

The third benefit is understanding patient expectations about how to use a solution. It is no secret that e-commerce, social media, travel and banking have set high standards for mobile app design. The more that pharma product development teams talk to patients about what makes them want to use an app, the more likely it is that they will design a digital solution that patients will actually use.

ENGAGE PATIENTS THROUGHOUT DESIGN AND DEVELOPMENT

The goal of patient involvement throughout the digital health development cycle is to understand patient needs, wants and preferences for using the solution alongside their therapy. This is especially important for patients managing chronic conditions or rare diseases, who are often prescribed therapies that they must take for the rest of their lives – and whose clinical outcomes and quality of life are significantly impacted by their ability to self-manage a care plan.

Aptar Digital Health and Noble's experience shows that knowing what patients are looking for ensures that the digital solution is easy-to-use, offers feedback in a way that positively impacts patient behaviour, provides trusted and reliable medical information and encourages ongoing interaction. Reaching this level of understanding depends on a six-step process (Figure 2):

1. **Patient journey discovery:** The goal of this step is to identify barriers for patients in managing their condition and to understand the clinical and non-clinical factors that drive their decision making. This study should begin as soon as a product team is considering a molecule for development.

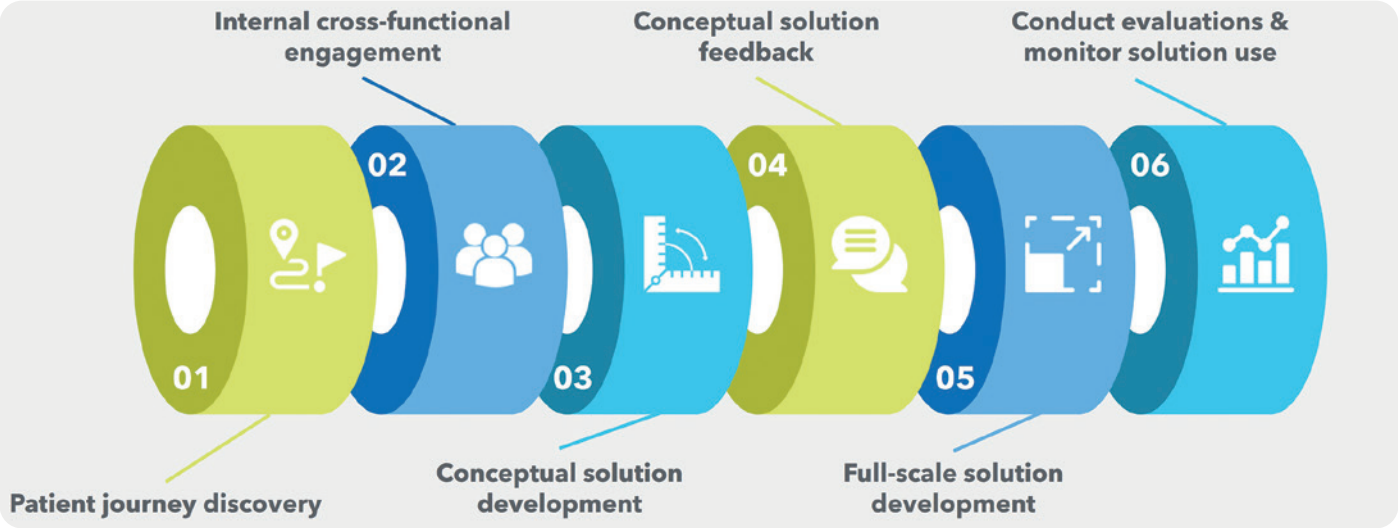

Figure 2: Engage patients throughout design and development.

2. **Internal cross-functional engagement:** After gathering patient feedback, product teams should convene a multidisciplinary group of key stakeholders to discuss the findings. The goal here is to look holistically at patient needs – therapy-specific, injection anxiety, symptom tracking, adherence, etc. – and discuss the user experience elements and app workflows that would best address these needs.
3. **Conceptual solution development:** Solution development should only begin once internal stakeholders have processed patient feedback and brainstormed general user experience design and workflow. Furthermore, the solution should not be a fully baked product at this stage; the idea is to create a sort of prototype for those inside and outside the organisation to react to.
4. **Conceptual solution feedback:** Obtaining feedback early on will help product managers ensure that not only are the primary needs of the patient being met, but that they are addressed properly within the context of the digital solution. This step also allows for concerns to be addressed or errors to be corrected before full-scale development commences.
5. **Full-scale solution development:** Digital solution development should take place as soon as the clinical development of a therapeutic begins. This helps to ensure that patient needs remain at the centre of the development process. This also aligns the solution with clinical care models for prescribing, administering and tracking the use of a given therapeutic.
6. **Conduct evaluations and monitor solution use:** With regulatory approval as the goal, the digital solution should be subject to the same types of human factors studies and evidence-generation strategy as the therapeutic itself. Likewise, any problems with the solution – from bugs in the software to broken workflows or erroneous information – need to be addressed before the next evaluation phase begins.

ADDRESSING ONBOARDING, ADHERENCE AND MAINTENANCE AT A PERSONAL LEVEL

The digital solution that emerges from the iterative design and development process described above should cover the key moments of taking a therapeutic – onboarding, adherence and maintenance. The solution should provide a personalised experience while also addressing some of the most common challenges that the patient faces when managing a given condition.

Onboarding

Qualified videos and interactive support modules can enhance physical training kits and give patients easy-to-use reference materials. Solutions should account for previous treatments that a patient may have used and consider important differences, such as storage, injection angle or frequency of dosage. By reducing errors associated with patients applying their previous experience to a new therapy, digital solutions can help avoid adverse outcomes.

Adherence

Here, the balance between n = 1 and n = all is critical. A solution should monitor patient behaviour and modify engagements accordingly. For example, notifications should reduce in frequency if adherence is improving to avoid annoying a patient to the point that they stop using a solution altogether. Similarly, if self-injection anxiety is persistent, the solution should alter the tone of notifications or provide more supportive resources.

Maintenance

Enabling patients to monitor their symptoms and report their side effects helps bridge the gap between doctor appointments that may be many months apart, as it provides a continuous record of how a patient has been feeling. An effective digital solution will use this information to help both the patient and their healthcare provider discuss how a therapy is working and whether a care plan should change.

AGILE DEVELOPMENT AND ACCELERATED DE-RISKING

As pharma companies engage patients throughout the digital solution development process, it is possible that the highly agile nature of this approach will clash with the industry's traditional aversion to risk. Fortunately, this agile approach is purposefully designed to be a counterbalance to risk aversion.

The reason for this clash is because continuously monitoring and building a digital solution throughout therapeutic product development is an example of accelerated de-risking. This upfront investment in time, energy and resources to support iterative development pays off in the long run as it greatly reduces the likelihood of large-scale changes that require restarting the entire development process further down the line. Just as it is too late in

> "This upfront investment in time, energy and resources to support iterative development pays off in the long run as it greatly reduces the likelihood of large-scale changes that require restarting the entire development process further down the line."

Phase III to move the button on a self-injection device, it is also too late in Phase III to revamp the symptom-tracking workflow of a digital solution.

Accelerated de-risking has the additional benefit of aligning with compliance requirements. Again, while the agile process may seem to contradict the rigors of regulatory approval, incorporating continuous improvements to a digital solution, and beginning this process at the product ideation phase, makes it easier to build compliance into the product development lifecycle. Issues can be addressed as they arise, within the parameters of a software "sprint", long before they become larger problems that pose a threat to regulatory approval.

In more traditional environments, the digital solution is built as a standalone product. Even if the development process follows industry best practices for discovery, journey mapping, user-experience testing and human factors, the finished product is unlikely to align with the specific needs of a particular therapeutic and its patient population. The digital solution may address a pharma company's business problem – the lack of a patient-facing mobile app – but it is not positioned to solve the patient usability problems that are at the core of poor adherence and worsening outcomes.

Agile development, on the other hand, further ensures that the digital solution and the therapeutic are co-created. Product managers on both teams work towards the same milestones, are part of the same feedback loop and address the same issues at the same time. As a result, the finished product addresses both the business problem and the usability problem, leading to the launch of a digital solution that patients are more likely to use.

CONCLUSION

Patient-facing digital solutions are increasingly popular in the life sciences industry, but the overall market for such solutions remains immature. Most pharma companies are unable to properly execute their vision for a digital solution. All too often, the solution is developed in a silo and regarded as an add-on to a therapeutic already in development. As a result, adoption rates are low and abandonment rates are high.

Equally, the most effective digital solutions are tightly coupled with their therapeutics from the ideation stage of product development. Aptar Digital Health and Noble are respected and experienced industry partners, working with pharma companies to ensure that their digital solutions support each step of the patient journey with a therapeutic, meeting their individual needs and improving their outcomes while creating long-term value for the company.

ABOUT THE COMPANIES

Aptar Pharma's Digital Health Division is part of AptarGroup, a global leader in the design and manufacturing of a broad range of drug delivery, consumer product dispensing and active material science solutions and services. Aptar Digital Health creates end-to-end solutions to enhance patient experiences every day, leveraging a holistic ecosystem of digital interventions. Amplified by an industry-leading portfolio of products and solutions, Aptar Digital Health's offerings combine mobile and web apps, connected drug delivery systems, onboarding, training and advanced data analytics services to actively empower patients and create a positive treatment journey. Aptar is headquartered in Crystal Lake (IL, US) and has 13,000 dedicated employees in 20 countries.

Noble, an Aptar Pharma company, is a patient-centric global leader in medical device training solutions. Noble has expertise in human factors engineering, market insights and device design and engineering to develop, manufacture and commercialise robust training solutions for patients who self-administer drug therapies. Noble's solutions encompass drug delivery training devices that mimic the exact feel, force and function of the real drug delivery device on which it is modelled, including autoinjectors, prefilled syringes and nasal and pulmonary devices.

For more information, visit: www.aptar.com/pharmaceutical/digital-healthcare-solutions.

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ABOUT THE AUTHORS

Benjamin D'hont is Director of Strategic Marketing at Aptar Digital Health, where he uses his knowledge of the healthcare industry to build company strategy, based on inputs from end-users, partners and clients. Mr D'hont has over 15 years of experience in innovation in life sciences gained through global consulting services for pharmaceutical, medtech and healthtech companies. He earned his engineering degree from École des Mines and earned his MSc in Medical Imaging from University Jean Monnet.

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

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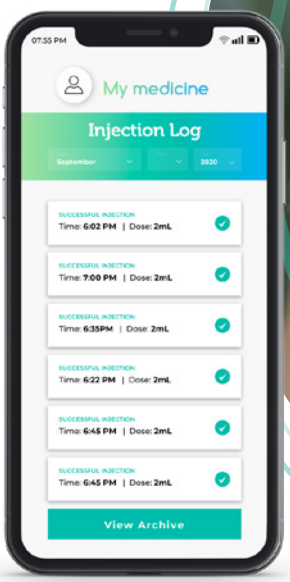

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PATIENT JOURNEY AS THE FOUNDATION FOR HOLISTIC CONNECTED DEVICE DEVELOPMENT

Here, Mark Tunkel, Global Category Director Services, and Cécile Gross, Global Category Manager, Parenteral, both at Nemera, consider the development of connected drug delivery devices and identify how understanding the patient journey from diagnosis to treatment can be used as an early-stage decision-making tool.

AN INCREASINGLY COMPLEX LANDSCAPE FOR CONNECTED DEVICES

The methods available to pharmaceutical companies and device suppliers to support the patient journey and experience offer more possibilities than ever before. Traditionally, the focus of the patient experience has been on optimising the "administration task" as outlined in the instructions for use, with an emphasis on the reduction of use error risk. However, as clinical outcomes increasingly drive payer decision making, developers are expanding their efforts to support the patient journey more broadly. This is being achieved through enhanced methods of training, value-added packaging and longitudinal methods of engagement that span from the onset of a disease state through various life stages.

In addition to these measures, virtually every developer in the branded and generic space is formulating some variation of a digital health approach. Often, this includes add-ons or accessories that are compatible with a commercially available device and provide users with device performance feedback – such as when an autoinjector is ready to inject or when an injection is complete. They can also provide error correction and other means of feedback to help eliminate use errors. The SmartPilot accessory from Ypsomed (Burgdorf, Switzerland) is an example of a device providing this level of functionality.[1]

> "Virtually every developer in the branded and generic space is formulating some variation of a digital health approach."

These devices are very effective at helping to mitigate potential use errors with more mature devices. These devices also feature a mobile app that can collect and curate use information for potential integration into a patient's health plan.

There has also been convergence within the drug delivery ecosystem, where all aspects of managing a disease state are integrated through connectivity that often requires partnerships to address broader steps in the patient journey to leverage complementary technologies. A good example of this is the partnership between Abbott Laboratories' Diabetes Care division (CA, US) and Novo Nordisk (Bagsvaerd, Denmark) that gathers and transmits insulin dose data from Novo Nordisk connected pens directly into the Abbott Diabetes Freestyle Libre sensor-based glucose management technology to allow patients to manage their disease states more holistically.

All these ecosystems are reliant upon sensor technology and mobile apps that act as the primary interface for all the component pieces. Similar to the add-

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ons scenario, these ecosystems are addressing known workflows and device component constraints and are beginning to be developed into the devices themselves, which will mark the next phase of electronics and connectivity in drug delivery devices (Figure 1).

THE PATIENT JOURNEY AS THE FOUNDATION FOR INTEGRATING CONNECTIVITY

Achieving success requires establishing a broad baseline of patient needs. A critical tool in helping developers formulate a user-driven strategy is a thorough mapping of the patient journey – to develop an intimate understanding of foundational user needs so that the entire journey is considered at the earliest stages of development.

A comprehensive understanding of the user enables the team to determine how these needs can be most effectively addressed, whether through the device, a software capability or with an interplay between the two augmented by other assets. This approach helps ensure developed technologies are not only meeting actual market needs but doing so in an optimal way – eliminating potential redundancies and conflicts that are inevitable when developing a device and software in isolation.

Understanding, characterising and prioritising user needs is best achieved through applied ethnography, which consists of a combination of interviews and observation within the context of use. This method can yield a deep, longitudinal understanding of the patient journey from diagnosis to treatment selection, onboarding and ongoing use. With an emphasis on system touchpoints like education/training materials, secondary packaging and device interaction, the patient journey can then be leveraged as a critical early-stage decision-making tool.

Nemera's design research team at its Insight Innovation Center uses a method called applied ethnography to achieve this goal. This relies on interviews and in-context observations of practices, processes and experiences within the patient's home or use environment. Potential use cases are looked at broadly beyond the administration event or complying with instructions for use. This starts from when a patient is diagnosed, to receiving their device, through the entire process of preparing, administering and disposal, and the times in between treatment to understand how the process changes over time and how frequency of administration may impact the patient experience. It is equally important to gain an understanding of the experience of healthcare professionals to consider relevant settings in clinical environments. This is important in applications where care is provided in both in-home and clinical environments as well as a migration of care, for example, from an oncology ward with significant support systems to an environment of self administration where clinical personnel are not present and the burden of support falls to a family member or caregiver (Figure 2).

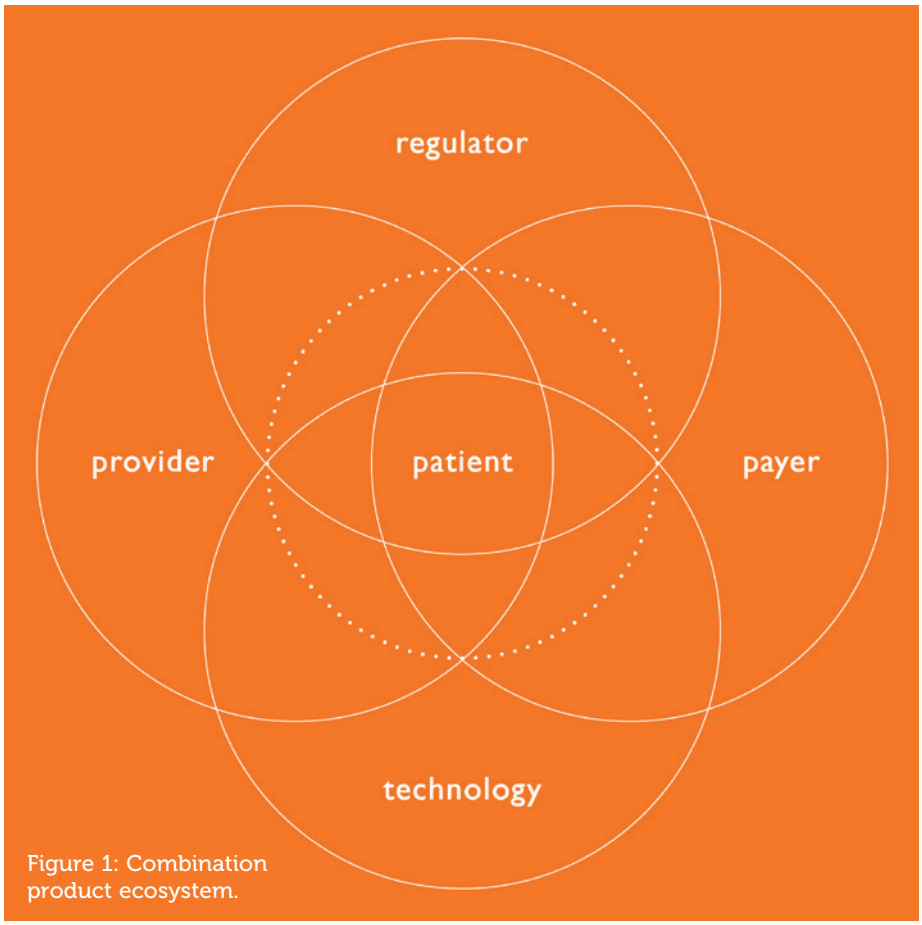

Figure 1: Combination product ecosystem.


Figure 2: Contextual inquiry.

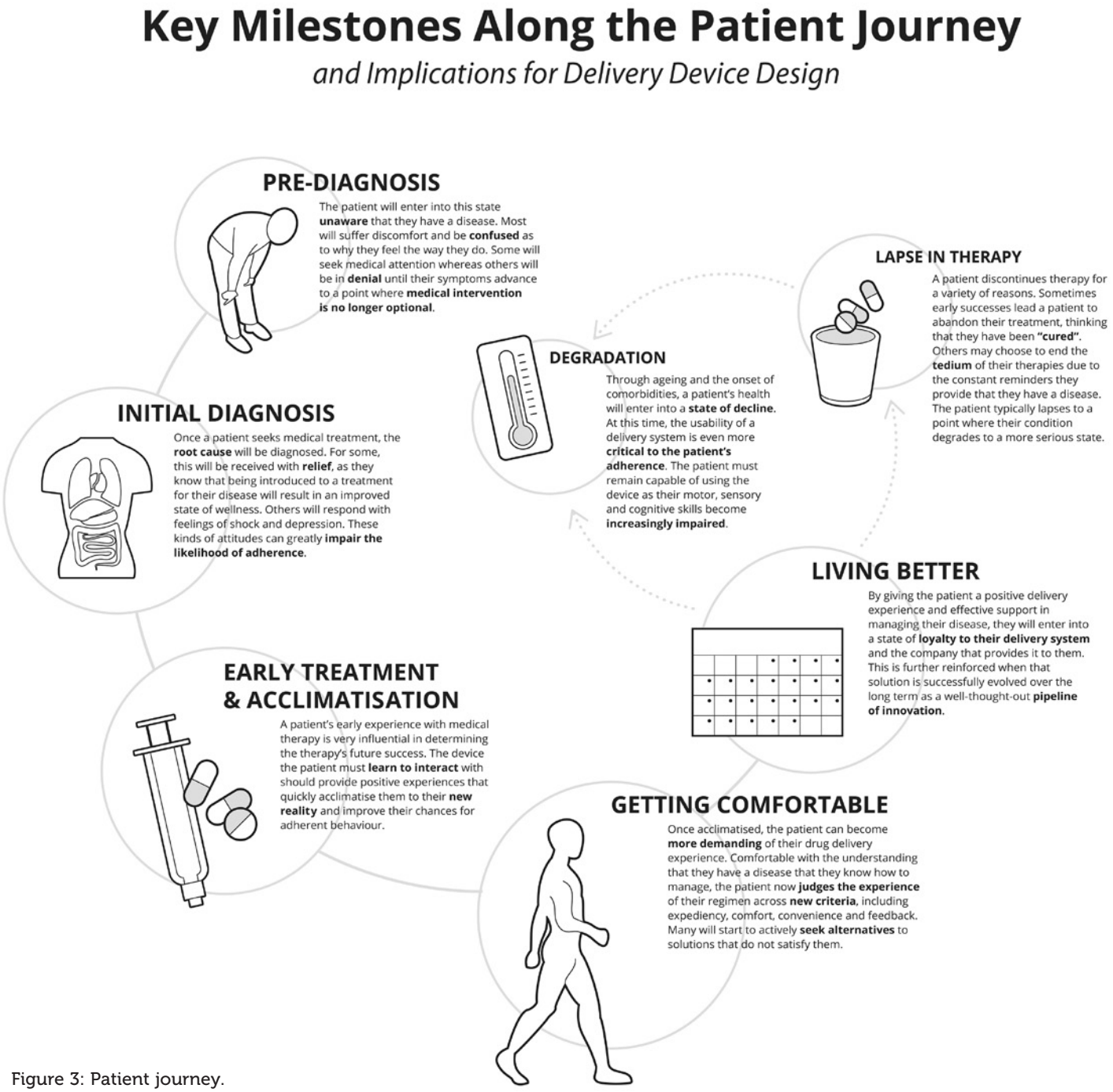

Figure 3: Patient journey.

Like drug discovery, this type of research should be started as early as possible in the development process – user needs are the cornerstone in defining the path forward. While some believe considerations surrounding the patient and device should be suspended until drug attributes are clearly defined, this approach can lead to decision making on device development or selection that can take a developer too far down a development path to make meaningful changes.

While usability testing activities are well understood when it comes to device selection and are critical at this stage, discovery research is a fundamentally different type of activity that seeks to define and understand user needs rather than help ensure they are met. User needs should be characterised as soon as there is a known target patient population – to most effectively drive the development of solutions covering the device, connectivity, mobile applications, data analytics and enhanced training that address the whole of the patient journey. The outputs from this effort include patient journey maps, clinical process maps, an understanding of prioritised user needs and values, and pain points that can be leveraged to improve the patient and provider experience (Figure 3).

OPTIMISING THE USER EXPERIENCE

Ultimately, this information can be synthesised into a development framework. This consists of mapping identified needs with the corresponding device and supporting element opportunities and capabilities. The road map can then be used to guide early mapping of the envisioned ideal patient and healthcare professional journey, and the process of exploring solutions that best meet the needs at each phase of the journey while enabling the team to consider solutions more holistically.

This is particularly important when determining where the integration of

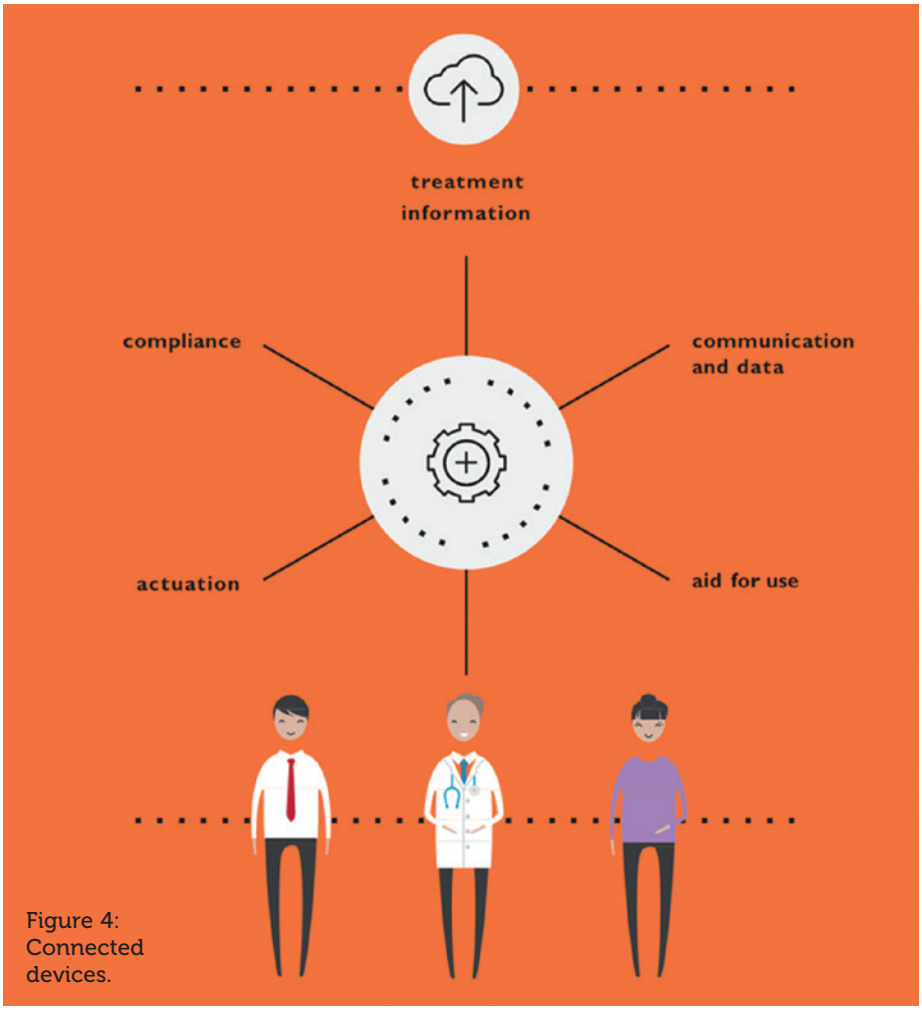

Figure 4: Connected devices.

connectivity is that can meaningfully support the experience. The road map also becomes the foundation for later requirements definitions for the device, the mobile application and any other clinical interface required, ensuring that requirements stem from user needs, rather than known technical capabilities and limitations. This helps developers ensure that all elements of a device strategy for a new drug product effectively address user needs optimally and holistically (Figure 4).

Nemera's Insight Innovation Center can use this foundation to develop all device aspects, from product design to mobile app user interface development, through an iterative process of design and evaluation sprints that integrate touch points with patients and clinical stakeholders to ensure solutions optimising all aspects of the experience and providing customers with robust assets for implementation by software development teams. Beyond mobile apps, needs can be addressed holistically in terms of packaging, both paper and digital instructions for use, and training. This approach of "surrounding" a device ensures that the entire experience is assembled by design and not in a piecemeal approach. Assets such as the mobile app for device connectivity can be used in clinical trials as well to monitor patient experience and provide critical feedback that can be incorporated into the system prior to commercial launch.

"The focus has been, when designing the product, on an automated and safe injection process totally invisible for the user as well as secure administration of the prescribed drug."

APPLICATION IN A REAL CASE: SYMBIOZE®, A SMART AND SUSTAINABLE ON-BODY INJECTOR

Targeting mid- to long-term medication in therapeutic areas such as oncology or immunology, the Symbioze® drug delivery system is a connected and reusable on-body injector suitable for large-volume injections.* The use of such devices is more than likely to expand, as many drugs in these fields are transferred from intravenous to subcutaneous delivery, which makes the disease burden even more cumbersome on the patients' shoulders. To alleviate part of this burden, the focus has been, when designing the product, on an automated and safe injection process totally invisible for the user as well as secure administration of the prescribed drug. Therefore, combining electronics and "proximity card" technology is Nemera's choice to address these issues. In the same way, a Bluetooth connectivity feature has been built in to allow functionality such as data recording and sharing, notifications and reminders.

Although such a feature is common and well accepted in diabetes care, it remains innovative in cancer treatment and inflammatory pathologies (Figure 5).

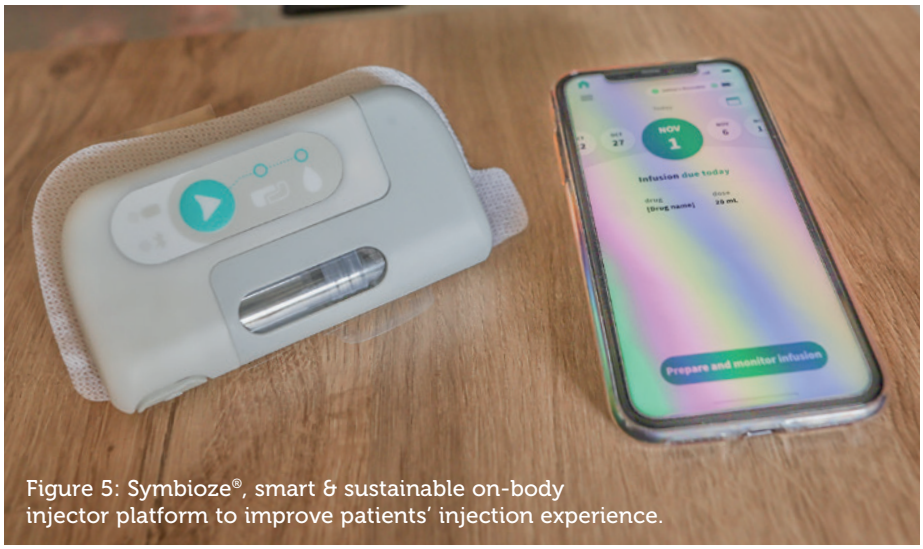

Figure 5: Symbioze®, smart & sustainable on-body injector platform to improve patients' injection experience.

To refer to the example above, oncology patients need, on top of a seamless device, to achieve treatment adherence outside the hospital setting successfully, as well as to keep a link with remote healthcare professionals. Symbioze® can be easily integrated into the patient journey.

To fulfil these requirements, Nemera has chosen to entrust the German company Zollner (Zandt, Germany). This new alliance will enable Nemera to offer enhanced connected drug delivery device solutions to customers and patients. As a partner of choice, Zollner will support the design, development and manufacturing of electronic drug delivery systems for both Nemera's proprietary and customer-owned products.

BENEFITS OF PARTNERING WITH AN INTEGRATED PRODUCT AND SERVICE PROVIDER

Successful navigation of these challenges often requires a partner with a broad set of capabilities, products and services. Nemera's integrated development, consulting and manufacturing services guide its customers from understanding the patient journey to inform device design decisions, through to clinical trials, registration and, ultimately, to market introduction and beyond with a single partner applying an agile process across the device and combination product value chain. Nemera can support every device strategy a customer may be considering, from organic development to use of its intellectual property platforms, as well as a wide range of services to support the customer's journey to a combination product. This is linked to Nemera's global manufacturing footprint. Ultimately, the benefits of this approach will drive:

Patient-Centricity and Engagement

The needs of patients and clinical stakeholders are centred from the onset of the programme to develop a customised patient engagement strategy that is consistently considered throughout the process to maximise effectiveness when launched into the market to drive loyalty from stakeholders.

Innovation Across the Journey

Nemera's world-class design, development and its Insight Innovation Center ensures the deployment of innovative development strategies as unique as its customers' apps for both intellectual property products and custom development services regardless of point of engagement.

Reduction of Risk and Increased Speed of Market Access

A single partner working across the journey limits transitions between suppliers and ensures consistent execution of strategy. Nemera also provides a wealth of options for developing and realising a device to accelerate time to registration and market from small-series to large-scale manufacturing and interim supply required in between. When combined with Nemera's service offering, this can significantly reduce timelines.

ABOUT THE COMPANY

As a world-leading drug delivery device solutions provider, Nemera's purpose of putting patients first enables it to design and manufacture devices that maximise treatment efficacy. The company is a holistic partner and helps its customers succeed in the sprint to market for their combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open minded, the company works with its customers as colleagues and goes the extra mile to fulfil its mission.

** Symbioze® is a trademark of Nemera la Verpillière SAS registered in the EU and pending in the US.*

REFERENCE

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ABOUT THE AUTHORS

Mark Tunkel is Global Category Director, Services, at Nemera. He was previously a partner at Insight Product Development, which was acquired by Nemera in 2019 and became the Insight Innovation Center. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharma industry, Mr Tunkel has advised many of the world's leading companies on their product development and innovation strategies, with an emphasis on driving realisation and the most favourable business outcomes.

Cécile Gross is Marketing Global Category Manager at Nemera, focusing on parenteral devices. She oversees the product portfolio strategy, development and lifecycle for safety system, pen injector and on-body injector platforms. She has more than two decades of experience in the medical device industry, marketing business-to-business technological products and implementing product lifecycle management for various kinds of devices. Ms Gross holds a degree in International Business and completed her initial training with a master's degree in Marketing and Management in the Healthcare Industry at IMIS Institute, Lyon, France.

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CONNECTED DRUG DELIVERY DEVICES: BENEFITS AND CYBERSECURITY

In this article, João Budzinski, R&D Director at Debiotech, discusses the benefits of connected drug delivery devices and the importance of cybersecurity when developing them, including the threats, key considerations and potential solutions.

There are many reasons to connect drug delivery devices. Firstly, there are benefits for the patients. However, healthcare providers and medical device manufacturers can also benefit greatly from connecting devices and opening communication channels to send or receive information. Obviously, there is more to consider than just the potential advantages; connecting a drug delivery device also requires careful consideration of several issues, including regulatory requirements, data protection and cybersecurity.

"There is more to consider than just the potential advantages; connecting a drug delivery device also requires careful consideration of several issues, including regulatory requirements, data protection and cybersecurity."

ADVANTAGES FOR PATIENTS, HEALTHCARE PROVIDERS AND DEVICE MANUFACTURERS

Home-based devices bring obvious benefits to patients; enabling patients to perform their therapy at home instead of having to go to a clinic or hospital improves their quality of life. In some cases, the liberty of being able to perform the treatment at home can actually improve the therapy's results due to more frequent dosing and better adherence to treatment. Connected home-use devices allow these benefits to go one step further.

Physician Advice, Based on Data

Connected home-use devices can provide physicians with a wealth of valuable data to improve a patient's therapy. Connected drug delivery devices can inform them of the exact doses that were administered and when, meaning a physician can see when doses were skipped and try to understand why – there is no more need for guesswork. With access to this data, physicians are no longer left wondering, "Did my patient forget a dose? Did they really take it regularly? Am I getting the whole story?"

Connected drug delivery devices also enable physicians to act on the data before the patient's next consultation. Indeed, devices that can receive prescription updates over the cloud can enable physicians to improve a patient's therapy quicker and more effectively than by traditional methods.

Device Diagnostics

A connected device can easily transmit logs and information about its usage. Sensor data can provide early warnings about device failures. This data is extremely valuable for device manufacturers to understand their device's behaviour in the field, providing priceless insights in how to build better devices or improve current ones.

Coaching for Better Therapy

Many use cases for a connected drug delivery device involve passing on information so that other stakeholders can analyse it. However, advances in machine learning and artificial intelligence are proving their effectiveness in adapting therapies to patients' unique physiological responses. Although this is a new field, there are efforts to create regulatory pathways for this type of technology.

If it is indeed deployed, this type of technology can coach each patient individually to improve their therapeutic results, such as by proposing doses precisely tailored to a patient's physiological response. This is particularly notable in the case of insulin, where there are general rules to calculate insulin doses but each person responds differently to therapy. In this case, connected drug delivery devices could allow

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> "Ransomware has boosted the motivation for hacking medical devices to a whole new level, making it vital to consider every aspect of cybersecurity on connected medical devices – patient safety is very much at stake."

access to advanced and powerful algorithms that can analyse substantial amounts of patient data and propose improvements to a patient's individual therapies at a much higher frequency than clinicians could.

CYBERSECURITY

Motivation

Not so long ago, cybersecurity was not a great concern for medical device manufacturers. Hacking was perceived as a threat for activities like banking and other high-profit apps, where the motivation for hacking was considered high. There was the misconception that the only reason a hacker would want to attack a medical device would be to harm a patient. There is an argument that, if you want to kill someone there are much easier and more effective methods than hacking their medical device. As such, motivation for hacking drug delivery devices was considered low.

Enter ransomware. Now, hackers can hold entire hospitals hostage, waiting for payment to release the hacked computer systems from their grasp. If a model of connected drug delivery device is vulnerable, a hacker could prevent an entire group of patients from getting their therapy until their demand for payment is met. The requested ransoms for these attacks can be astronomical. Ransomware has boosted the motivation for hacking medical devices to a whole new level, making is vital to consider every aspect of cybersecurity on connected medical devices – patient safety is very much at stake.

Sources of Cybersecurity Risks

An attacker has several potential points of entry into a system, so it is important to protect a device against as many types of attack as possible. The best way to ensure this is by a systematic analysis of potential threats and making sure none of these can be exploited by a malicious entity.

Interfaces

Obviously, connected devices will have internet access, via some kind of physical interface, such as wi-fi or an ethernet cable. It is vital to restrict the attack surface on these interfaces. However, there are other interfaces that must also be considered. For example, a connected drug delivery device could connect to a smartphone over Bluetooth. Bluetooth interfaces are notably a weak point for cybersecurity; therefore, a device manufacturer must take extra steps to ensure this interface cannot be exploited by an attacker.

Even lower-level interfaces, such as JTAG connectors used to install software on a processor during the manufacturing process, must be considered. Such interfaces might be neglected; the argument for doing so is that an attacker needs physical access to a device to exploit such an interface. While it is true that this interface is difficult to exploit once the device is on the patient's body, it is important to consider the risk that an attacker could gain access to the device at other moments of a device's lifecycle – after manufacturing, during transport or in a warehouse. There are ample opportunities for attackers to insert malicious software.

Services

Beyond the physical interfaces, at a higher level, software services provided with a device may introduce new security weaknesses. For instance, the ability to remotely update, enabling the quick deployment of new software versions, is a necessity for cybersecurity patches. Ironically, such remote update services are a favourite target among hackers – if exploited, they allow a hacker to deploy virtually any software they wish onto a device.

Software Supply Chain

There are potentially vulnerable steps on the software supply chain. During these steps, an attacker could alter the software to include malicious code:

- **Build:** Even with perfectly secure software on a drug delivery device, an attacker could render all that security worthless if they attack its build environment. This is a particularly insidious type of attack, as the hacker can use the developer's own infrastructure to generate a valid certificate for their malicious software.
- **Delivery:** How a developer sends its software to the manufacturing site is also critical. An attacker could intercept this delivery and alter the software at this stage.
- **Manufacturing:** If a hacker successfully attacks the manufacturing plant, they could use the plant's manufacturing capabilities to deploy devices with their malicious code installed on them directly from the factory.
- **Maintenance:** Maintenance usually requires elevated privileges on the device for a technician to perform the necessary work in the field, including software updates. It is important to consider the possible consequences of these privileges carefully; otherwise, an attacker could exploit this privileged access to a device.

WHAT TO DO

Unfortunately, there is no easy one-size-fits-all solution for cybersecurity. As with any medical device development, it starts with risk analysis. From a regulatory perspective, the US FDA has more detailed guidance and stricter requirements than the EU when it comes to cybersecurity. However, when considering data protection laws, the EU has stricter regulations than the FDA.

Consider the following example of a connected device being developed for the American market. Knowing the strict cybersecurity requirements from the FDA, the developer secured the device – the threat model was done, all interfaces were analysed, sensitive data at rest was encrypted, all communication with the cloud services was encrypted, public key infrastructure was deployed and secure, and all applicable vulnerabilities were analysed and treated.

This was all fine for the FDA, but the first feedback required the developer to go one step further – they also needed to implement secure boot mechanisms to ensure that every step of the boot process is verified and secure. Implementing such mechanisms naturally slows down development. With this requirement, the developers became unable to simply install new software on the device for necessary

development tests – for the devices to boot at all, the software must be signed correctly. This required significant effort, but it paid off – the device in question received 510(k) clearance this year.

Cybersecurity Risk Analysis

It is useful to make a clear distinction between security and safety. For cybersecurity issues, one of the most useful methods for identifying threats is threat modelling. In threat modelling, the goal is to identify all external interfaces and perform a systematic analysis of the common threats for each interface. A useful model for this analysis is the STRIDE model – for each interface, the goal is to identify the consequences of Spoofing, Tampering, Repudiation, Information disclosure, Denial of service and Elevation of privilege.

Given the wealth of information available, it can be challenging to identify the correct methods and resources for each device. Furthermore, once everything is identified, there is a lot more work to be done – analyse all the results, make the necessary modifications to the software, go through usually hundreds (if not thousands) of applicable vulnerabilities and document the results. However, being able to provide a secure device for the patients is worth the effort. The following are useful sources of information to help build cybersecure devices:

OWASP

The Open Web Application Security Project (OWASP) provides a wealth of resources, including security-testing guidance, dependency tracking, a list of source code analysis tools, threat modelling tools and lists of software composition analysis tools, among others.

FDA Guidance

The FDA provides detailed guidance on cybersecurity and is a useful support for cybersecurity activities. However, while FDA guidance tends to be practical and detailed, the challenge is how to interpret the guidance most appropriately for the particularities of a given device.

UL 2900 Series

The UL 2900 series particularly can be useful in the development of cybersecure devices. Obviously, not all the clauses apply to all drug delivery devices, but it is a useful exercise to analyse all the clauses and decide explicitly if each clause is applicable to a given device – a systematic analysis of all clauses helps protect a device against the most common threats. It is key to document what is applicable, what is not applicable and the rationale behind each decision.

> "When it comes to cybersecurity, it is best to use standard, state-of-the-art components with proven efficacy."

Cybersecurity Risk Control Measures

Safety and security risks are not mitigated by the same type of risk control measures. For example, while a drug delivery device may have proprietary safety measures, some of the security measures could be based on open-source solutions. This may be the case because cybersecurity risk control measures often require algorithms for encryption, certificate generation and signatures, which may be outside the scope of a digital drug delivery device's development process. When it comes to cybersecurity, it is best to use standard, state-of-the-art components with proven efficacy.

Secure the Software Supply Chain

This is a remarkably interesting area when looking to take security one step further. There are three frameworks to note regarding software build and update processes. Indeed, as mentioned before, software-update mechanisms can be a significant security breach if exploited by a hacker.

- **in-toto:** Full supply chain framework from initiation to end-user installation
- **The Update Framework (TUF):** A software framework designed to protect mechanisms that automatically identify and download updates to software
- **Uptane:** Similar to TUF, but tailored for the automotive industry and therefore particularly well-suited for embedded applications such as drug delivery systems.

CONCLUSION

Connected drug delivery devices offer remarkable benefits to patients, physicians and manufacturers. However, these benefits come at the cost of security risks. A thorough process for cybersecurity throughout the software development and deployment chains is necessary to ensure that all stakeholders enjoy the benefits of connection, without worrying about attacks by malicious players.

ABOUT THE COMPANY

Debiotech has a long history in the design and development of highly innovative medical devices. The company started with complex mechanical systems and incrementally developed its team and expertise to develop compliant and fully connected medical devices, allowing patient monitoring and remote patient treatment definition. Debiotech's expertise is available to the community; it provides design and development services for medical devices, components or other solutions with similar cybersecurity and data-management constraints. The company's know-how has been recently highlighted by the 510(k) clearance of the home-use peritoneal dialysis system developed by Debiotech for Fresenius Medical Care.

ABOUT THE AUTHOR

João Budzinski completed his academic training at the Federal University in Brazil and started his career in safety-critical devices at Dräger Safety in 2002, developing both hardware and software for toxic gas detection devices. Later, he joined SICPA in 2004, where he was responsible for the development of security solutions against counterfeiting and tax evasion. There, he started as a hardware and embedded software engineer for security solutions, later becoming Project Leader for the development and deployment of these solutions for international customers, and finally becoming Engineering Manager and Principal Engineer. Mr Budzinski joined Debiotech in March 2015 and was appointed R&D Director in 2022.

COULD VIVERA BE THE NEXT MEDTECH UNICORN START-UP?

Few technology companies reach unicorn status. US medtech company Vivera is hoping to be the next one, with its innovative approach to prescription drug delivery that aims to increase patient adherence and stop prescription drug abuse.

Unicorn start-ups are private companies with an investor value of at least US$1 billion (£830 million). They are rare and difficult to find. Companies do not become unicorns without solving a big problem or disrupting the way an industry or market operates.

Vivera is an innovative pharmaceutical, biotech and medtech company with an extensive intellectual property portfolio. Its most noteworthy subsidiary is Vivera Technologies, with its leading tech solution ZICOH – a patented, dose-controlled, secure, electronic prescription drug delivery solution (Figure 1) that aspires to foster patient adherence and stop prescription drug abuse. With US patents for the most commonly prescribed medication formats – including oral, vapour, aerosol and liquid medications – ZICOH is set to disrupt how prescription drugs are prescribed, managed, used, tracked and traced across the entire value chain.

> "The opioid epidemic costs the US billions of dollars annually to manage a crisis without a solution."

Figure 1: Vivera Technologies' ZICOH, a patented, dose-controlled, secure, electronic prescription drug delivery solution.

How Will ZICOH Disrupt the Prescription Drug Industry?

Conventionally, prescription drugs – including those with a high propensity for abuse and addiction, such as Adderall (amphetamine, Takeda) and oxycodone – are routinely dispensed as an entire month's supply in a plastic, orange bottle. Medications with low adherence rates are supplied in the same way. A childproof cap is the only security measure to protect patients from abusing, overdosing or diverting medication.

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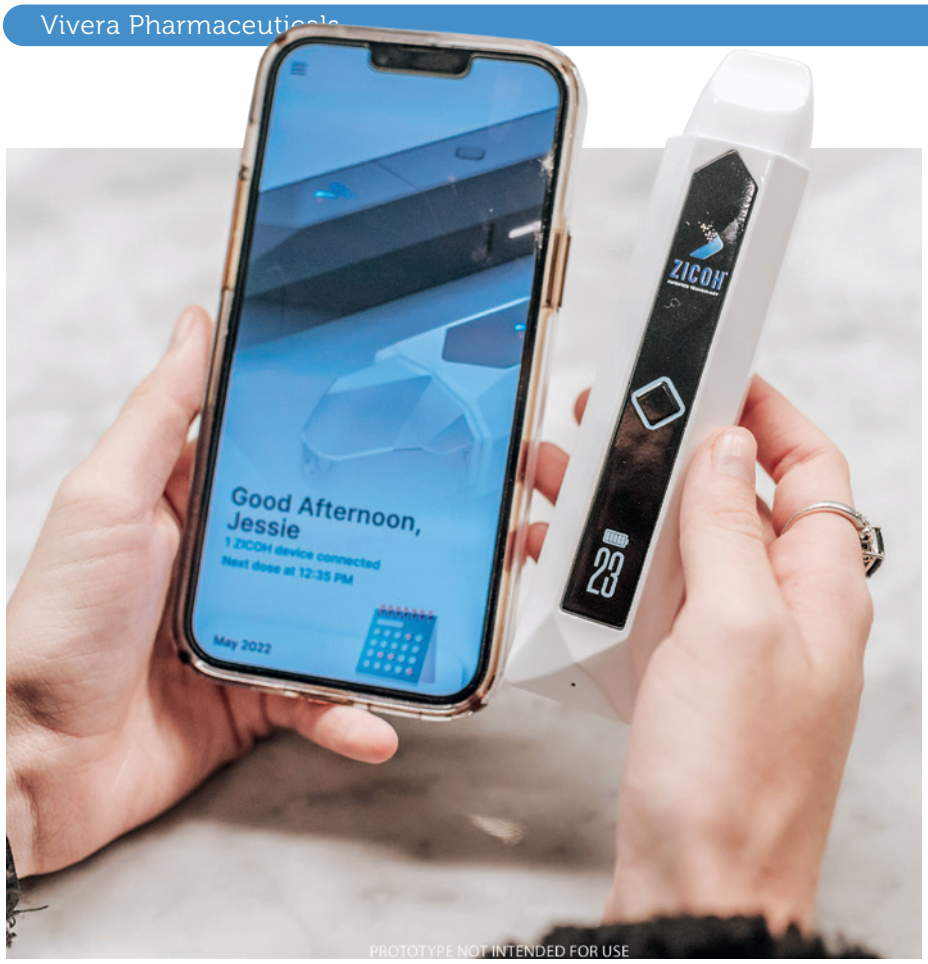

Figure 2: ZICOH connects the patient's device and mobile app to a secure software system.

"ZICOH can be used for any medication, including prescription drugs associated with low adherence rates."

The opioid epidemic costs the US billions of dollars annually to manage a crisis without a solution, and it is a multi-trillion-dollar expense worldwide. In 2017 alone, the economic cost of opioid use disorder and fatal opioid overdose totalled more than $1 trillion.[1] Nearly 80% of opioid addictions start with prescription drugs. Prescription nonadherence, whether intentional or not, costs the US healthcare system $300 billion annually.[2]

ZICOH is the first patented smart drug delivery solution for prescription medications with routine identity verification and a diversely interconnected software system. The device provides a unique, customised and user-friendly experience where the prescriber, pharmacy, caregiver and patient are involved in the medication prescribing and delivery process. ZICOH is programmed and registered to the patient, according to the prescriber's orders, with preset dosages and a continuously logged medication delivery history to monitor whether the intended patient is taking the correct dosages at the right times.

While it is a suitable solution for highly abused and addictive drugs, ZICOH can be used for any medication, including prescription drugs associated with low adherence rates. ZICOH will be offered to include patient-friendly features, such as medication reminders and mobile app check-ins, to guide patients towards proper medication adherence. The interactive device and software system can provide families and caregivers with peace of mind, knowing that the patients they care for are constantly monitored and prompted to take their medications as prescribed. ZICOH also allows the patient and prescriber a direct communication platform to adjust dosing as needed or report adverse effects.

"The interactive device and software system can provide families and caregivers with peace of mind."

"Accurate and real-time data will benefit physicians, consumers, insurers, and government and healthcare regulators."

In building a robust and integrated solution, Vivera has taken advantage of technology and software advancements to create a closed-loop ecosystem for prescription medications by connecting the drug developer, manufacturer, wholesaler, prescriber, pharmacy, insurance company, caregiver and patient.

The ZICOH solution connects the patient's device and mobile app (Figure 2) to a secure software system that, in turn, is linked to the doctor's office, pharmacy and, ultimately, the entire supply chain. This solution will enable stakeholders in the pharmaceutical supply chain to obtain pertinent data, including real-time drug supply use. Currently, the healthcare data collection system is fragmented, costs tens of millions of dollars to obtain and is not available in real time. Because data analysis and conclusions are often delayed by years, current methods are costly to the healthcare system – especially for pharmaceutical companies, patients, employers, their insurance plans and government insurance plans that rely on data to make decisions every year.

The McKinsey Global Institute estimates that applying big-data strategies to better inform decision making could generate up to $100 billion in value annually from across the US healthcare system. Accurate and real-time data will benefit physicians, consumers, insurers, and government and healthcare regulators by optimising innovation, improving efficiency and building new tools for pharmaceutical companies, beginning as early as the research and development phase. Unlike the current healthcare system's data collection methods – which often fragment data into silos – ZICOH will electronically capture uniform and real-time data seamlessly through each phase of the drug supply chain. With ZICOH, data collection will be carried out from the clinical research stage through the commercialisation stage to build "smart" algorithms and produce consistent, reliable and interconnected data.

Introducing Vivera's High-Profile Advisors for ZICOH

While there is not a recipe for building a unicorn product or company, Vivera has brought on a solid team of technology executives and subject-matter experts to build on the company's foundations, drive value and growth, and scale ZICOH effectively.

Just a few years ago, Vivera's Founder, Chairman and Chief Executive Officer, Paul Edalat, and Chief Scientific Advisor, Mehdi Hatamian, envisioned a solution that would reduce the risk of patients developing addictions to prescription opioids. Today, their patented vision has evolved into a mission to transform the availability of actionable healthcare data; revolutionise the drug supply chain; and provide patients with a customised experience with their prescription medications – honouring Vivera's core mission of putting patients first.

Advisory board members leading ZICOH's initiatives include Stephen J McColgan as Chief Medical Officer, Guido Jouret as Senior Technology and Business Advisor, Robert Massoudi as Senior Technology and Business Advisor, Bryan Hughes as Senior Technology Advisor, Geetha Rao as Regulatory Advisor, Saurabh Radhakrishnan as MedTech Operations Advisor and former DEA Special Agent Executive Alan Poleszak as Government Affairs Advisor.

ZICOH, the Future of Safe Drug Delivery

Similar to how Tesla changed the automotive industry, how Uber transformed the way we use transportation and the way Apple revolutionised and created a smartphone category, ZICOH is set to revolutionise the prescription drug industry. With a launch around the corner, it is poised to take on the title of a medtech unicorn.

ABOUT THE COMPANY

Vivera Pharmaceuticals is an innovative, science-driven pharmaceutical company located in southern California (US). The company has global exclusivity to license the patented and patent-pending TABMELT sublingual drug delivery system for pharmaceutical use and holds its own issued patents on ZICOH, a smart dose-controlled electronic medical device, and MDZone, a portable telemedicine station. With multiple divisions, including its technologies, biosciences, medical devices and advanced diagnostics divisions, Vivera Pharmaceuticals is vertically integrated with patented technology, manufacturing capabilities and distribution for its products.

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2. *Aungst T, "Does Nonadherence Really Cost the Health Care System $300 Billion Annually?" Pharmacy Times, Jun 2018, accessed November 18, 2022.*

- Design more compact, intricate components for connected wearable devices
- Integrate electronic functionality into structural components
- Increased patient utility, comfort and concealment
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- Manage overall device costs with rapid cycling and more parts produced per hour

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