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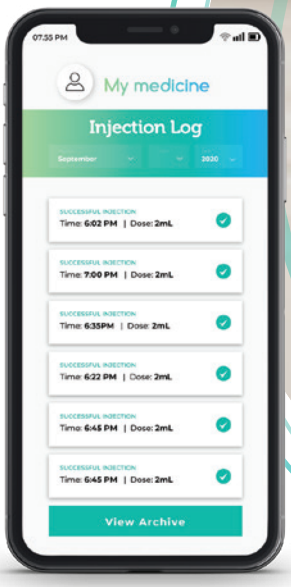

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ONdrugDelivery Issue N° 134, June 13th, 2022

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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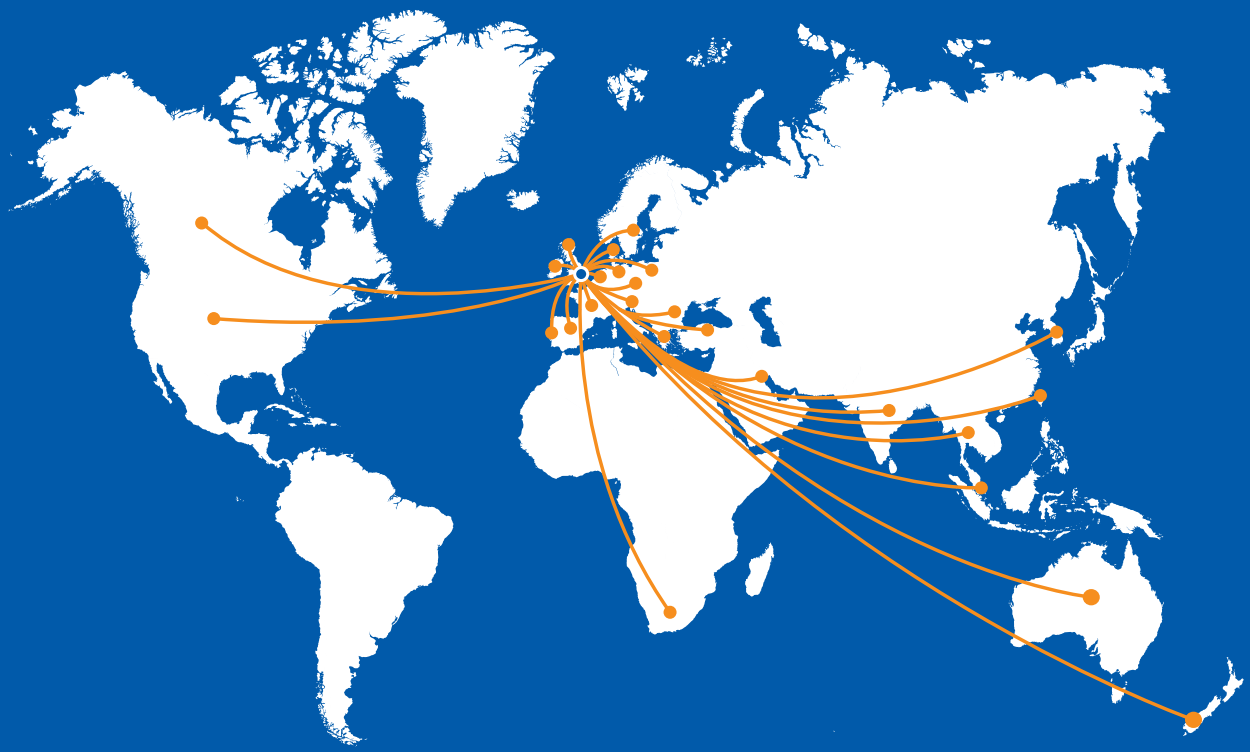

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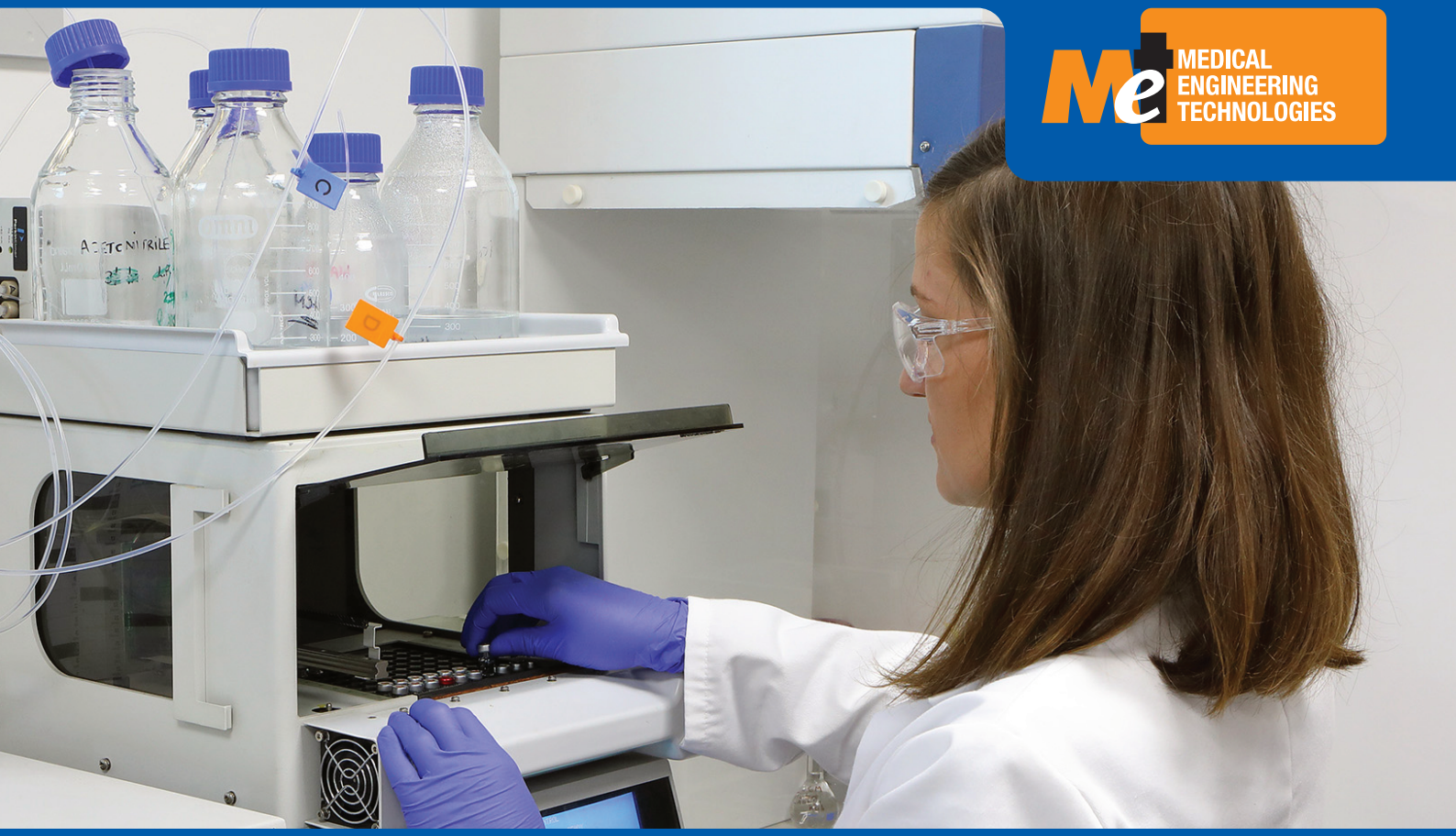

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CONNECTIVITY IN HEALTHCARE – FROM THE MILLENNIUM TO THE PANDEMIC AND BEYOND

In this article, Napoleon Monroe, Managing Director at New Directions Technology Consulting, looks back at the factors that influenced the underwhelming uptake of connectivity-enabling technologies in the healthcare sector over the first two decades of the 21st century, how the covid-19 pandemic changed everything and what current healthcare challenges connectivity might solve.

FROM 2000 TO 2019

As we entered the new millennium, connectivity enabling technologies were readily available and had matured to the point where they could provide real value to the field of telemedicine. However, a number of factors, including the traditional in-person fee-for-service payment model, inertia, success measured by product sales rather than patient outcomes, state licensure requirements, litigation and legacy expectations significantly limited the adoption of telemedicine and post-market surveillance.

"A number of factors significantly limited the adoption of telemedicine and post-market surveillance."

However, in recent years, specialty pharma and other biotech products came to dominate pharma sales volumes, profitability and new product filings. This led to at-home administration becoming a more important factor in the healthcare ecosphere, and digital therapeutics supporting at-home drug administration became increasingly available.

During this period, pharma companies and many contract development and manufacturing organisations (CDMOs) concentrated primarily on producing drugs, with some placing a secondary focus on mechanical drug delivery devices, although some also put work into connected devices (Box 1). Several companies attempted to establish patent protection on their connected products. However, most of Pharma's patent efforts remained on drug formulations, carriers or mechanical devices. Meanwhile, non-practising entities accumulated patents related to connected drug delivery, and a few pharma companies patented and introduced connected drug delivery products.

"Meanwhile, non-practising entities accumulated patents related to connected drug delivery, and a few pharma companies patented and introduced connected drug delivery products."

The US has strong, enforceable intellectual property regulations, with patents being key to the growth of US Pharma and other US industries (Box 2). US leadership in producing new medicines was at this point already well established, and Pharma's product patent coverage was essential to avoid competition for breakthrough production. The US was leading or developing leadership in consumer healthcare-related products and services, such as wearable health devices (Apple), online research (Google), office software (Microsoft) and e-commerce (Amazon, which began offering its web-based infrastructure to businesses in 2006).

At this point in time, electronic medical records (EMRs) were a requirement in the US, but were primarily for billing purposes and were not interoperable. Automated identity and data capture (AIDC) was discussed but was only mandated by legislation for high-risk pharma and device manufacturers and distributors in 2013. In the relatively recent past, US Pharma developed a reliance on direct-to-consumer "Ask your doctor" style advertising after regulators closed other marketing channels.

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BOX 1: GLOSSARY OF TERMS

Connected Devices – Devices that incorporate means claimed in the mMed portfolio to communicate for purposes such as data sharing to provide patients, healthcare practitioners, caregivers and many others with near real-time or stored and forwarded information. These devices also are "smart", in that they incorporate means that allow for analysing data to enable assisted intelligence and machine learning. Connected drug delivery devices are important to remote administration of specialty, personalised and targeted drugs.

covid-19 – All variants of the covid-19 pandemic.

Drugs – Small-molecule chemicals or large-molecule products, including biologics and cell, gene and other DNA-based therapeutics.

Medication Compliance – The act of taking medication on schedule or taking medication as prescribed.

Medication Adherence – The act of filling new prescriptions or refilling existing prescriptions on time.

Pharma – The pharmaceutical industry.

pharma – Abbreviation of "pharmaceutical".

BOX 2: PATENTS AS PART OF THE CHANGE IN CONNECTED HEALTHCARE

New Directions' research shows that many organisations, including non-practising patent aggregators, have anticipated the introduction of connected medication management by filing and/or licensing patents, investing, merging, securing regulatory approvals, promoting and using connected medication management products to further their financial objectives and improve patient outcomes.

Forward patent citations are a well-known measure of patent value. In 2021–2022, New Directions funded research showing that there have been more than 500 first-generation forward citations of New Directions' US patents (Figure 1), more than 6,400 subsequent generation citations and a substantial number of 102/103 US Patent Office actions. Research provided evidence of use by multinational pharma and drug delivery companies. Analyses of forward citations have been prepared for some companies. Based primarily on continuing forward patent citations and the intense commercial activity in connected drug delivery, as estimated by a leading patent research company, patent valuations have continued to increase over the 2020s.

New Directions entered the medication management field with patent filings early in the era of connected medication delivery product development. New Directions was able to secure claims that are of significant value to companies engaged in activities related to connected drug delivery.

Figure 1: The mMed portfolio comprises five granted US patents, as well as the counterpart Israeli and Australian patents, on products invented by Napoleon Monroe and assigned to New Directions Technology Consulting, LLC, as shown on New Directions' website.

> "Emergency-use approvals were granted for telemedicine and pharma compounds to help stop the spread of the virus, and insurers began paying for telemedicine."

Low borrowing costs and the prospect of broadened anti-trust regulation drove mergers and acquisitions. Many pharma, device and healthcare companies were rolled up, reducing the number of big healthcare players while, simultaneously, US tax policy provided benefits to big corporations. Outsourcing and offshoring became rampant. When Pharma exited some foreign operations, lower quality producers often took over. In general, this timeframe saw drug prices and healthcare costs increase rapidly. Meanwhile, the gig economy and movement away from expensive corporate employee and retiree insurance significantly reduced the number of individuals in the US who had good healthcare insurance. Indeed, the number of underinsured and uninsured people grew significantly.

THE PANDEMIC AND BEYOND

Although the epidemiologic threat of a pandemic had been discussed, governments largely failed to make preparations for such. A contributing factor, especially in the US, was the increasingly fractious nature of the political landscape. Therefore, when covid-19 struck, sweeping, and often draconian, emergency measures were

Figure 2: The covid-19 pandemic has been a key driver of connectivity and telehealth's acceptance in mainstream healthcare. However, now that it is here, it is time to realise the full potential that it offers.

required to combat the ensuing pandemic. It is these restrictions that finally drove acceptance and adoption of telemedicine into the mainstream (Figure 2).

Emergency-use approvals were granted for telemedicine and pharma compounds to help stop the spread of the virus, and insurers began paying for telemedicine. Concerns about medications and healthcare were generally heightened worldwide. In the US, the government funded emergency Pharma responses to covid-19, as well as stimulus payments to businesses and individuals. Pharma responded to covid-19 by shifting strategies, intensively researching and successfully producing vaccines and antiviral treatments. Research accelerated across the spectrum of biotech healthcare product classes, leading biotech to advance rapidly, even beyond covid-19-related treatments.

However, covid-19 also resulted in labour shortages, demand volatility, uncertainty and logistics failures that demonstrated supply-chain weaknesses affecting everything from plastic resin supply to patient treatment. Counterfeit, adulterated, misbranded, off-label and diverted products became widespread, while waste, fraud and other abuses also flourished. Price gouging was frequent. Automation resourcing and telemedicine were adopted in crisis mode to help ease the effects of supply chain dislocations. Pharma's wealth grew from research, production and sale of vaccines and treatments.

Pharma, insurers, providers and others made big-data storage and analytics investments. Complex, ever-changing covid-19 news, including of actual and potential mutations and variants, caused confusion and science denial, leading to widespread misinformation, disinformation, conspiracy theories and public malaise. The virus highlighted disparities in the healthcare system, as well as the societal costs of inaction. Medical treatment institutions were stressed and understaffed. Necessary chronic – even emergent – disease treatments and other procedures were postponed.

Companies that were not part of the traditional healthcare system, such as CVS, Walmart and Amazon, provided covid-19 vaccinations and became more deeply involved in healthcare. They and traditional healthcare companies contracted and merged with or acquired providers and other stakeholder companies – partly due to the fact that, while inflation accelerated, borrowing costs remained low in the early phases of the covid-19 pandemic.

ACCELERATING BREAKTHROUGH PRODUCTS

There has been an emphasis on accelerating approval for marketing of generic, biosimilar and breakthrough products. The US FDA issued new guidance for sponsors to make the development of generic versions of complex products more efficient. It prioritised review of many complex generic drug applications and developed a path for approving generic versions of complex combination products that did not require the generic to be an exact copy of the innovator delivery system. Teva's EpiPen (adrenaline, Teva Pharmaceuticals, Tel Aviv-Yafo, Israel) was the first approval under this programme. This was part of an effort to prioritise the approval of medicines with little or no generic competition, within an overarching goal of removing barriers to generic development and market entry for critically important medicines at lower prices.

The FDA has moved to rely more on standards, such as ISO 13485, that emphasise design control, defect analysis, adverse reaction reporting and post-market surveillance. Complex drug delivery systems have been known to struggle with component changes, responses to which include the Drug Supply Chain Security Act (DSCCA) and the implementation of unique device identifier (UDI) AIDC systems, both having serialisation requirements for prescription pharma and critical medical devices. The DSCSA and UDI implementation schedules are currently being finalised after much delay.

The FDA is ahead on the regulation of connected devices and software as a medical device, essential for automated and assisted intelligence. Both US and EU device regulators are now focused on patient outcomes, a principle often referred to as "patient-centricity". The EU Medical Device Regulation (MDR 2017/745) requires post-market clinical follow-up. Both the EU and US are making moves to bring clinical outcomes under the purview of their regulatory agencies to ensure the safety and efficacy of healthcare products.

A NEW CONNECTED REALITY ON THE HORIZON

Connected devices enable the gathering of real-world information on patient outcomes, presenting both devices and drugs with opportunities for ensuring efficacy beyond clinical trials. This data gathering potential also presents the opportunity for stakeholders to pay for only the products and treatments that provide the most significant improvement to health outcomes.

"This data gathering potential also presents the opportunity for stakeholders to pay for only the products and treatments that provide the most significant improvement to health outcomes."

In recent presentations, an FDA executive used the term "market intelligence" in her title. Furthermore, FDA digital initiatives and the newfound FDA patient-centricity model make a compelling case that, while the FDA does not regulate dental or medical practice, change is on the horizon for the healthcare sector. Medication compliance issues and post-market efficacy questions are inspiring the industry to offer new connected drug delivery products.

There is also movement towards greater, or even universal, EMR interoperability. This has been required by legislation and incentivised by payers. A 2020 Office of the National Coordinator (ONC) ruling required that information be more standardised and imposed terminology standards on the structure and meaning of information in EMRs. The objective was, and is, making patient data more interoperable for patients, providers, payers and the greater healthcare ecosystem.

Prescriber EMR systems, such as those in the dental industry, which have traditionally not been interoperable, are becoming so with the adoption of Health Level 7 and Fast Healthcare Interoperability Resources. This is a further step towards meaningful use of patient records in the fuller sense. Additionally, stakeholders are increasingly adopting computerised provider order entry (CPOE), which is integral to medication and device management, for home-use and other prescription products. Some EMR products now come equipped with CPOE modules that enable electronic entry of patient medication data.

The FDA has advised that they are monitoring the post-market performance of medical devices and pharma products to a greater degree than before. They have also announced that the Safety Signals and the National Evaluation System for health Technology (NEST) programmes are being included in the Manufacturer and User facility Device Experience (MAUDE) database. While these two programmes were device specific, note that a programme in one FDA division often has an agency-wide impact overall.

AIDC and EMRs are facilitators for healthcare data collection. While AIDC is still not widely used by many practitioners, the newfound regulatory focus on post-market information is making AIDC more appealing and, in some cases, necessary. Regulators and payers are encouraging, or even requiring, the use of UDI in the transaction set defined by the American National Standards Institute X12 electronic data interchange (EDI) standard that prescribes the exchange of information between two businesses using electronic means. A type of EDI transaction set is the EDI 810, which covers how invoices are to be exchanged between trading "partners", so any party wishing to get paid for their services will be required to conform to this standard.

Pharma and CDMOs have devised a strategy of adding connectivity to existing mechanical devices, such as inhalers and injection pens, using add-on devices. These connected platforms, including connected labels, could be approved as devices and added to multiple designs of drug delivery devices. With the expansion of broadband availability, particularly to underserved communities, this would be a boon to healthcare. Pharmacists are encouraging comprehensive medication management to improve information availability, medication adherence and compliance and limit adverse reactions.

OVERCOMING HEALTHCARE OBSTACLES THROUGH CONNECTIVITY

Price control legislation and policies regarding pharma products are advancing, with patient support groups and large associations, such as AARP (Washington DC, US), are pushing for price controls. Connectivity and connected devices can be a means to help demonstrate a pharma product's value and resultant improved patient outcomes, as well as to gain brand loyalty.

The current emergency measures to extend telemedicine and accelerate new, generic and biosimilar drug approvals may expire. These expirations could cut both ways. Connectivity and connected devices can play a part in strategies to enhance corporate value to patients, whatever the political decisions on extensions may be.

The Centers for Medicare & Medicaid Services recently refused to pay for the Alzheimer's disease treatment Aduhlem (aducanumab-avwa, Biogen, MA, US) unless patients were entered in a clinical trial. Furthermore, restrictions on pharmacy benefit managers and

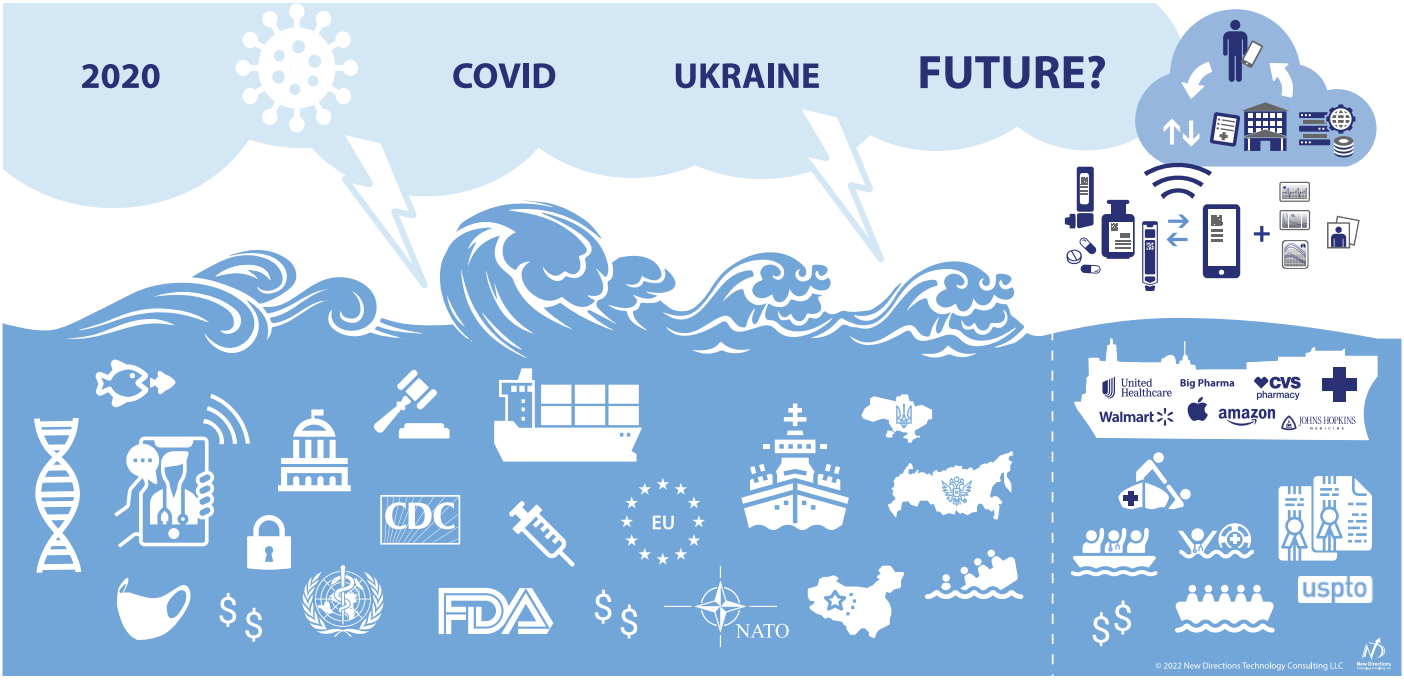

Figure 3: Navigating storms towards calmer seas and the rescue of patients from a battered and ailing healthcare system.

insurer formularies are expanding. Payment for outcomes rather than products is becoming more of a reality. AIDC (via serialised barcodes), connected devices and product support using telemedicine can help demonstrate outcomes and secure reimbursement.

The US is exceptionally litigious – settlements and incarcerations related to opioid marketing, price fixing and fraud have accelerated. Without knowledge of the entire supply chain, up to and including the patient and patient compliance, specious liability claims are harder to counter. As such, knowing the full supply chain is critical for avoiding specious liability claims.

US manufacturers and distributors are focused on strategic shifts in their mix of products and choice of foreign partners, with a focus on shortening supply chains, multisourcing and reshoring. Some pharma companies are in the process of divesting themselves of their foreign assets. Connectivity and AIDC can help discover and understand the changes occurring deep in supply chains as these changes take place. Additionally, cyberwarfare and unreliable suppliers are known to have disrupted some healthcare efforts and supply chains – connectivity and AIDC can help uncover both.

The covid-19 pandemic heightened the media's focus on other current and potential US epidemics, such as mental health; medication over-prescribing; the opioid crisis; obesity; cancer; drug non-compliance, non-adherence resistance, and ineffectiveness; and un- and undertreated diseases. In all these cases, increased compliance, as can be achieved using connected devices, can help improve patient outcomes. Pharma, government, patient support groups and various other corporate entities are keen to improve healthcare messaging. Connectivity allows stakeholders to tailor communication to those individuals who most need it and who can best use the available information to improve health outcomes.

> "Connectivity and connected devices could play a key part in rebuilding trust for all healthcare stakeholders."

Inflation has accelerated dramatically worldwide, and the US Federal Reserve has indicated that more interest rate increases are likely – costs are increasing in every sector and Pharma is no exception. However, any added cost resulting from connectivity can be justified based on the benefits it provides for all stakeholders, and is less likely to be apparent when all costs are rising across the board. Additionally, it should be noted that the known unreliability of some foreign intellectual property systems presents a great cause for concern about enforceability of patents in some out-of-US jurisdictions. This lends even greater weight to US patents.

It is becoming increasingly evident that, currently, there is a significant level of corporate and personal insecurity across society, which has led to the realisation that change must come to US civil society – including the broken US healthcare system. Connectivity and connected devices could play a key part in rebuilding trust for all healthcare stakeholders.

CONCLUSION

All these events flowed and continue to flow into waves of efforts to promote improvements in US healthcare that will lead to better patient outcomes. Some elements will continue to influence the 2020s and beyond. Of course, change is not without its downsides; changes are sometimes badly designed and badly communicated. The influx of non-MD healthcare practitioners has led to errors, miscommunication, confusion and non-responsiveness. The pace of change has accelerated. The events and attitudinal changes we are currently witnessing are both disruptive and invigorating (Figure 3).

Ultimately, the coming changes will necessitate connectivity in healthcare, drug delivery and packaging, allowing for more timely corrective actions as they are needed. It is inevitable that, going forwards, well-managed connectivity and connected devices will improve healthcare.

ABOUT THE COMPANY

In the area of drug delivery, New Directions Technology Consulting is the assignee for all patents in the mMed patent portfolio. Medication telemanagement systems based on the portfolio can be used to develop innovative health and wellness programmes.

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ABOUT THE AUTHOR

Napoleon Monroe is Managing Director of New Directions Technology Consulting, LLC, and the sole inventor on all the patents in the mMed patent portfolio. The filings in the portfolio were based on Mr Monroe's experience managing the development and post-market activities for the original EpiPen and nerve agent autoinjector drug delivery products, where he learned the value of understanding post-market events. Mr Monroe's diversified background ranges from developing and producing emergency pharmaceutical delivery systems to managing private brands for a Fortune 500 company, to building and managing the intellectual property portfolio for a company that is now part of Pfizer. His expertise includes product development, licensing, regulatory processes, risk management and international marketing, with experience managing business relationships in more than 30 countries.

Mr Monroe has been a Vice-President at two public companies where he was responsible for leading teams that invented, patented, prototyped, tested, performed clinical trials, commercialised, scaled-up, marketed and oversaw many post-market activities. One of the autoinjector developments led by Mr Monroe, the Antidote Treatment Nerve Agent Auto-Injector (ATNAA) delivery system, is still the leading drug delivery system for protection and treatment for the US and allied militaries, as well as US Homeland Security. Mr Monroe supported work towards the formation of Shahal Medical Services in Israel (parts of which were acquired by Shanghai Jiuchuan) and Raytel (now part of Philips in the US).

Mr Monroe is widely published on drug delivery and is active in several organisations that support connected drug delivery. He is an individual lifetime member of the American Telemedicine Association.

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SMART DRUG DELIVERY DEVICES IMPROVE MEDICATION ADHERENCE: HERE'S HOW

Here, Paul Edalat, Chairman & Chief Executive Officer, and Mehdi Hatamian, PhD, Senior Scientific Advisor & Interim Chief Scientific Officer, both at Vivera Pharmaceuticals, take an in-depth look at medication non-adherence and how technology can be used to improve compliance rates and optimise patient outcomes.

Prescription medication non-adherence is a significant concern for medical providers as it can negatively affect patient outcomes and accounts for a notable portion of treatment failures, deaths and hospitalisations every year. Yet, despite the recognition this issue receives, it is estimated that nearly half of patients do not take their medications as prescribed.[1]

WHAT IS MEDICATION ADHERENCE AND WHY IS IT IMPORTANT?

Medication adherence refers to how well a patient takes their medication as prescribed, meaning taking the correct dose correctly, at the right time and frequency. Adherence plays a crucial role in patient outcomes, including patients managing both acute and chronic conditions. Failure to adhere to medication instructions when trying to control any condition can worsen or progress the state of disease, prolong hospitalisations and adversely impact a person's overall quality, and even length, of life.

Non-adherence can also increase the cost of care. According to a 2018 study, non-optimised therapies cost the US an estimated US$528.4 billion (£421.4 billion) in 2016, placing a significant burden on an already strained healthcare system.[2]

IDENTIFYING NON-ADHERENCE

A patient is considered non-adherent if they take their medication according to their provider's instructions less than 80% of the time. The three main types of non-adherence include:

- **Primary non-adherence** – when the patient does not fill the prescription after their physician writes the order
- **Non-persistence** – when a patient stops taking their medication without their physician's consent
- **Nonconforming** – when a patient does not take their medication as prescribed. This type of non-adherence includes skipping doses, taking medicines at incorrect times and taking more or less than prescribed.[3]

CURRENT METHODS TO MONITOR ADHERENCE

Currently, several direct and indirect methods are used to measure medication adherence. Direct methods include direct observation or taking measurements of drug or metabolite concentration in body fluids. While direct methods are the most accurate, they are expensive and can be burdensome.

Patient self-reports are the simplest tool for measuring adherence. Other indirect methods include patient questionnaires, pill counts, prescription refill rates, patient clinical response assessments and diaries. These techniques are often inaccurate, as there is significant room for error, and patients often overestimate their own adherence.[4]

USING SMART TECHNOLOGY TO IMPROVE MEDICATION ADHERENCE

It can be challenging to track and monitor medication adherence. Without an accurate measurement of compliance, it can be difficult to evaluate the efficacy of a

> "A smart drug delivery device that collects patient usage data, such as dosage and timing, and shares it with the physician can improve medication adherence."

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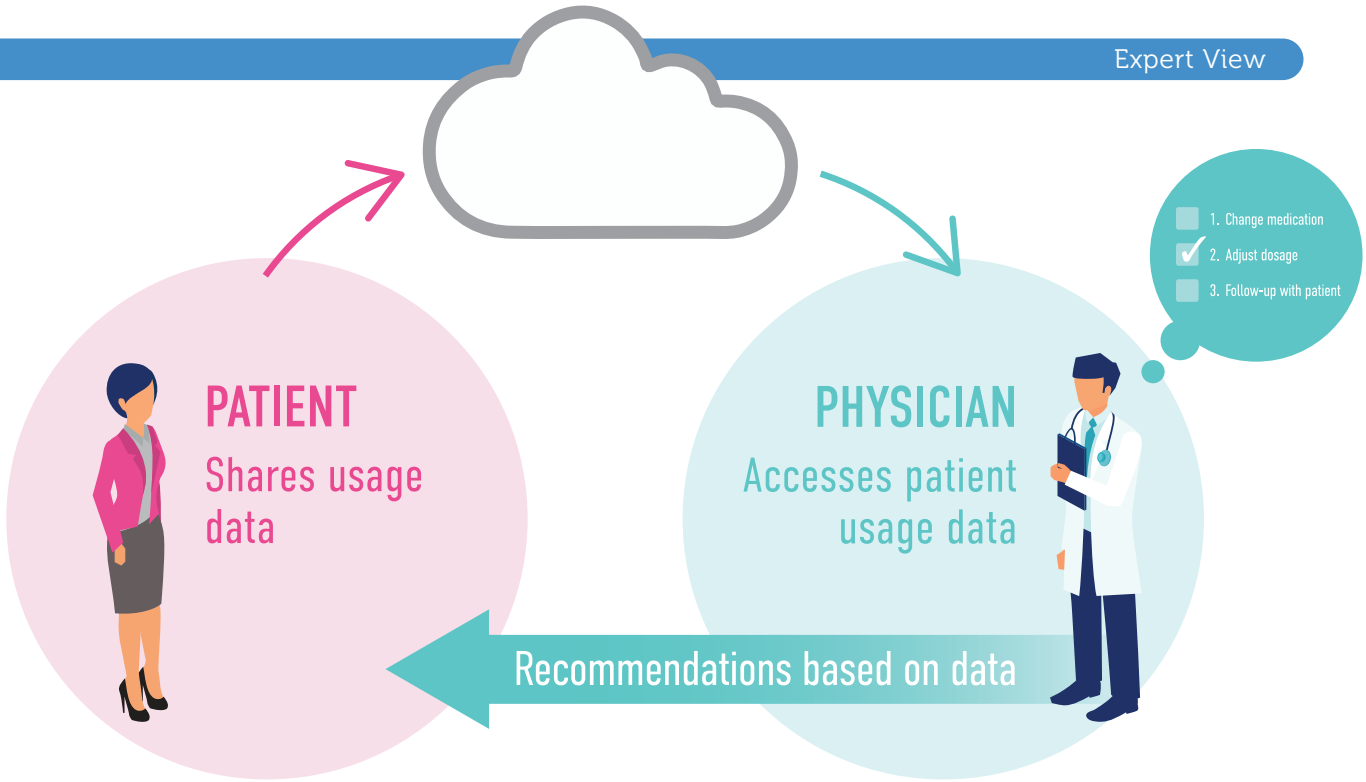

Figure 1: The patient uses the smart dosing device and the usage data is transmitted to a centralised database. The doctor can monitor and assess the patient usage data to make recommendations or adjustments to the patient's treatment plan.

> "If the patient is adhering to their regimen, the doctor can make appropriate adjustments, such as modifying the dose, changing the dose frequency or selecting a different drug altogether."

treatment plan, especially if an issue arises and a provider is unable to tell if a medication is not working or needs to be adjusted because the patient is not adhering to their regimen.

A smart drug delivery device that collects patient usage data, such as dosage and timing, and shares it with the physician can improve medication adherence. Such a device can allow physicians to track and monitor how well their patients are sticking to their prescribed medication regimen in real time, which can offer several benefits (Figure 1):

1. **Better-Informed Decision Making**
   Physicians will have accurate data to analyse how well a patient follows their medication schedule. This information will enable the physician to adjust a patient's treatment plan based on their actual behaviour instead of their reported behaviour.

   If the patient is adhering to their regimen, the doctor can make appropriate adjustments, such as modifying the dose, changing the dose frequency or selecting a different drug altogether. These changes will be ineffective if a person is not sticking to their instructions in the first place.
2. **Identify Underlying Reasons for Non-adherence**
   Accurate data can allow physicians to discover trends, which can then enable the physician to ask better questions about why a patient is not adhering to their medication regimen. For example, a patient prescribed to take medication twice a day may consistently take their medication as prescribed at night but not in the morning. The physician may uncover that the medication makes the patient sleepy or drowsy and may be able to adjust the dosage or prescribe a different medication altogether.
3. **More Productive Follow-up Appointments**
   In addition to making adjustments to the patient's treatment plan, physicians can also use the data from prescription delivery devices to have more productive follow-up appointments. Common reasons for non-adherence include forgetting to take doses, high drug prices, limited access to a pharmacy, the fear of or unreported side effects and the patient questioning if their medication is even necessary.

   By identifying issues related to an individual patient's adherence, physicians can have better conversations with them. The physician can help implement a programme or provide a smart device to help patients who forget to take medications on time. If a patient's insurance doesn't cover a drug, they can find a similar or generic drug that is covered under their plan. Physicians can also help patients understand the necessity of their medication and the consequences of not taking it.

SPECIAL ATTENTION TO OPIOID NON-ADHERENCE

There is an elevated risk of overuse when considering potentially addictive medications, such as opioids. A patient's side effects from overusing opioids include excessive sedation and respiratory depression. The rapid development of tolerance is also a significant concern, as it can increase the likelihood of addiction – a chronic disease characterised by compulsive drug-seeking behaviour despite any adverse effects.

> "Monitoring adherence to opioid medications has unique challenges because these medications are more likely to be hoarded, diverted or sold than, for example, medications for blood pressure management."

According to the results from a prospective evaluation, the implementation of adherence monitoring can reduce opioid abuse by as much as 5%.[5] However, monitoring adherence to opioid medications has unique challenges because these medications are more likely to be hoarded, diverted or sold than, for example, medications for blood pressure management.[6]

Using technology to connect the medication delivery device to the physician can alert the physician as soon as a pattern of misuse is detected. Additional technological advances, such as dose-controlled delivery, medication reminders and the ability to programme usage instructions into the device and only allow the prescribed dosage amount to be accessed according to the provider's orders, can make it easier for patients to comply with their medication regimen.

ABOUT THE AUTHORS

Paul Edalat has over 30 years of brand and product development experience in the nutraceutical, pharmaceutical and medical device sectors. He brings a keen eye and vision for business development and growth opportunities to Vivera. His forward-thinking management approach as Chief Executive Officer has seen Vivera grow from a single division to over six and counting. Leading Vivera's business development domestically and internationally, Mr Edalat works closely with the sales and marketing teams to anticipate and meet market demands. With trusted global relationships built over the decades, he has worked to leverage his connections and expand Vivera's reach.

Mehdi Hatamian, PhD, is a former NASA space shuttle programme engineer and, after a 20-year career at Broadcom (CA, US) as the Chief Scientist for Central Engineering, brings an engineer's mindset to Vivera. With over 100 issued patents and 50 scientific papers published, he is a scientist at heart. Dr Hatamian works closely with Vivera's team to expand its medical technology and medical device divisions, bringing not only his engineering expertise but also his knowledge of medical research. Dr Hatamian is currently developing ZICOH and next-generation cancer detection devices and technologies.

THE NEED FOR IMPROVED SOLUTIONS

How well a patient adheres to their medication regimen is directly correlated to the overall efficacy of a treatment plan – patients who take their medications as prescribed have better results than those who do not. Given that many patients do not adhere to their medication regimens, the need for smart drug delivery systems to improve patient adherence is evident.

ABOUT THE COMPANY

Vivera Pharmaceuticals is an innovative, science-driven pharmaceutical company located in Southern California. 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 medical device. It also has patents pending on its telemedicine station, MDZone. With multiple divisions, including its pharmaceutical, neuroscience, medical technology, bioscience and advanced diagnostics divisions, Vivera is vertically integrated with patented technology, manufacturing capabilities and distribution for its products.

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ON drugDELIVERY

2022/23 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
July 2022	Novel Oral Delivery Systems	Deadline passed
August	Industrialising Drug Delivery	Jul 7, 2022
September	Wearable Injectors	Aug 4, 2022
October	Prefilled Syringes & Injection Devices	Sep 1, 2022
Oct/Nov	Drug Delivery & Environmental Sustainability	Sep 15, 2022
November	Pulmonary & Nasal Drug Delivery	Oct 6, 2022
December	Connecting Drug Delivery	Nov 3, 2022
January 2023	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 1, 2022
February	Prefilled Syringes & Injection Devices	Jan 12, 2023
March	Ophthalmic Drug Delivery	Feb 2, 2023
April	Pulmonary & Nasal Drug Delivery	Mar 2, 2023
April/May	Drug Delivery & Environmental Sustainability	Mar 16, 2023
May	Delivering Injectables: Devices & Formulations	Apr 6, 2023
June	Connecting Drug Delivery	May 4, 2023

CYBERSECURITY AND THE CHALLENGES OF CLOUD CONNECTIVITY

Here, Gabrielle Whitworth-Smith, Engineering Consultant, and Thomas Watts, Engineering Consultant, both of Team Consulting, look at the benefits and risks associated with cloud connectivity and the accompanying cybersecurity challenges.

For the past few years, cloud connectivity has been creeping into every aspect of our lives, from doorbells to smart meters that track our energy usage. In the medical device and healthcare industry, cloud connectivity has the potential to unlock a wealth of benefits, both for the user and the manufacturer. Before you can begin, however, you first need to consider what you are trying to achieve and which technology best suits your needs. Building in cloud connectivity can also open up a host of cybersecurity challenges that need to be navigated, so it is important to be fully prepared for what this will involve when starting out on your development.

WHAT PROBLEMS CAN CLOUD CONNECTIVITY HELP SOLVE?

From allowing patients to share data about their condition and treatment direct with their clinicians, to offering manufacturers valuable insights into how their devices are being used, there are many reasons to consider building cloud connectivity into your system. While cloud connectivity can seem appealing, it is important to know exactly which problems you are seeking to solve with this technology before committing to building it into your development. Here are some of the common problems cloud connectivity can solve:

> "Monitoring aspects of device use with real patients can provide data to allow early identification of any malfunctioning devices or unforeseen use cases."

Post-Market Surveillance

With medical device regulation requiring more rigorous post-market surveillance, manufacturers need to proactively collect and review experience gained from their devices on the market. Cloud connectivity offers a means to collect this data in real time. Monitoring aspects of device use with real patients can provide data to allow early identification of any malfunctioning devices or unforeseen use cases.

Patient Adherence

Cloud connectivity can also be used to encourage adherence by tracking elements of patient interactions and providing more targeted feedback. For example, data can be gathered on a patient's administration approach and fed back to help improve their technique and efficacy. Tracking medication dosage and delivery time can also help patients manage their conditions through the use of reminders and alerts, while use data can also keep patients' clinicians informed.

Data Processing

You may wish to have some of your processing and analysis take place directly on your app, which can allow you to display information in real time to the patient. One of the benefits of cloud connectivity, however, is that potentially complex analysis and power-hungry data analytics can be sent to the cloud, allowing the hardware in the device to be kept simple and low cost. In addition, algorithms can continue to be developed and improved if calculations are performed offline.

How Can I Make My Device Connected?

Fundamentally, a cloud connected system collects, stores and shares data to servers accessed over the internet. When considering adding cloud connectivity to a device, it is important to determine how the data are going to be transferred to the cloud (Figure 1).

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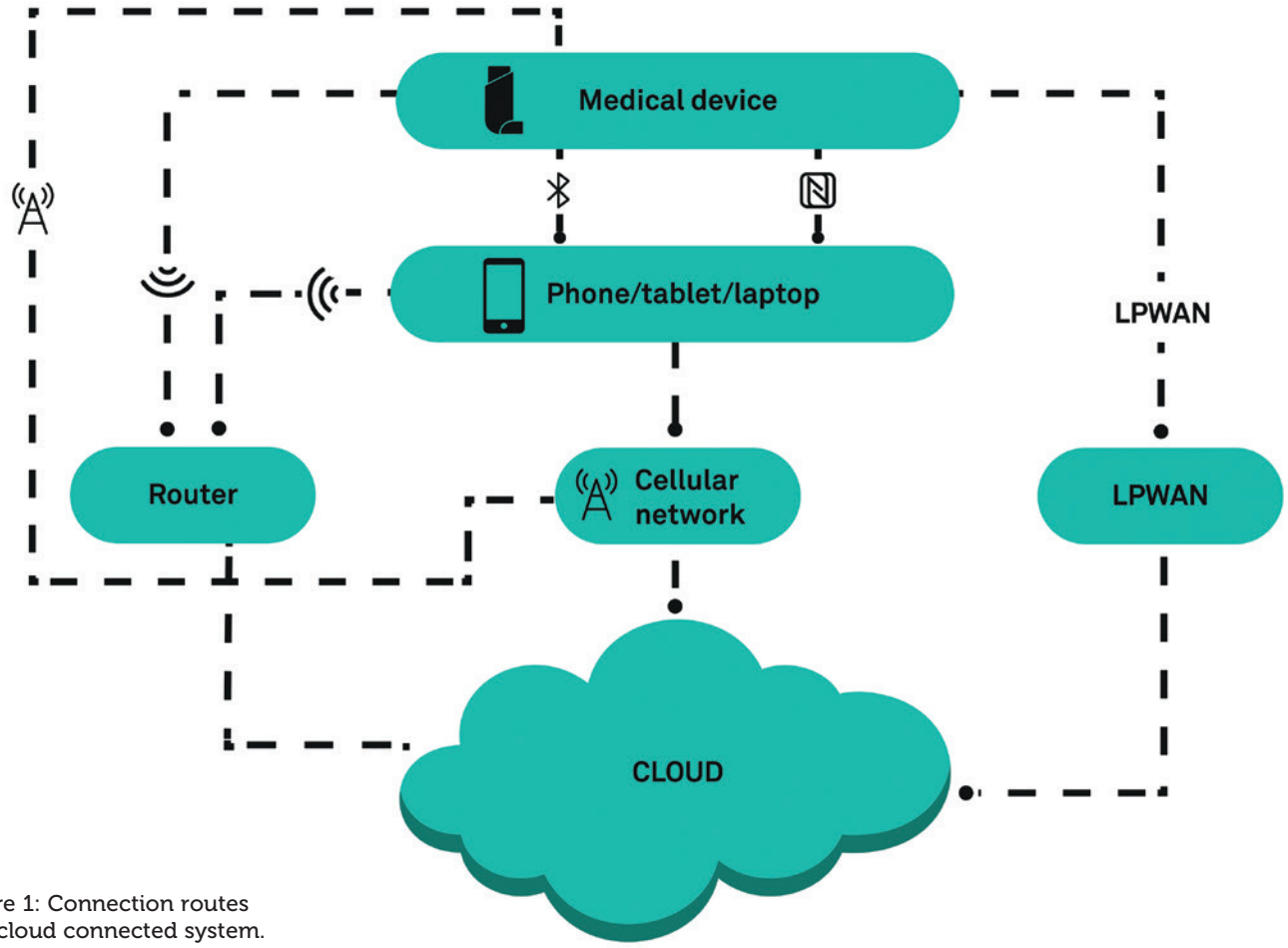

Figure 1: Connection routes of a cloud connected system.

"A smartphone approach to cloud connectivity presents an opportunity to build a custom smartphone app to help facilitate this, offering engaging ways to present the data back to the user, as well as a variety of other benefits."

Smartphones are a popular choice for facilitating this transfer. Using Bluetooth, Bluetooth low energy (BLE) or near-field communication (NFC), data can be sent from medical device to a user's phone. From the phone, data can be transferred to the cloud servers using its active network connection. It is worth noting that if the user's phone is connected via cellular networks this will add costs for the user.

Another mechanism to implement cloud connectivity is to build Wi-Fi, cellular or low-power wide area network (LPWAN) connectivity into the medical device directly, and access the cloud through a router, a cellular network or base station.

Once the data has been collected, you then need to consider how it will be analysed and displayed using a dashboard. A smartphone approach to cloud connectivity presents an opportunity to build a custom smartphone app to help facilitate this, offering engaging ways to present the data back to the user, as well as a variety of other benefits. It is also worth investigating how data could be shared and integrated with existing healthcare systems, such as electronic patient records, if this would be beneficial.

Which Connectivity Approach Should I Use?

When choosing an approach to relay data to the cloud, it is important to consider system requirements regarding power, range, speed and cost.

Bluetooth / BLE	
Features	• Low power (BLE) • Medium range • Medium data transfer rate • Well adopted among many modern devices • Existing support for making Bluetooth devices secure.
When to use it	**You want to provide a rich user interface** Bluetooth connectivity typically involves using a smartphone as a gateway, which creates the opportunity to develop a rich user interface via an app. **You have a low-power device** BLE has low power requirements for wireless communications, enabling connectivity to be added without needing significantly larger batteries.
Challenges	**Gateway device required** Bluetooth often requires a smartphone or similar device to act as a gateway to the cloud, although there are now routers with Bluetooth radios as well as Wi-Fi that allow BLE devices to connect directly. **Cybersecurity and user engagement** Pairing and bonding a device via Bluetooth will involve extra security steps, while exchanging encryption keys to protect data during transfer. This additional security may also require user to facilitate the bonding process.

NFC	
Features	• Low power • Short range • Low data transfer rate • Cheap.
When to use it	**Minimal data to transfer** NFC offers a low-cost and low-energy approach to extract data from a device. In some cases, the sensor could be powered passively, removing the need for an onboard battery.
Challenges	**Data packet size** This approach is only useful when a small amount of data is being transferred. A purely NFC solution does not provide continuous sensor monitoring **Data download and user interaction** You will need to consider how to make using the NFC feature a natural part of the user steps **Gateway device required** NFC requires a smartphone or reader device to act as a gateway to reach the cloud.

WiFi	
Features	• High power • Medium range (further than Bluetooth) • High data transfer rate • Widely available.
When to use it	**Static devices** Useful for devices which remain in one location **You need to transfer large volumes of data** With high-speed data transfer, Wi-Fi offers an effective connection to transfer larger volumes of data.
Challenges	**Range of use** The device needs to remain in range of the router to transfer the data to the cloud. **Access credentials** How to share access credentials on initial set-up of "headless" devices can be challenging.

Cellular	
Features	• Long range • High speed • Global coverage • Easy to scale, using existing network.
When to use it	**Operating in remote locations** You are able to get access to the cloud in places where Wi-Fi might not be available. **Non-static devices** Useful for devices which move around and don't remain in one location.
Challenges	**Power hungry** High data rate cellular, such as 5G, can consume significant amounts of power. However, LPWAN can provide a lower power alternative at the cost of lower data rates. **Additional costs** Cellular access incurs an additional cost from paying the mobile network provider for access, and the hardware solution component cost is also more expensive.

Cloud Services

When considering a cloud-based system, you need to decide whether to use an existing provider or if you want to create your own private cloud. Typically, existing cloud providers will have great tools to help with analysis and can enable fast set up, however, they will come with a regular fee.

Some of the main cloud service providers currently available are:

1. Google Cloud Platform
2. Amazon Web Services (AWS)
3. IBM Cloud Services
4. Microsoft Azure.

There are, of course, some benefits to creating your own private cloud. This approach will have a lower cost in the long run compared with the existing providers, which become more expensive as you

> "The level of cybersecurity protection within your system will be driven by the severity of harm that could be caused if a breach were to occur."

scale up. In contrast, creating your own will require a higher upfront cost but a lower cost as you scale up. When designing your system, it is typically best to design and architect it in such a way as to make it easy to transfer over to a private cloud either way. It is best not to be too reliant on one provider of specific cloud service tools as this will make migration between platforms more challenging, and it exposes your platform to risks associated with suppliers removing services and tools.

WHAT ARE THE CHALLENGES OF MAKING YOUR DEVICE CONNECTED?

Costs

Along with the many benefits that cloud connectivity can offer, there are, of course, also significant challenges. Adding cloud connectivity to a device will incur higher development and device costs due to the additional hardware and software required. Incorporating any electronics into a device will also result in a higher carbon footprint, increasing the environmental impact of the development. There will also be continuous maintenance costs for cloud hosting services and to support post-launch application updates, for example, maintaining compatibility with mobile operating system upgrades. It is important to weigh up the benefits that connectivity will bring against these increased costs.

Cybersecurity

Patient Safety

When determining the cybersecurity protections necessary for your system, the potential risks of a malicious or unauthorised user accessing different elements of your system should be considered. For example, could they intercept the data being transferred from the device to the user's phone? What harm could be caused if they manipulate the data undetected? Serious injury? Death? The level of cybersecurity protection within your system will be driven by the severity of harm that could be caused if a breach were to occur. It is equally important to consider what would occur if the system were susceptible to a denial-of-service attack and what harm could result to the patient if they were not able to access the system.

Data Privacy

In addition to patient safety, data privacy is also paramount to avoid large fines and protect your organisation's reputation. Compliance with data privacy regulations is key when handling healthcare data. For example, in the US Health Insurance Portability and Accountability Act, compliance must be demonstrated that an organisation has protected the privacy, security and integrity of protected health information.

Approach

Because of the potential risks of cybersecurity attacks, cybersecurity management for connected devices is of high importance, and the regulatory authorities are putting a lot of emphasis on this. The Association for the Advancement of Medical Instrumentation has published a guidance document for cybersecurity management of medical devices called "TIR57 Principles for medical device security – Risk management", which describes how to perform cybersecurity risk management within the requirements of the ISO 14971 standard. As part of the cybersecurity risk management, a threat model and threat analysis are performed to establish possible routes of attack, vulnerable assets to protect and the mitigations to put in place. Typical mitigations include end-to-end encryption of data, device authentication and keeping regular data back-ups. Penetration tests are carried out to investigate the existing protection and help identify any security issues. The important thing to remember is that cybersecurity should be considered early on in device development and not as an afterthought.

CONCLUSION

There are clearly many benefits and challenges that come with integrating cloud connectivity into a device. System requirements should be considered from an early stage, and make sure you choose the appropriate connectivity approach to best suit your needs. But most importantly, you need to ensure you have a clear plan for how you are going to use your connected solution. Do not expose your device to the challenges that accompany cloud connectivity without first understanding what benefit it will bring to both the device developer and the patient.

ABOUT THE COMPANY

Team Consulting is a leading medical device design and development consultancy focusing on the pharmaceutical and healthcare industries. Team is an expert in drug delivery device development and works with companies both large and small across Europe, the US and beyond. Combining its expertise and experience in industrial design, engineering and human factors, Team develops medical devices from early concept through to commercial launch. Team is accredited to ISO 9001:2000 and 13485:2003.

ABOUT THE AUTHORS

Gabrielle Whitworth-Smith is an engineering consultant at Team Consulting. In her role, Ms Whitworth-Smith applies her background in biomedical engineering to a wide variety of ongoing and potential projects. She has a first-class MEng Honours degree in Biomedical/Medical Engineering from Imperial College London (UK).

Thomas Watts is an electronics and software engineer at Team Consulting, where he specialises in embedded software development for medical devices. Before joining Team, Mr Watts worked for a company focusing on neonatal ventilator systems. He has an MEng in Biomedical Engineering from Imperial College London (UK).

HOW DIGITAL THERAPEUTICS ADD VALUE TO TREATMENTS FOR COMPLEX CONDITIONS

In this article, Romain Marmot, Chief Business Officer, Aptar Digital Health, discusses how external partners with a track record of developing digital therapeutics for numerous chronic conditions and therapies can help life science organisations implement digital solutions across their pipeline, adding value to each therapy while improving medication adherence and clinical outcomes.

While the term "digital therapeutics" has only been widely used for the last few years, the concept of delivering treatment and prevention programmes through digital applications has been studied since the turn of the century, when researchers were calling them "Internet interventions".

This means that the market for digital therapeutics is more mature than it may seem. The Digital Therapeutics Alliance product library lists nearly two dozen products that meet the organisation's core principles. These include publication of peer-reviewed outcomes, clearance or certification by appropriate governing bodies, and collection and analysis of real-world evidence.

It is clear that digital therapeutics have established their value proposition for care delivery and patient outcomes. The challenge for today's life science organisations is being able to deliver this digital experience at scale for the therapies they are bringing to market and for the various patient populations they are aiming to serve, all while remaining aligned with established provider workflows and standards of care.

HELPING PATIENTS MANAGE THE COMPLEXITY OF CHRONIC CONDITIONS

One important element of the value proposition for digital therapeutics is their potential to assist patients who must manage a chronic condition, such as diabetes, cancer or an autoimmune disease, throughout their lives. Lifelong management is possible today, largely due to the development of therapies that increasingly target the biological process, rather than simply treating the symptoms of the disease.

If there is a downside to highly targeted therapies, it is that they tend to require more engagement than a once-a-day pill. Inhalers for asthma or other respiratory conditions are most effective when patients shake the device and take a breath before actuating the inhaler. Injectable therapies for conditions ranging from diabetes to autoimmune diseases require a specific angle for properly dispensing each dose. Other medications come with dosing requirements that change over time.

This is a key unmet need in chronic condition management. Clinical teams can train patients at the point of care, but they typically cannot be present when patients

> "For therapies that patients may take only once every few weeks, the consequences of a missed or incorrect dose can be significant."

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administer a therapy at home. Additionally, dosing requirements and other aspects of self-administration often differ from one patient to another. It can be difficult for clinical teams to address the nuances of dosing, self-administration, actuation or angle of injection in a short clinical appointment. For therapies that patients may take only once every few weeks, the consequences of a missed or incorrect dose can be significant.

This is where digital therapeutics can play a pivotal role. Instead of receiving generic pamphlets about managing their chronic condition, a digital solution can provide patients with a mix of educational materials, individualised dosing guidelines, self-administration support and tools for tracking and managing potential side effects – all specifically created for their targeted therapy. Advanced solutions may even come with a training device to help patients better understand what it feels like to spray or inject the proper dose without needing to administer the therapy itself.

"A digital solution can provide patients with a mix of educational materials, individualised dosing guidelines, self administration support and tools for tracking and managing potential side effects – all specifically created for their targeted therapy."

BEST WHEN ALIGNED WITH CLINICAL WORKFLOWS AND STANDARDS OF CARE

Through these features, digital therapeutics have the potential to increase the clinical effectiveness of a therapy, boost patient confidence in their ability to manage their condition and reduce the friction that clinical teams often face when patients have been prescribed a highly targeted therapy with a steep learning curve.

That third benefit – reducing friction – is an important factor in the effective development, implementation and use of digital therapeutics. After all, a digital solution that does not align with existing standards of care or with existing clinical workflows will only add complexity to the care process, limiting adoption among prescribers and access to patients who would benefit from a digital solution.

Let us consider each of these points in greater depth. First, there are standards of care for the management of chronic conditions already in place in hospitals, health systems and clinics around the world. These standards are based on a wide body of peer-reviewed clinical evidence and, through the experiences of frontline caregivers, have been uniquely tailored to meet the needs of local populations.

"By increasing the visibility of numerous aspects of a patient's response to a given therapy, digital therapeutics give clinical care teams new insights into patient outcomes."

Rather than create a new standard of care, the most effective digital therapeutics elevate this existing standard of care. These solutions address the key challenges of chronic condition and medication management, while routinely collecting valuable data on metrics such as medication adherence, potential side effects, disease progression and changes in vital signs.

By increasing the visibility of numerous aspects of a patient's response to a given therapy, digital therapeutics give clinical care teams new insights into patient outcomes. Providers can make more informed care decisions, proactively change care pathways instead of waiting for patients to come to them and take action without requiring an in-person visit, removing a barrier to care for many patients.

However, this can only happen if a digital solution aligns with existing clinical workflows. Integration with industry-leading electronic health record (EHR) systems is a must-have. Requiring providers to leverage a separate clinical application

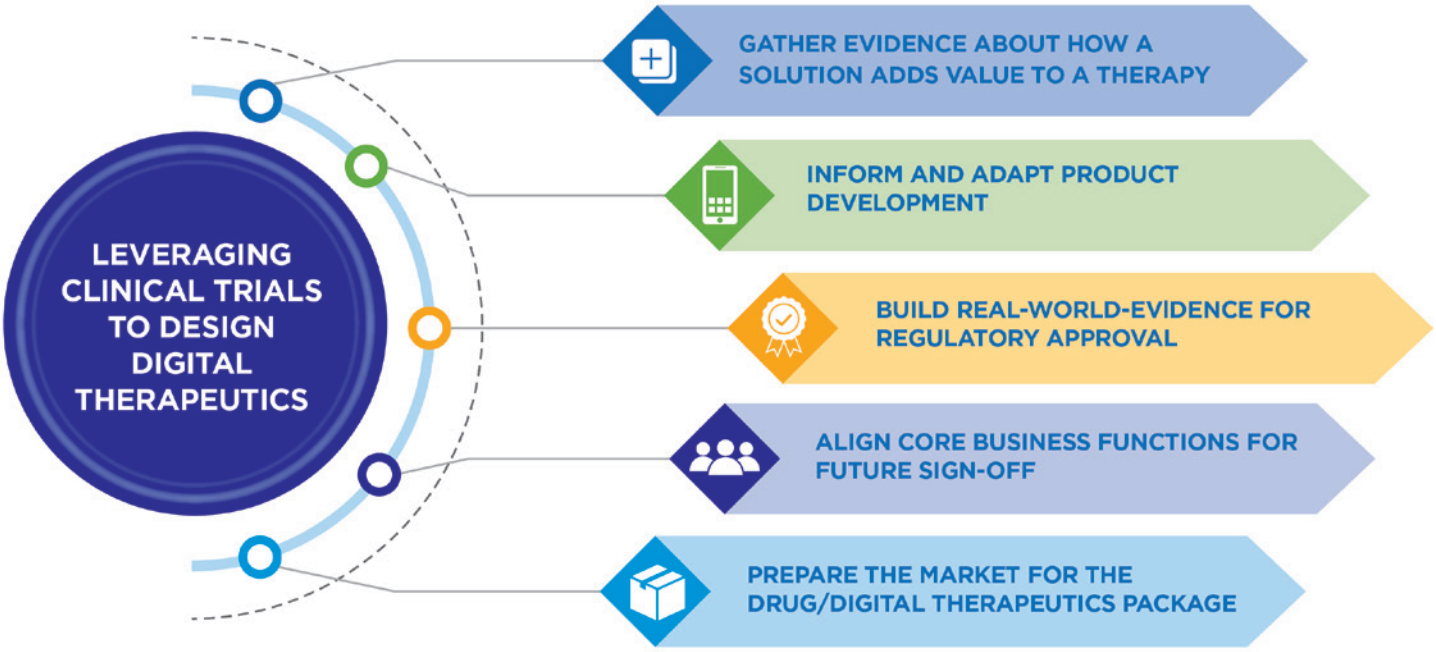

Figure 1: Making digital therapeutics design a product development priority.

with a unique username and password is a non-starter in any clinical setting.

Two additional factors contribute to successful alignment with clinical workflows, the first being where the digital therapeutic should integrate within the EHR. Research has shown that the average care appointment lasts 18 minutes – to make the most of this limited time, physicians need input and support from the digital solution at the moment when a conversation about therapeutic options is most likely to be taking place.

The second factor is how information should be presented within the EHR. As clinical teams are already inundated with data from numerous sources, any data coming from a digital solution needs to be presented contextually, focusing solely on what is actionable for the healthcare provider and what is relevant for the care decision that must be made at that time. This is true both at the point of care and as clinical teams review data between visits.

MAKING DIGITAL THERAPEUTICS DESIGN A PRODUCT DEVELOPMENT PRIORITY

While the benefits of digital therapeutics are clear, so too are the challenges of incorporating them into clinical workflows. The best way to meet these challenges is with a carefully planned and executed product design process that considers how a digital solution will be used alongside a given therapy (Figure 1).

"While the benefits of digital therapeutics are clear, so too are the challenges of incorporating them into clinical workflows."

This design process cannot be an afterthought. In order to bring value to patients in the real world, design of digital therapeutics should begin well before product launch, ideally in parallel with drug development. Starting the design process during clinical development offers five advantages:

1. Just as the life science organisation generates a body of evidence about the safety and efficacy of the therapy being studied, the developer of the digital therapeutic gathers evidence about how a solution adds value to a therapy – a vital component of product approval.
2. Feedback about how the digital therapeutic is used in conjunction with the therapy can inform numerous aspects of product development, such as integration into the clinical workflow or the patient-facing user experience. This allows developers to make early modifications and continue to test the solution on users (trial participants).
3. Evidence gathered through the digital solution provides the life science organisation with a key source of patient-reported data, which generates additional evidence that can supplement an application for regulatory approval, as well as inform decisions about additional use cases for a given therapy.
4. Conducting digital therapeutic design alongside the clinical development of the drug puts the digital solution in front of the core business functions that must ultimately sign off on it – legal, regulatory, clinical, compliance, quality assurance and, ultimately, marketing and commercial.
5. The therapy and its accompanying digital therapeutic can come to market at the same time and be promoted as an all-in-one package. This clarity in messaging will shorten the learning curve for educating providers and patients about the digital solution, which will contribute to increased adoption.

LEVERAGING THE EXPERIENCE OF PROVEN PARTNERS

Developing a digital therapeutic in parallel with the therapy it will support may make practical sense but many life science organisations struggle to do this, which is understandable. These organisations are steadfastly focused on gaining regulatory approval for the therapy under development, especially as a clinical trial reaches Phase III. In many cases, digital therapeutics are not a core competency for such organisations.

Figure 2: Leveraging the experience of proven partners.

For these organisations, the value of partnership with industry leaders becomes clear – particularly partners with a proven track record of supporting therapy assets throughout the product lifecycle and a decade or more post-market (Figure 2). There are four areas where partnership proves valuable:

Moving at the Right Pace

It may take a life science organisation 15 years to develop a molecule for the market. This is in stark contrast to the pace of developing digital solutions, which could go through a dozen iterations in the same length of time. Experienced partners can balance the slow pace of drug development with the fast pace of software development and manage product timelines accordingly.

Future-Proof Development

Likewise, while a drug rarely changes in formulation, a digital solution will change frequently, primarily as web browsers or mobile operating systems and devices are updated. The right digital therapeutics partner will be ahead of the curve here, building product components in such a way that they are minimally impacted by updates to consumer devices and therefore require little downtime to fix.

The Flexibility of a Platform

A digital therapeutic developed as a point solution will quickly outlive its usefulness if it cannot be applied to a different therapy's unique challenges. The same is true of an underlying infrastructure that can only be accessed with significant custom development. Life science organisations should seek partners that offer a platform with a range of available services that can accommodate differences in clinical workflow, EHR integration, patient needs and hardware support. A broad spectrum of capabilities is better suited to meet the needs of multiple digital solutions.

Non-Technical Services

In addition to the platform and other technology infrastructure, a digital therapeutics partner should be able to provide non-technical support services. One example is market access, as regulations (as well as overall market characteristics) differ dramatically across different geographic areas. Another example is payer reimbursement, which can be significantly different for digital therapeutics than for therapies themselves.

CONCLUSION

In just a few years, digital therapeutics have evolved into valuable tools for helping patients manage chronic conditions. These digital solutions work best when they have been designed to complement a specific therapy, beginning from product development and extending into post-market support.

Many life science organisations lack the in-house expertise to build digital therapeutics on their own, especially amid the myriad challenges of bringing a therapy to market. External partners with a track record of developing digital therapeutics for numerous chronic conditions and therapies can help life science organisations implement digital solutions across their pipeline, adding value to each therapy while improving medication adherence and clinical outcomes.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, from formulation to patient, providing innovative drug delivery systems, components and active material solutions across the widest range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early-stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, Aptar Digital Health is leading the way in developing digital health solutions to help improve the patient treatment experience. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc.

ABOUT THE AUTHOR

Romain Marmot, Chief Business Officer, Aptar Digital Health, and Co-Founder of Voluntis, an Aptar Pharma company, has more than 20 years of experience in the digital health and software as-a-medical-device industries. He has led several development programmes of digital therapeutics that were ultimately cleared by regulatory authorities and reimbursed by payers, as well as engineered multiple long-term collaborations with global pharmaceutical leaders around companion apps and drug-digital combinations. Mr Marmot holds an MSc degree from CentraleSupelec (University of Paris-Saclay, France) in Applied Mathematics.

NO TYPE: AN APP TO PREDICT PATIENTS' LIKELIHOOD TO TAKE MEDICATION AS PRESCRIBED

Here, Louisa Harvey, Alper Hulusi, Bjarki Holm and Stefan Olafsson, all Co-Founders of No Type, introduce their quick and accessible app for identifying whether a patient is likely not to take their medication as prescribed.

WHAT IS NO TYPE?

No Type is an accessible, quick-to-use app that focuses on the psychological, attitudinal and environmental traits that affect medication-taking behaviour (Figure 1). These traits have been identified over decades of research involving over 10,000 people who live with a chronic condition. The No Type app can identify whether or not someone who lives with a chronic condition is likely to struggle with taking their medication as prescribed.

THE ISSUE AT HAND

Many people who live with a chronic condition struggle to take their medications as prescribed.[1–6] This has a substantial impact on patients, affecting their opportunities, health outcomes and quality of life.[6,7] The emotional, psychological and physiological burdens of life with a chronic condition can all play a part in impacting a person's medication-taking behaviour.[8]

Beyond the patient, the economic impact of patients not taking medication as prescribed is well documented, with the annual adjusted cost per person ranging from US$1,000 to US$44,000 (£806 to £35,500), depending on the condition.[9] In the UK alone, this issue is estimated to cost the UK NHS £500 million per year.[10]

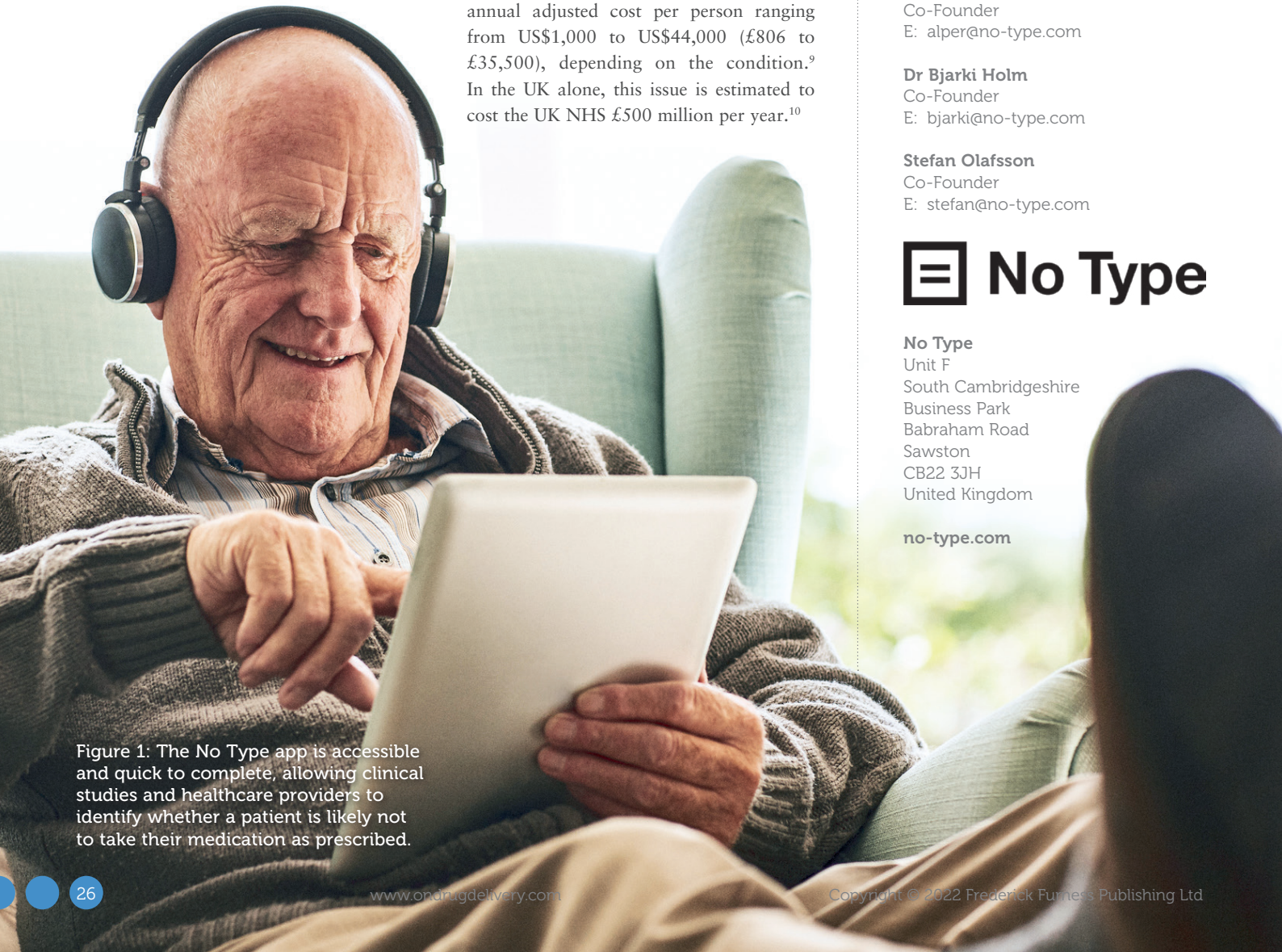

Figure 1: The No Type app is accessible and quick to complete, allowing clinical studies and healthcare providers to identify whether a patient is likely not to take their medication as prescribed.

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As well as the impact on patients living with a chronic condition and the wider economic impact, this issue increases the requirement for healthcare professionals to monitor their patients. In 2018, the global patient monitoring device market was $20.3 billion and is predicted to rise to $25.9 billion by 2023.[11] This expenditure significantly increases the cost per patient of medication and medical devices.

WHAT IS BEING DONE TO UNDERSTAND THE ISSUE?

Pharmaceutical and medical device companies regularly commission market research and human factors studies to understand the reasons why patients struggle to take their medication as prescribed or use their medical device as intended. However, patients who find it more difficult to take their medication as prescribed often represent a relatively low proportion of patients who take part in this type of research.

This issue stems largely from research companies unknowingly tapping into online communities and patient databases, and adopting recruitment approaches that tend to capture people who are more likely to take their medication as prescribed. Such people are more likely to respond to research invitations, search out research opportunities or be part of an online research database.

The outcome of this bias is that research insights and device developments are heavily influenced by a niche voice, representing patients who are more likely to take their medication or use a device as intended, regardless of the device design.

WHAT DOES NO TYPE AIM TO ACHIEVE?

The No Type App has four broad objectives, namely:

1. To give people who often struggle to take their medication as prescribed a greater voice in human factors and market research
2. To help improve the therapy experience, quality of life and health outcomes of people who live with chronic conditions
3. To avoid the natural bias involved in current participant recruitment practices, which tends to select for a niche population
4. To ensure device development incorporates a more holistically representative patient voice.

Let's be clear – there are sensitivities and errors that must be considered when discussing the issue of medication-taking behaviour. Discussions of this nature frequently come from a perspective and include terminology that is value-loaded, negative and places much or all of the blame on patients. In contrast, the No Type app was born out of a strong commitment to uphold the integrity of and empower people who live with chronic conditions, as well as to acknowledge diversity of views, experiences and challenges that people who live with chronic conditions live and breathe on a daily basis.

> "The No Type app was born out of a strong commitment to uphold the integrity of and empower people who live with chronic conditions."

DON'T TOOLS ALREADY EXIST?

The Medication Adherence Report Scale (MARS), a self-reported measure developed in 1999, is used extensively to measure medication-taking behaviour – often referred to as "adherence". However, this tool can be inaccurate in identifying someone's likelihood to struggle to take their medication because it only measures current behaviour (which may be influenced by a second party supporting a patient in taking their medication) and fails to tap into a patient's fundamental likelihood to take their medication as prescribed without external support. MARS, like other tools, sometimes gathers "false" information, with some people unintentionally responding to questions in a way that presents their life in a more socially acceptable light.

Many years of experience in the field of patient behaviour have demonstrated that, with skilful qualitative moderation, it is possible to identify and explore someone's medication-taking behaviour during in-depth interviews. Often, once rapport and trust has been established between a patient and a skilled interviewer, the patient starts to reveal their "true" medication-taking behaviour and the reasons behind it. In an ideal world, tools for exploring medication-taking behaviour would replicate the strengths and benefits of this qualitative dynamic to elicit true insights where medication-taking behaviour is concerned.

WHY IS NO TYPE IS BETTER THAN CURRENT TOOLS?

The No Type app offers a number of key benefits over the tools currently used to gauge a patient's likelihood to take their medication as prescribed (Figure 2). First, the app is as good as skilled qualitative interviewing for detecting people who are more likely to struggle with taking their medication. Second, the app is accessible and quick to complete on any tablet, phone or PC. Third, the app provides a quick output to those screening people into human factors and medical market research studies to ensure that they can include (or exclude) people according to their research objectives.

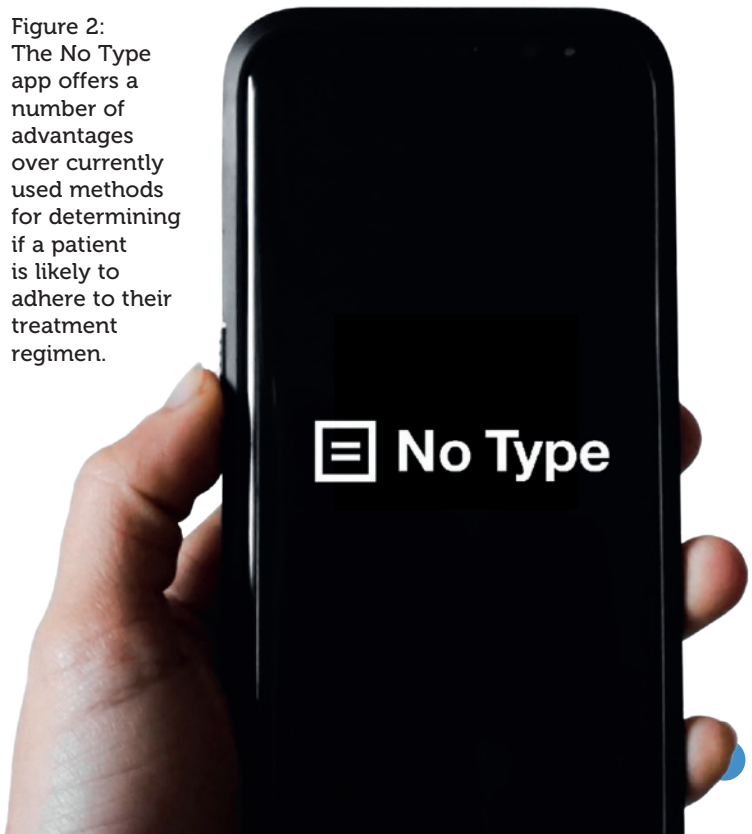

Figure 2: The No Type app offers a number of advantages over currently used methods for determining if a patient is likely to adhere to their treatment regimen.

HOW WAS THE APP VALIDATED?

A total of 118 participants were sent a link to the No Type app, along with a unique code, and were asked to complete the questions presented to them. The overall sample included a mix of men and women from the south of England aged 18–85 years, all of whom had a chronic condition and were taking regular medication – including for asthma (29.7%), anxiety (27.1%), depression (27.1%) and high blood pressure (24.6%). Most participants (86%) were taking tablets to treat their condition, but the sample included patients using inhalers, injectors and pumps. Over a quarter of the participants were using two or more medications with different modes of administration (e.g. tablets, an inhaler and an injection pump). Most of the participants were employed, and their level of education ranged from primary school through to PhD level.

The participants were recruited to the study using a broad range of approaches. To enable appropriate validation of the app, all participants had to be fluent in English and comfortable using technology such as smartphones. For the purpose of the study, factors such as geographical location and ethnicity were not purposefully screened for. The questionnaire contained in the app included 27 questions, formulated using information from a literature search on adherence algorithms, combined with the expertise in qualitative research that the No Type development team has developed over the course of thousands of interviews exploring medication-taking behaviour. Participants were blinded to the outcome and their responses.

Having completed the questionnaire, the participants were telephoned a few days later by an expert qualitative researcher who conducted an in-depth one-to-one telephone interview with them, lasting approximately one hour. Importantly, the interviewer was blinded to the participant's quantitative results from the online questionnaire. After building rapport with the participant through a discussion about their condition and treatment, the interviewer asked a series of questions about the participant's current medication-taking and factors that impact their ability or willingness to take their medication, as well as any changes they had noticed in their behaviour over time.

Based on the interview, the researcher was able to define, in their opinion, the participant's likelihood to take their medication as prescribed. Participants were categorised (internally) as either "likely to take their medication as prescribed" (takes their medication at least 80% of the time) or "unlikely to take their medication as prescribed" (takes their medication less than 80% of the time, or might take one medication as directed and not another owing to their beliefs about the medication). The insights gleaned from the follow-up qualitative interviews were then compared with the results from the online survey.

> "The results indicate that the app identified patients who are unlikely to take their medication as prescribed at a sensitivity of 90%, with a 95% CI of 73–98%, and a specificity of 94%, with a 95% CI of 87–98%."

HOW DID NO TYPE FARE?

Based on the qualitative interviews, 89 participants were identified as being likely to take their medication as prescribed and 29 as unlikely to take their medication as prescribed. The team witnessed a strong concordance between the qualitative interviews and the app, which also identified 84 participants as likely to take their medication as prescribed (true negatives) and 26 as unlikely to take their medication as prescribed (true positives). Compared with the qualitative data, the app incorrectly labelled five participants as "likely to take their medication as prescribed" as opposed to "unlikely to take" (false positives) and three participants as "likely to take their medication as prescribed" instead of "unlikely to take" (false negatives).

The results indicate that the app identified patients who are unlikely to take their medication as prescribed at a sensitivity of 90%, with a 95% confidence interval (CI) of 73–98%, and a specificity of 94%, with a 95% CI of 87–98%. Clopper–Pearson CIs were calculated using the epiR package in R. Therefore, the No Type app was determined to be over 90% accurate at predicting likelihood to take medication as prescribed.

POTENTIAL USES OF THE NO TYPE APP

The issue of whether or not someone takes their medication as prescribed is both complex and dynamic, with far reaching consequences for the patient (physiologically, emotionally and practically), healthcare system and the wider economy. The No Type app offers medical device market research and human factors companies the means to identify and recruit suitable participants for their research.

Beyond the world of market and human factors research, the No Type app has many other potential uses. These include enabling healthcare teams to identify patients' support and guidance needs at the point of being diagnosed with a chronic condition.

Moving forward, the No Type team is committed to putting the app and algorithm through its paces by running further studies

with broader and larger samples, including reflecting greater ethnic and condition-related diversity, as well as validating the app overseas. But for now, the results are exciting and represent a step forward in ensuring that medical device design efforts are inclusive of all patient voices, needs and experiences.

ABOUT THE COMPANY

No Type is a patient-centric medical behaviour technology company based in Cambridge, UK. No Type was founded by a team with experience across medical devices, usability research and technology with an aim to help improve patient voice and improve medical devices and pharmaceuticals globally.

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HOW RECENT NFC ADVANCES ENABLE ANTI-COUNTERFEIT DRUG CONTAINMENT AND SUPPORT ADHERENCE

In this article, Sylvia Kaiser-Kershaw, Senior Global Marketing Management, Connectivity & Security, at NXP Semiconductors Austria, discusses how recent near-field communication tagging advancements can enable pharmaceutical companies to protect the authenticity and integrity of their products, while also making it easier for healthcare professionals and patients to use medications more effectively through intelligent drug delivery systems.

THE RISE OF COUNTERFEIT DRUGS

Today's pharma industry faces an ever-increasing array of challenges, including rising numbers of counterfeit products, attacks on its supply chains, adverse conditions affecting the integrity of its products and how to ensure customer loyalty. The WHO estimates that around 10% of all medicines sold worldwide are counterfeit.[1] The latest intellectual property crime threat assessment report, produced jointly between Europol and the European Union Intellectual Property Office (EUIPO), found that an increasing number of counterfeit pharmaceutical products have been identified in recent years.[2]

The typical targets for pharmaceutical counterfeiting include expensive drugs, such as vaccines, cancer medicines and antibiotics; however, a significant number of counterfeit high-demand products, such as face masks and hand sanitisers, were also identified during the covid-19 pandemic. As supply chain complexity, from production to packaging, distribution and sales across different markets, and the prevalence of e-commerce, such as online pharmacies, increase throughout the pharma industry, this counterfeiting problem is becoming more widespread.

CONVENTIONAL ANTI-COUNTERFEITING METHODS

Pharma companies have tried numerous ways to fight drug counterfeiting by using item-level serialisation and optical codes, such as data matrix and QR codes. These coding systems are static and relatively easy to copy, which limits their ability to prevent counterfeiting. The data matrix system is based on serialisation legislation, providing traceability throughout the distribution supply chain until the point of dispensation but does not include the last mile to the patient. Additionally, optical devices lack the functionality to operate as advanced "sensor platforms" – they cannot register external events, such as tampering or a change in fill level or temperature.

Figure 1: Counterfeits are easy to spot because brand inspectors, pharmacists and consumers can verify product authenticity with their smartphones.

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"Some of the latest NFC smart tags come with a SUN authentication message for web authentication, which changes dynamically upon each scan or "tap", allowing pharma companies to combat counterfeits and supply chain fraud more effectively."

NFC FOR AUTHENTICATION AND TAMPER-PROOFING

Near-field communication (NFC) smart tags can be read by any NFC-enabled device. Globally, there are about 3.4 billion NFC-enabled devices, primarily smartphones, in use today.[3] This form of authentication does not require a costly specialised reader device and can be done by anyone involved in the authentication and tracking process.

Beyond a unique identifier, NFC authentication tags come with additional electronic security attributes. Some of the latest NFC smart tags come with a secure unique NFC (SUN) authentication message for web authentication, which changes dynamically upon each scan or "tap", allowing pharma companies to combat counterfeits and supply chain fraud more effectively. By adding a unique ID, tap counter and status value to the programmed NFC message, along with a cryptographic message authentication code, only an original tag can generate a valid SUN message, and each tagged item can be reliably authenticated, while its digitised status value is protected against malicious changes.

When using NFC authentication, counterfeits are easy to spot because brand inspectors, pharmacists and consumers can all verify product authenticity using their smartphones without downloading a special app (Figure 1). Patients can even become more deeply engaged with their medication supplier by taking advantage of on-demand access to product information and dosage instructions, including videos, helpful digital tools and more.

A unique tag ID can be assigned to a specific distributor and location, reporting their origin and intended destination at any point in the supply chain. In addition, some tags offer a mutual authentication option with a cryptographic key, ensuring that only an authorised reader or server can access the tag's data. The tag only releases data to an authenticated reader when the tag is confirmed, protecting sensitive tag data against unauthorised access and/or malicious change attempts in the supply chain.

Electronically tamper-evident NFC conductive seals and labels can be attached to drug packaging at the point of manufacture to protect against unauthorised opening. When the conductive loop in the seal breaks, it irreversibly writes the "once opened" status into the tag memory and sends the opened status to the cloud with the tap of a phone. In comparison, capacitive tamper-proof tags measure capacitance and compare it with preconfigured limits upon readout with an NFC-enabled smartphone. When these limits are exceeded, the open status is added to the SUN message. This mode of tamper detection is difficult for fraudsters to reconstruct and is suitable for integration into physical form factors such as bottle closures. Both tamper-evident modes work with web-based authentication.

Innovative NFC tags with a capacitive structure can also be used as passive sensing devices to detect changes in a condition, such as moisture or fill level, without a battery. Here, if values are outside the predefined range, changes in capacitance are captured by the NFC device and then interpreted by a cloud or smartphone application.

"Innovative NFC tags with a capacitive structure can also be used as passive sensing devices to detect changes in a condition, such as moisture or fill level, without a battery."

NFC FOR MANAGING CHRONIC CONDITIONS

Beyond counterfeit and illicit drugs, the healthcare industry and, in particular, pharma companies are facing another challenge, which is the global increase in chronic illnesses and how best to treat them. In 2019, the Global Burden of Disease (GBD) study reported that chronic conditions now account for millions of deaths worldwide each year.[4]

While metabolic conditions, such as obesity, diabetes, hypertension and high cholesterol, have the most significant impact on health, other conditions, such as asthma, arthritis and mental disorders, are also on the rise. Treatments for these illnesses typically require long-term use of medications, and it is not always easy for patients to stay on track. Not getting their prescription filled on time or forgetting to take their medication are just two common ways patients can struggle to stick to their prescribed dosing regimen. For patients taking multiple medications for a range of conditions, there can also be an issue of not understanding the directions for proper dosing or uncertainty of when to take each medication, also known as medication adherence.

According to the WHO, patient adherence to long-term medication therapy in developed countries averages 50% of patients, with even lower rates in developing countries.[5] The consequences of lapses in medication adherence can lead to poor health outcomes for patients and increased healthcare costs. This is a challenge NFC tags can help with.

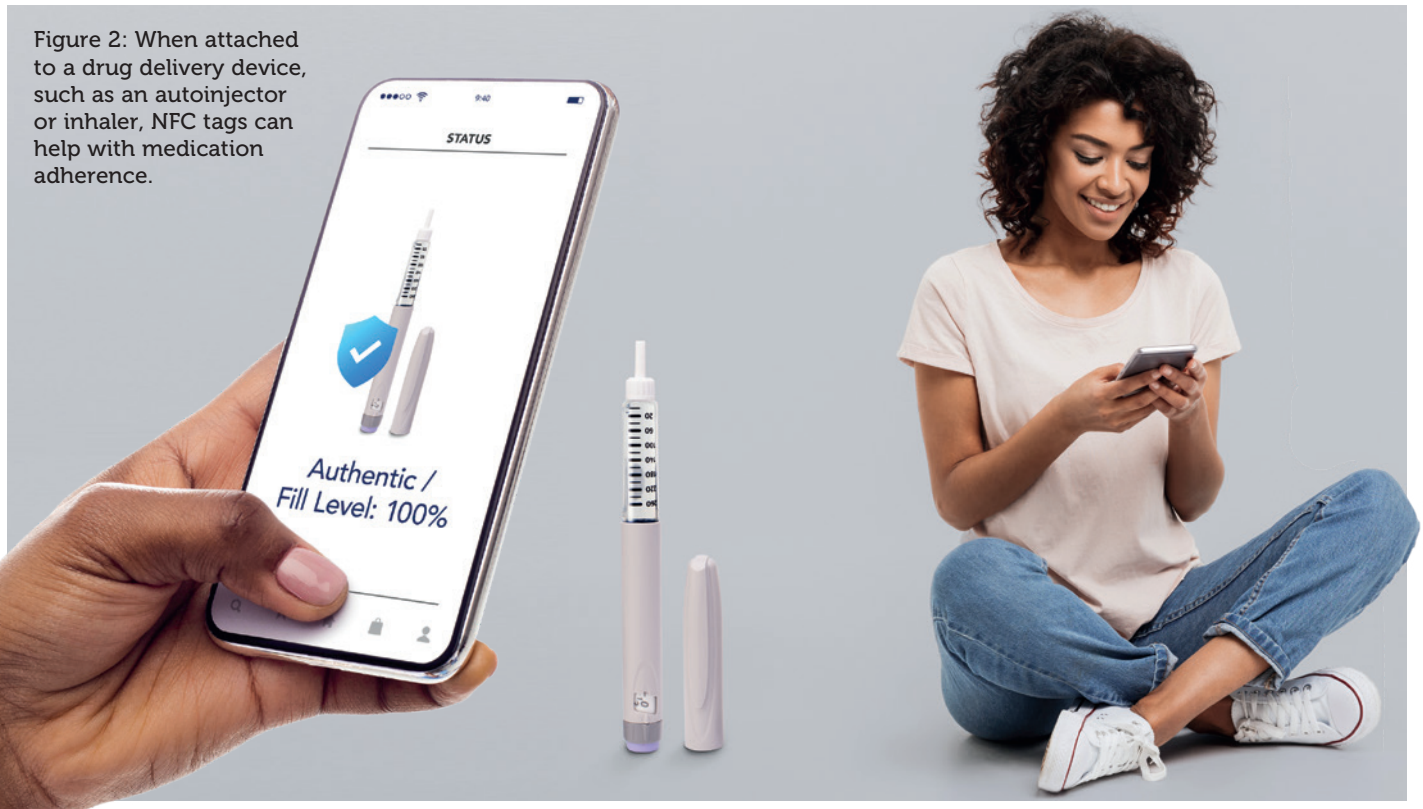

Figure 2: When attached to a drug delivery device, such as an autoinjector or inhaler, NFC tags can help with medication adherence.

"When attached to a drug delivery device, such as an autoinjector or inhaler, NFC tags can aid patients with medication adherence."

When attached to a drug delivery device, such as an autoinjector or inhaler, NFC tags can aid patients with medication adherence (Figure 2). By simply tapping a tagged device with a smartphone, a link can be created to medication guides and usage videos, including advice on possible side effects and other helpful information. Patients can also set up daily reminders for their treatments by downloading a specific app.

For multi-use refillable drug delivery devices, adding an NFC reader can help in additional ways. When built into the drug delivery device, the reader can authenticate the NFC tag on a prefilled drug consumable, such as a cartridge, confirming that it is from a trusted source. If the NFC tag is encoded with the drug's expiration date, the reader on the device can also confirm that it remains viable. In addition, the reader can record that the medication has been taken after each dose, and the tag can even store the incremental counter value. Adding Bluetooth connectivity to the drug delivery device can ensure that this data syncs with the patient's mobile app. This data can also be stored securely in the cloud so that, with a patient's permission, their healthcare practitioner can track their adherence history and provide personalised feedback (Figure 3).

Advanced battery-free capacitive sensing NFC technologies can also detect fill levels. Smart injection devices can verify the dosage level when tapped with an NFC phone with the right app to ensure that the medication has been taken correctly. This technology can also be used to check the fill level of medicines stored in opaque packaging and send the patient a reminder, via an app, to replenish their prescriptions when the level is below a predetermined threshold. NFC tags with an integrated sensor and

Figure 3: With a patient's permission, data about their adherence can be stored securely in the cloud, enabling a healthcare practitioner to track their adherence history and provide personalised feedback.

microcontroller can also support smart temperature measurements; for example, an insulin injection pen could signal when the dose is at room temperature, making the injection less painful for the user.

CONCLUSION

Pharma companies play an essential role in protecting the supply chain with end-to-end security and combating counterfeiting. With their ability to verify authenticity, report opening status and help ensure safe handling, NFC-enabled security tags can help deliver drugs to patients safely and efficiently. At the same time, for patients with chronic conditions, advanced NFC smart sensing tags can support medication adherence and remind patients to replenish their prescriptions on time. NFC tags can also deliver highly personalised and status-aware user experiences, adding value for both pharma companies and patients.

ABOUT THE COMPANY

NXP Semiconductors NV (NASDAQ: NXPI) enables a smarter, safer and more sustainable world through innovation. As a world leader in secure connectivity solutions for embedded applications, NXP is pushing boundaries in the automotive, industrial & IoT, mobile and communication infrastructure markets. Built on more than 60 years of combined experience and expertise, the company has approximately 31,000 employees in more than 30 countries and posted revenue of $11.06 billion in 2021. Find out more at www.nxp.com.

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Sylvia Kaiser-Kershaw is a Senior Global Marketing Manager in the Connectivity & Security business line at NXP Semiconductors. She is in charge of NFC product marketing and market development. As part of her role, she also develops smart NFC solutions for applications in pharmaceuticals and medical devices, including for anti-counterfeit protection and patient adherence applications. Ms Kaiser-Kershaw has over 20 years of experience in strategic brand and product marketing, working across a variety of industries. She is based in Austria.

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THE SMART INHALER REVOLUTION: ARE WE THERE YET?

Here, Mark Allen PhD, Consultant Mechanical Engineer, David Blakey, PhD, Former Senior Consultant Physicist, and Karla Sanchez, PhD, Senior Consultant Biomedical Engineer, all of Cambridge Design Partnership, discuss the benefits of smart inhalers and how they could influence the commercialisation of respiratory drugs in the future.

Asthma inhaler products have been employing electronic sensor technology with increasing sophistication and functionality since the 1980s, despite that, these devices have never achieved mainstream use – why? Several studies have shown the potential value of sensors in enhancing patient engagement and adherence – but the cost of these added features appears to outweigh their clinical utility. However, we may now be approaching a tipping point where smart inhalers can deliver new functionality that revolutionises respiratory therapy.

CLINICAL UTILITY OF A SMART INHALER

Smart inhalers employ sensors to monitor how people use their inhalers and employ feedback indicators to highlight errors and guide patients through onboarding and ongoing training. Sensor functions and electronic communications are typically integrated into an add-on device that is clipped onto the inhaler. The sensor data can be processed on a smartphone, which will usually have access to more comprehensive functions that help the patient with therapy support information, training, monitoring inhaler use, improving their technique and tracking adherence.[1]

The health benefits of a smart inhaler are measured by treatment outcomes, with better outcomes closely related to improved adherence to the dose regimen, leading to more stable symptom control and a reduced burden on secondary and emergency care.

> "Patient engagement is critical for the success of smart inhalers, including improvements in adherence."

Patient engagement is critical for the success of smart inhalers, including improvements in adherence. A range of smart features has been tested to improve engagement, including repeat prescription automation, environmental trigger alerts, exacerbation prediction, lung health monitoring and patient support services. Patients and physicians can use these features to train, monitor and support the use of new inhaled therapies.

However, a demonstration of universal clinical improvement for patients remains elusive – partly because not enough studies have been performed and partly because individuals respond to engagement cues differently. The broad range of patients and different treatment pathways means that large numbers of patients are needed for sufficient data to draw conclusions. The personal engagement between patients and their inhalers can lead to further issues for clinicians when designing a suitable treatment plan.

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"If these smart inhalers can be shown to improve adherence in COPD patients, they would decrease the need for further medical interventions."

One recent study highlights different barriers to adherence in asthma and chronic obstructive pulmonary disease (COPD), as well as how patients need different interventions according to the underlying reason for their non-adherence.[2] However, clinicians often do not have enough time or data to identify these in a single consultation.[1,2]

Patients will respond differently to engagement cues depending on the reason behind their lack of engagement. A patient who has made a deliberate decision to stop using their inhaler because they do not want to be reminded of their condition needs different engagement cues to one who has forgotten a dose on holiday or misunderstood how to use their device correctly.

Could smart inhalers assist by providing data to help understand the cause of non-adherence and be designed for specific engagement needs? For example, an inhaler could be designed to identify inconsistent dosing with a simple timestamp to record use. Another, more complex, device could monitor airflow and activation co-ordination for training. If these smart inhalers can be shown to improve adherence in COPD patients, they would decrease the need for further medical interventions.[3,4]

Beyond clinical utility, smart inhalers could also help decrease net healthcare costs. Every visit to a clinician or instance of hospitalisation is costly both financially and environmentally (because of the carbon dioxide release associated with treatment and infrastructure).[5]

"Smart sensors could be used to control the drug delivery process itself – or even control the aerosol particle size to suit each patient by age, breathing pattern or disease state."

SMART TECHNOLOGY BEYOND SENSORS

Clipped-on smart inhaler modules can be designed with a range of sophisticated sensor fusion controls and analyses, enabling additional benefits for users and healthcare professionals alike, such as the ability to review the actual delivery event against the expected clinical dose. This technology can also be integrated into the inhaler itself, for example, Digihaler[6] (Teva, Tel Aviv-Yafo, Israel) logs the time and date of actuations and provides instant feedback on the inhalations in its associated app, including training prompts if needed.

But beyond integration, how will smart inhalers develop? With recent advances in technology, it may be possible to grasp an opportunity that has remained out of reach until now. Smart sensors could be used to control the drug delivery process itself – or even control the aerosol particle size to suit each patient by age, breathing pattern or disease state. However, such dose control would require clinical trials to demonstrate safety and any claimed efficacy advantage. This method of digitally personalised dose control has recently been demonstrated in the Personalised Aerosol Loading and Management (PALM) device (Monash University, Melbourne, Australia),[7] but could this use of technology be applied to other inhaler types? This could, in theory, improve patient outcomes and provide a new pathway for commercialising respiratory drugs that require either a tighter control or higher efficiency of the dose delivery process.

Inhalers typically use energy stored in a compressed propellent or the airflow energy from the patient's inhalation. Electronic triggering systems for these mechanisms are challenging to develop but innovations, such as those found in vibrating mesh nebulisers,[8] may provide convenient aerosol delivery technologies that are automatically triggered by inhalation.

The concept of a closed-loop smart inhaler may not be new, but with recent advances in digital and sensor technologies and delivery systems, now may be the time to revisit closed-loop dose delivery control and explore its benefits for clinical utility. With new inhaled therapies on the horizon, innovative smart inhaler solutions will need to step up their game to facilitate this revolution in respiratory care.

ABOUT THE COMPANY

Cambridge Design Partnership is an end-to-end innovation partner, propelling global brands and ambitious start-ups to success. The company builds breakthrough products and services – from insight to ideas, prototypes to production – bringing innovation to life. Its teams are multi-disciplinary, uniting scientific rigour, design ingenuity and engineering excellence for consumer, healthcare and industrial clients.

People-centred, deeply collaborative and, above all, expert, Cambridge Design Partnership is uniquely positioned to shape the future for consumers, patients and industry. Even the company's ownership model is innovative – the company is 100% owned by employees, ensuring an open culture and a total commitment to each project's success.

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David Blakey, PhD, is a Former Senior Consultant Physicist at Cambridge Design Partnership and has spent over 25 years creating new medical device technologies, products and processes, including mesh nebulisers, dry powder inhalers and autoinjectors. Before joining CDP, he worked in pharmaceutical R&D, leading device design teams and supporting process engineering and manufacturing at GSK. Dr Blakey's interests include aerosol science and micro-engineering of mechanical and fluidic systems.

Karla Sanchez, PhD, is a Consultant Biomedical Engineer at Cambridge Design Partnership, working as a mathematical modeller, researcher and bioengineer with over 10 years of experience in medical product development. She obtained her PhD from Imperial College London (UK) at the Physiological Fluids Group, where she focused on blood flow of the cerebral vasculature and distribution of cerebrospinal fluid. She has also worked alongside clinicians and academics to study blood flow in the kidney and complications of chronic kidney disease. Dr Sanchez has managed several successful commercial projects, launching a large range of infusion sets, orthopaedic and surgical devices. She is an enthusiastic STEM ambassador and holds an honorary visiting researcher position at Imperial College London.

A GAME CHANGER FOR HIGH-RISK MEDICATIONS VIA INTRANASAL DRUG DELIVERY PLATFORM

In this article, Marcel Botha, Chief Executive Officer at Validose, Andreas Bilstein, PhD, General Manager, and Houssam Elghobary, Business Development & Sales Manager, both at URSATEC, and Rouven Kraus, Head of Sales, at Aero Pump, discuss the benefits of the Validose digital health platform for the safe delivery of high-value and/or high-risk products.

The tide is finally turning when it comes to covid-19 – and the world is ready to return to normal. Nevertheless, normal will mean facing several healthcare challenges that have been hiding in the shadow of the pandemic. The good news is that next-generation, evidence-based treatments exist for some of these insolvable dilemmas, such as widespread substance abuse, depression and chronic pain. The bad news is that those treatments include highly regulated drugs that have the potential to be abused.

According to the Centres for Disease Control and Prevention's (CDC) National Vital Statistics System, 103,598 Americans died from prescription opioid misuse in 2021.[1] Every day, 46 people in the US die from overdosing on an opioid that was prescribed by a doctor. Of those who use heroin and other illegal opioids, 86% say they were put on that road by a legal opioid prescription for themselves or someone they knew.[2] Prescriptions do not always go where they are supposed to when they leave the pharmacy – diversion is the black side of the opioid dilemma. And the majority of people who abuse these medications get them from family or friends.

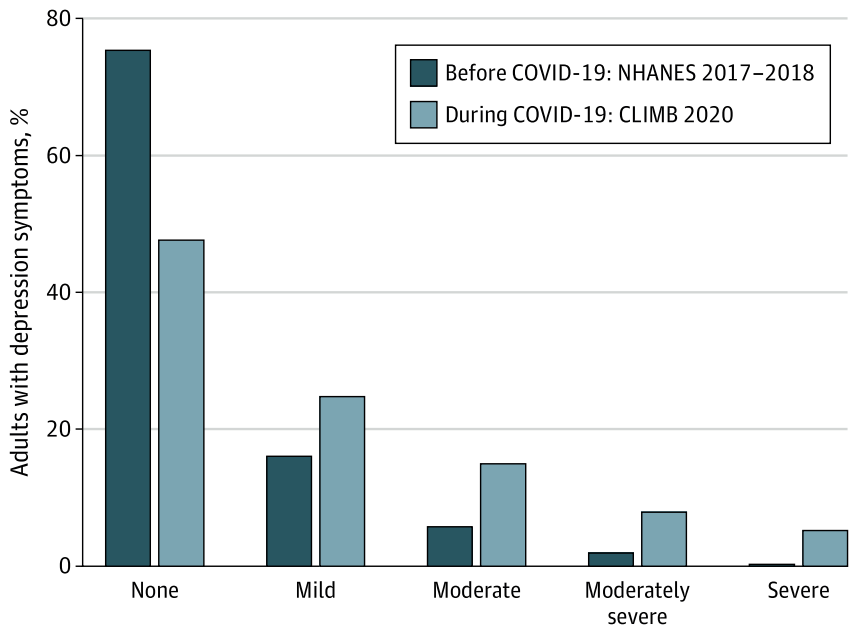

Figure 1: Depression symptoms in US adults before and during the covid-19 pandemic.

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During the covid-19 pandemic, the prevalence of moderate-to-severe depression in the US increased more than threefold from 8.5% before covid-19 to 27.8% during covid-19 (Figure 1).[3] The estimated number of unreported cases is even worse.

Coming to the second crisis, the psychiatric community is on high alert, and more promising medications are being developed now than in previous decades. Ketamine, a tightly controlled substance that has traditionally been used as a form of anaesthesia, has been shown to have transformative potential in the treatment of severe depression. Patients with depressive disorders, particularly treatment-resistant depression, have been found to benefit from ketamine nasal spray. It is quick acting, with clinical trials indicating that patients are relieved of suicidal ideation in as little as a few hours, and its effects can last up to a week. In comparison, most oral antidepressants can take weeks to start working.

These two crises have had a significant impact on Americans' life expectancy. Safely delivering opioids and antidepressants could reverse these trends permanently, offering a high quality of life for those patients. This ongoing dilemma of how healthcare providers administer and monitor controlled substances triggered the invention of a device to solve these problems. And this was the spark to generate an innovative digital solution to address many of the trickiest modern problems in patient care, including the misuse of prescription medicines, the monitoring of dosage/adherence and, most importantly, the ability to improve patients' lives.

Approximately 235 million prescriptions for painkillers, antidepressants and substance abuse treatments are written each year. Fentanyl and buprenorphine, for example, are high-risk medications. All these high-risk medications with lifesaving potential could potentially be used with a device offering advanced drug intake control and biometric features.[4]

> "The Validose system delivers scheduled medications based on an integrated but separately filled pump system."

Figure 2: The current Validose device design.

Such a device has been presented under the name of Validose, and it has been sketched out to offer a solution that brings the future of safer medications through the nasal route of administration in which every dose is validated.

TEAM UP FOR AN INTEGRATED SUPPLY CHAIN

The Validose system delivers scheduled medications based on an integrated but separately filled pump system. It can only be activated by the patient's fingerprint, which is detected by a sensor like that found on a smartphone. Fingerprint security is used to lock every single dose – ensuring that the right dose is delivered to the right person at the right time. Data about the dose is immediately shared with the physician's office. A set of security measures built into the design of both the hardware and software prevents patients taking extra doses or sharing one with a friend and, if the patient misses a dose, the device can alert the user, prompting him to check-in. It is a simple idea that could transform the delivery technology for a whole spectrum of potentially serious medications (Figure 2).

But the Validose device is only one part of the story. It needs to integrate with a precise and high-quality dispersing pump. Through a synergetic partnership between Validose, as the digital augmentation device designer, Aero Pump, as one of the world's leading manufacturers specialising in the production of pharmaceutical spray pumps and droppers with high dosing precision, and URSATEC as the inventor of preservative-free multidose applications, an integrated device including nasal spray pump system, bottle, filling and integration into the digital augmentation was envisioned, to allow a fast and easy transfer of existing products or an optimal development of a new product.

> "One of the crucial considerations during the development of nasal dosage applications is to offer the possibility of avoiding preservatives, wherever possible."

THE RIGHT PUMP SYSTEM IN THE RIGHT DEVICE

The combined approach of Validose, Aero Pump and URSATEC allows optimisation of existing products by the use of precise metering pumps for preserved products from Aero Pump, with a toolbox of adjustments to fit the device to the existing product and the opportunity to either develop new products or switch the current product to a preservative-free application to enhance patients' application experience. One of the crucial considerations during the development of nasal dosage applications is to offer the possibility of avoiding preservatives, wherever possible, as per the majority of global healthcare authorities' recommendations.[5] That is why the patented 3K®-nasal dosage system and the COMFORT® airless systems were invented. The 3k® system is a "non-airless" dosing pump that is used for the delivery of liquid

pharmaceutical and medical preparations with triple protection technology against microbial contamination (Figure 3):

1. Coil with a bacteriostatic surface
2. Microbial tightly closing valve
3. Air-purifying filter.

THE COMBINED APPROACH/ THE RIGHT SYNERGY

A complete hardware approach from the primary packaging system, including device-specific modifications, to the filling and assembly of the product and the digital augmentation of the container closure system, has been achieved by the collaboration between technology provider leaders to create high value for an integrated value chain of innovative personalised precision medicines.

The smart "Internet of Things" (IoT) exoskeleton that enables digital locking and unlocking is augmented to integrate with either Aero Pump's pump portfolio or URSATEC's patented triple-protection 3k® or COMFORT dosage pumps. For example, the specific modified and completely pre-assembled and sterilised 3k® pump is snapped on the sterilised primary container after the filling process, which is carried out under aseptic conditions to offer maximum protection against microbial contamination even for long-term safe use without the need for any preservatives (Figure 4). Another option would be Aero Pump's spray-nozzle-unit-based nasal spray for optimised deposition for nose-to-brain delivery. In any case, the exoskeleton itself is reusable and can be used over a long period, whereas the nasal-spray system itself can be exchanged regularly. Even a leasing model with the patient and/or medication change could be realised with one exoskeleton.

The exoskeleton is controlled by the Validose app. The app is focused on enabling the user to participate in real time. It drives adherence through schedule and dosage reminders to the phone and other digital peripherals such as smartwatches. Other stakeholders like doctors, caregivers and elected family members will have different app experiences derived from the same macro data set. Validose can automatically adjust for dynamic dosing protocols if the dose has to fluctuate during prescribed therapy. It records all aspects of delivered dose history, delivery compliance and dose adherence and gives accurate remaining dose information. The app

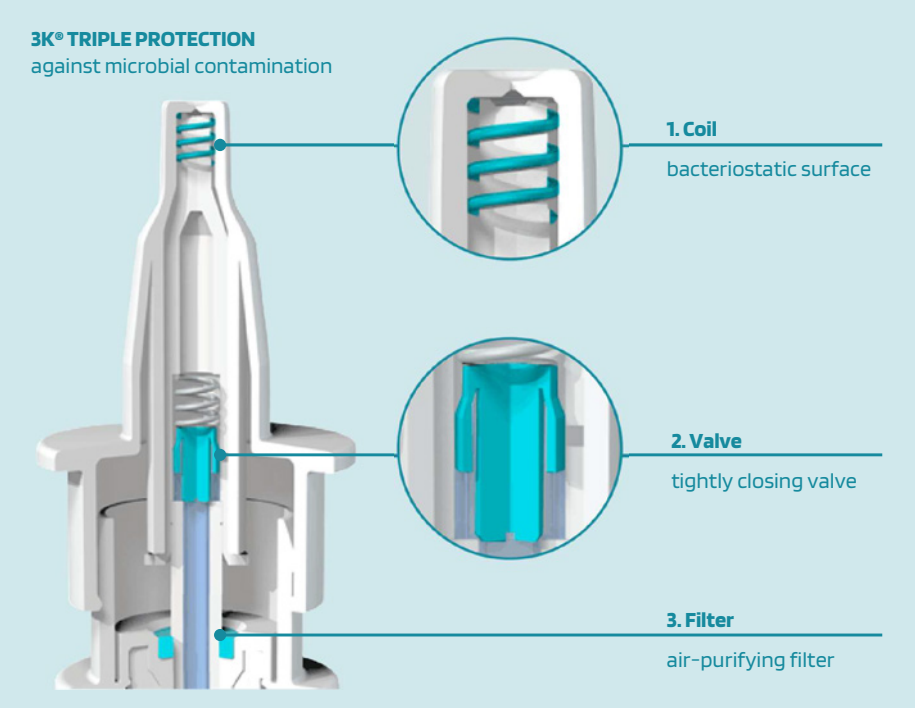

Figure 3: The triple protection technology of the 3k Pump®.

Figure 4: The synergistic approach of pump device and digital augmentation.

Figure 5: The Validose software is simple and user friendly.

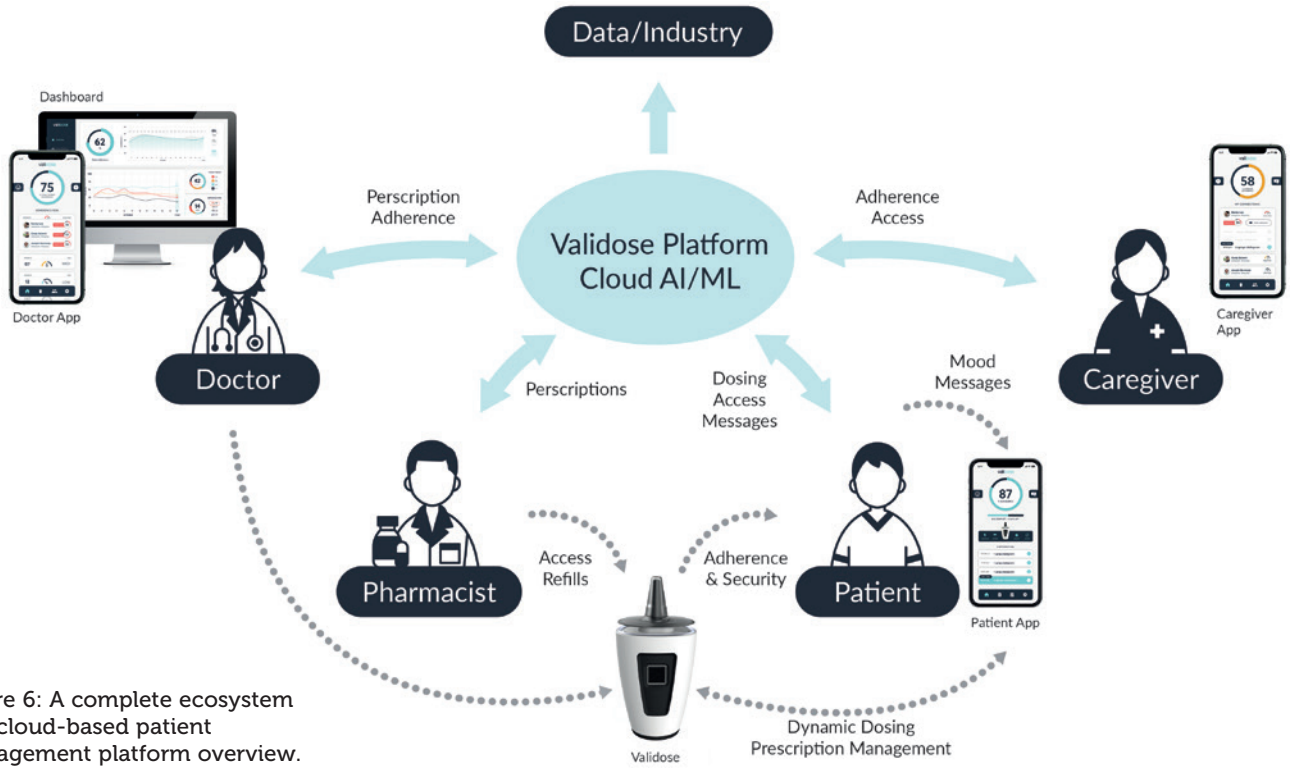

Figure 6: A complete ecosystem and cloud-based patient management platform overview.

receives both real-time and asynchronous data from the device. Figure 5 shows how simple the app is. It allows the user to have full data access to know the percentage of adherence, dose history, doses remaining and medication types.

To complete the ecosystem, a cloud-based patient management platform was established (Figure 6), which aims to give physicians real-time insight into large patient populations such as indication interactions, medication type or concentration, patient adherence and prescription tracking. The platform aggregates patient data over time and at scale, giving the provider's office granular monitoring of patient-care quality and outcome over the entire course of their treatment. The quantitative data can then be matched with qualitative feedback from caregivers, providers and patients themselves to get a holistic picture of the patient's perceived and observed progress.

WHAT IS IN IT FOR THE ENGAGED STAKEHOLDERS?

The patient:

- One device, one user, no diversion – a pocket-sized device provides only one patient with a secure and reliable way to get high-risk medications. If the user unlocks his dose and hands it over to a second user, motion-sensing technology immediately locks the device.
- Unlock to have your dose – a dose is only delivered when a patient places their fingerprint on a small sensor; it prevents accidental double dosing while verifying every dose taken.
- An integrated cloud ecosystem – the device sends a tracking report digitally when a dose is taken, including the time and location of the treatment, keeping both the patient and the prescriber informed.
- Tamper-resistant design – the patient can only get his prescribed dose and then the device is locked. A mechanical security feature is triggered if someone tries to force open the device. If the device is intentionally crushed, the internal glass bottle will break, allowing all medication to leak out and be neutralised by an absorption layer in the surrounding chamber.
- A long-life solution – a pharmacist can easily refill the device. Patients would get access to a smartphone app that tells them when their refills are due, how their medication usage is tracking over time and when their next appointment with the physician is.
- The combination of a highly precise nasal-spray system with a preservative-free product.

The provider:

- A unique combination of application technology, digital augmentation and product realisation capacities which allows the transfer or development and manufacture of all kinds of nasal-spray products.
- Unbiased care – cutting-edge treatments like ketamine are often only accessible to a selected group of people who reach a restricted audience. These high-risk medications can be distributed more widely and equitably if providers have more control.
- Case tracking and adherence:
  - Pharmaceutical companies have a dashboard that shows when the device is used, making patient communication more efficient, especially during the clinical trials phase.
  - Clinicians can also track patient usage and adherence habits, allowing them to follow up if a dose is missed.
- Cost savings:
  - Patients avoid unnecessary visits to the doctor's office to receive their high-risk medications that need to be taken on-site.
  - Better adherence with a lower risk of abuse reflects significant cost effectiveness and improved patient health outcomes.
- Medico-legal support:
  - Security features prevent misuse by healthcare professionals.
  - Any professional misconduct attempt to order a refill from the pharmacy, for example, will lock out the provider and trigger emergency alarms in the reporting system.

"The Validose digital health platform offers the safe delivery of high-value and/or high-risk products while providing long-term adherence solutions for all engaged stakeholders."

CONCLUSION

There is a current, and accelerated, need for novel at-home continuity of care solutions. Beyond remote consultations and monitoring, there is a need for self-administration and better adherence to high-risk drugs. The Validose digital health platform offers the safe delivery of high-value and/or high-risk products while providing long-term adherence solutions for all engaged stakeholders – for example, patients, physicians and payers.

Validose provides a standardised augmentation strategy by digitally enabling the application devices from Aero Pump and URSATEC. The existing medication packaging supply chains can be augmented to integrate with the smart IoT exoskeleton, and no change in function is required for the existing packaging manufacturer or supplier.

Custom-developed drugs or new drug launches can directly use the combined development services for the digitised product line available. Aero Pump and URSATEC offer development expertise for primary packaging, high-tech medical devices and dosage systems, as well as pharmaceutical formulations, to create new business. Collectively, the partners of the combined approach have in-depth

ABOUT THE AUTHORS

Marcel Botha is a product development leader with 20 years of experience ranging from medical and consumer devices, and sustainable industrial practice, to automotive and construction technologies. His expertise centres around building high-value and intellectually agile innovation teams to best approach new product development and commercialisation efforts. Mr Botha has founded and invested in many companies covering diagnostics, drug delivery, mobility, sensing and consumer applications.

Andreas Bilstein, PhD, has been Managing Director of URSATEC since August 2020, responsible for marketing and sales, and product development. He is a biologist and has more than 15 years of experience in developing preservative-free products for various applications.

Houssam Elghobary is a pharmacist and has more than 12 years of experience in the sales and marketing of prescription medication. He started his career in sales for MSD (Egypt) then moved to Pfizer in Saudi Arabia, and in 2022 he joined URSATEC as a business development and sales manager after earning his master's degree in international business consulting from Offenburg University of Applied Sciences (Germany).

Rouven Kraus has more than 10 years of experience in the drug delivery market. He started his career in sales for a domestic iron foundry in Mainz (Germany) and joined Aero Pump in 2012 to augment the sales of the company's drug delivery device portfolio. In his role, Mr Kraus manages global sales as well as the strategic approach to new developments and delivery technologies.

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Finally, there is no end in sight for the telehealth and remote care changes that the pandemic brought about. What felt new and early to market in 2019 has become mission critical for continuity of care in 2022. In the US, Europe and beyond, we will see continued investment expansion and integration of digital health services with the intent of improving access, reducing risk and, ultimately, enhancing patient outcomes.

ABOUT THE COMPANIES

URSATEC was founded in 1993 to accomplish one mission: the establishment of preservative-free applications based on its proprietary packaging systems in different application areas, primarily the nasal, dermal, buccal and ontological fields. Having sold almost two billion units within the last 25 years, URSATEC systems are widely established. URSATEC is consistently expanding its business and offers full development service, dosage systems, primary packaging materials and filling services for OTC and prescription applications to the healthcare industry.

Aero Pump was founded in 1976 and is headquartered close to Frankfurt (Germany) airport. It is a leading manufacturer of high-precision application systems for the pharmaceutical and healthcare industry, focused on innovation, multifunctionality and contemporary design. Its spray pumps and dropper systems are widely established in the market and are primarily used in nasal, ophthalmic, pulmonary and dermal fields, suitable for preserved and preservative-free OTC and prescription drugs.

Validose was founded in 2017 on the principle of solving drug delivery personalisation and adherence to high-risk, high-value and long-term therapies without introducing new risks of addiction. Its technology platform presents a powerful approach to enable an exponential reduction in prescription drug abuse through present and future risk management solutions that are seamlessly integrated into various drug delivery product lines.

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YPSOMED
SELFCARE SOLUTIONS

PAVING THE WAY TO INTEGRATED DEVICE-DIGITAL SOLUTIONS

In this article, Andreas Schneider, PhD, Innovation and Business Development Director, and Philippe Müller, Innovation and Business Development Manager, both of Ypsomed, discuss the potential benefits and challenges of implementing connected device-digital solutions within the healthcare sector to improve the treatment of chronic conditions.

"Seems like you have just missed another dose, Adam, let's discuss how to best fit your injections into your daily routine. Surely, I can help you with that." The warm and empathic voice gently gives the necessary instructions to Adam, who has suffered from atopic dermatitis for years and has been prescribed a new biologics treatment that must be self-injected every two weeks. Surprisingly, however, this voice does not come from his attending physician, but from an artificial intelligence engine that issues its commands straight from the speakers of his smartphone. It is barely recognisable as a robotic voice.

The algorithm that fuels the digital solution recognised that Adam had repeatedly missed his dose and identified him as a patient at risk of prematurely stopping self-injection and not achieving his treatment goals due to medication non-adherence. If Adam continues like this, he will suffer from debilitating pruritus, disturbed sleep and mental distress. As with up to half of the more than 26 million other Americans diagnosed with atopic dermatitis, these effects will also negatively impact Adam's lifestyle, work and education. These are effects that Adam is well aware of in principle, but which are only marginally present at this time.[1–6]

"Since 2017, the US FDA alone has approved more than 40 digital therapeutics and health apps addressing chronic conditions, including diabetes, back pain, ADHD and asthma."

RECENT ADVANCES WITH DIGITAL THERAPEUTICS

Integrated device-digital solutions to support behavioural change and empower patients diagnosed with chronic conditions to manage and improve their symptoms are currently gaining traction within the healthcare sector. Since 2017, the US FDA alone has approved more than 40 digital therapeutics and health apps addressing chronic conditions, including diabetes, back pain, ADHD and asthma.

These solutions encourage patients to engage with their specific disease and symptoms to optimise their treatment pathway and outcomes (Figure 1). Moreover, new pathways are presently being established for digital health apps to be paid for through existing healthcare systems. For example, in Germany, 12 digital solutions have provided sufficient clinical evidence to be permanently approved and reimbursed.[11]

TOWARDS INTEGRATED DEVICE-DIGITAL SOLUTIONS

Consider Adam, who may require a device-digital solution that provides sustained and holistic support to achieve effective disease control and comfort. Such a solution

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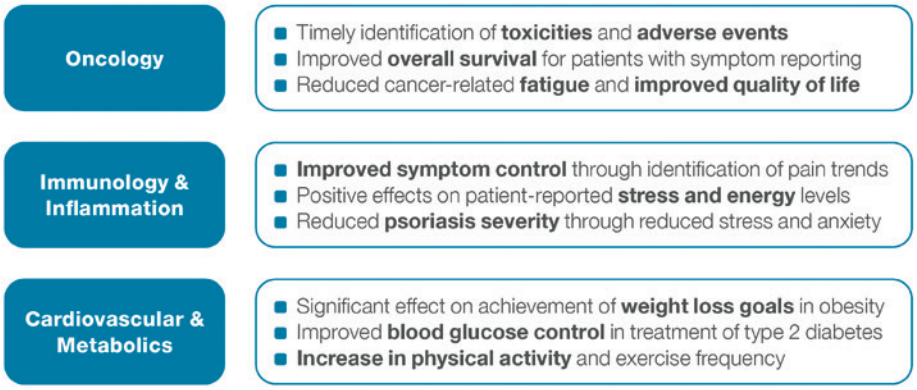

Figure 1: Added value of digital therapeutics per exemplar chronic disease areas.[7–10]

should fully support him in managing, and ultimately improving, his medication intake and disease symptoms. Ideally, the digital health app is paired with a connected drug delivery device that seamlessly feeds data into the digital system. The connected device should require minimal user interaction, passively log injection events and support Adam through the most critical use steps. After being integrated with other data sources and enriched with electronic patient-reported outcomes, the data aggregated from such a system can be presented to the attending physician to enable them to manage medication and evaluate treatment for their patients efficiently and effectively.

Such an integrated device-digital solution, as illustrated in Figure 2, may be available on prescription and rolled out in conjunction with the medication to improve medication adherence, preventive measures and programme engagement, as well as to deliver improvements in health outcomes. In addition, the anonymised connected device and patient-reported outcomes data can provide valuable real-world evidence for pharma companies, including for medication adherence, therapy persistence and quality of life. These insights might then be used as inputs to feed predictive algorithms for treatment evaluation and further research activities.

> "An integrated device-digital solution may be available on prescription and rolled out in conjunction with the medication to improve medication adherence, preventive measures and programme engagement, as well as to deliver improvements in health outcomes."

Regardless of the focus disease area, significant efforts are being made to improve treatment adherence. Medication non-adherence is a major problem across the healthcare sector that affects treatment outcomes and imposes significant costs on healthcare systems. In fact, 50–60% of patients being treated for chronic conditions either miss doses, take the wrong doses or discontinue treatment within the first year.[12] Non-adherence to medication results from patient-specific interactions within five sets of factors (Figure 3):

1. Disease-related factors
2. Socio-economic factors
3. Health-system-related factors
4. Therapy-related factors
5. Patient-related factors.[9]

NEED TO ADDRESS SPECIFIC ADHERENCE BARRIERS

Consequently, any device-digital solution aimed at improving medication adherence must address specific barriers and should be tailored to the specific needs of the patient and their therapy context.[13] A device-digital solution boosts medication adherence by adapting to the patient's needs – not the other way around. This observation has been echoed by the pharmaceutical industry, which has shifted its attention from the development of generic adherence management systems to the development of personalised and therapy-specific device-digital solutions.

Modern designs aim to improve medication adherence by adapting the provision of support, including type, timing and intensity, to an individual's

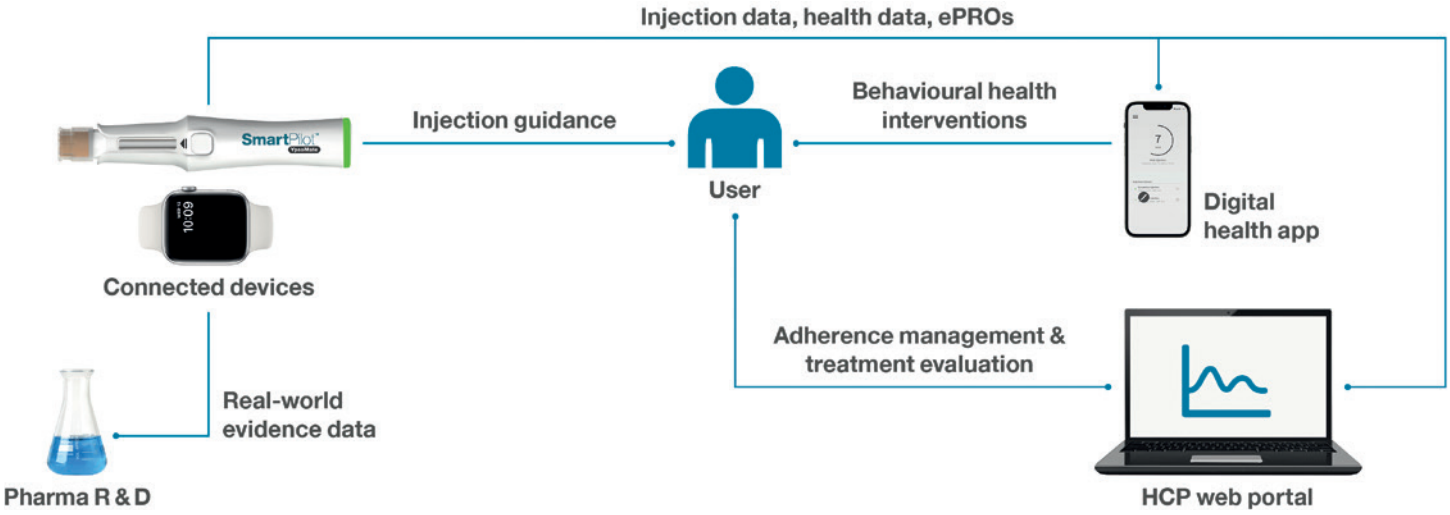

Figure 2: Illustration of an integrated device-digital solution to support behavioural change and empower patients to manage adherence and disease symptoms.

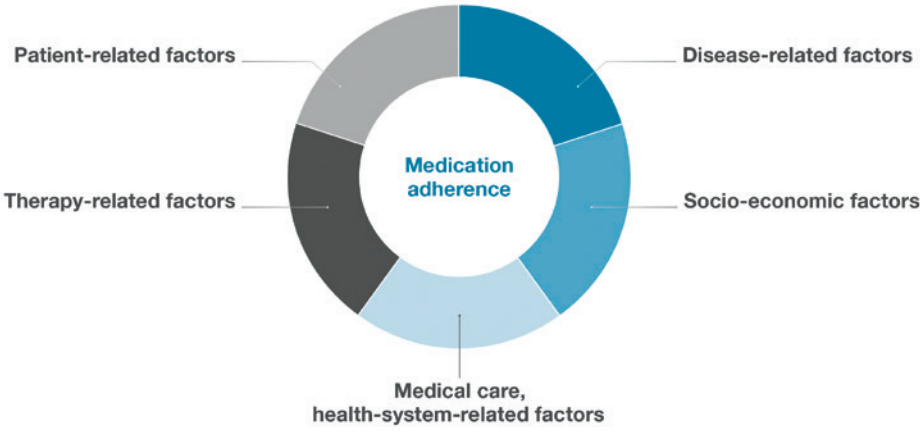

Figure 3: The multidimensional nature of medication adherence.

changing status and contexts over time. The underlying goal is to deliver support when the patient most needs it and is most likely to be receptive – the point at which they are most likely to change their behaviour.[14] To this end, smart connected drug delivery devices are key because they can act on both the timeliness and adaptive nature of these interventions by monitoring the dynamics of an individual's state and context in real time (Figure 4).

Consider Adam, who may have concerns relating to the use of his drug delivery device. Should his connected drug delivery device detect a use error, it may trigger a digital health intervention that is carefully tailored to the type of use error and Adam's specific user profile. In addition, the connected device reports the use error in nearly real time, which allows it to trigger an intervention at the point when the error happens, which is when Adam will be most receptive to tips on how to improve his behaviour.

Thus, data from connected devices serve as an important input for digital therapy management solutions, enabling effective behavioural health interventions in terms of both content and timing. Such functionality can help patients to more effectively manage their injection regimens and set their expectations regarding their treatment that may, in turn, propel more successful treatment outcomes.

> "Ypsomed is advancing a broad portfolio of connected injection devices that can be structured both into connected add-ons for its proven mechanical self-injection devices and into autoinjectors with integrated connectivity."

ADVANCING A BROAD PORTFOLIO OF CONNECTED DEVICES

Therefore, Ypsomed is advancing a broad portfolio of connected injection devices that can be structured both into connected add-ons for its proven mechanical self-injection devices and into autoinjectors with integrated connectivity (Figure 5). First, SmartPilot is the reusable connected add-on for the two-step autoinjector YpsoMate. SmartPilot captures injection events, detects use errors and provides comprehensive real-time injection support, including drug authentication at point of use and step-by-step guidance. Second, YpsoMate On is a prefilled autoinjector with integrated connectivity that can automatically log injections based on advanced proximity measuring protocols, similar to the working principle of covid-19 contact tracing apps.

While YpsoMate On provides a narrower feature set compared with SmartPilot, it retains YpsoMate's proven two-step device handling and enables automated data capture. Moreover, the device includes LED-based visual feedback to signal an ongoing injection and completion of the injection, including the hold time. The device choice ultimately depends on the intended use of the overall system, as well as the specific user population, injection frequency and other disease-and therapy-specific aspects.

CONCLUDING REMARKS

There is growing evidence of the benefits of device-digital solutions across various disease areas. However, to ensure broad market acceptance, the industry must overcome the challenges associated with the implementation of such device-digital solutions. As Norbert Lauber (Director Autoinjectors & Pump Systems, Novartis Pharma) aptly put it at the SMi Wearable Injectors and Connected Devices conference in 2021, "Adding connectivity expands the combined product into a complex collection of components".[15]

As such, close collaboration between device manufacturers and digital therapy management providers is needed both to

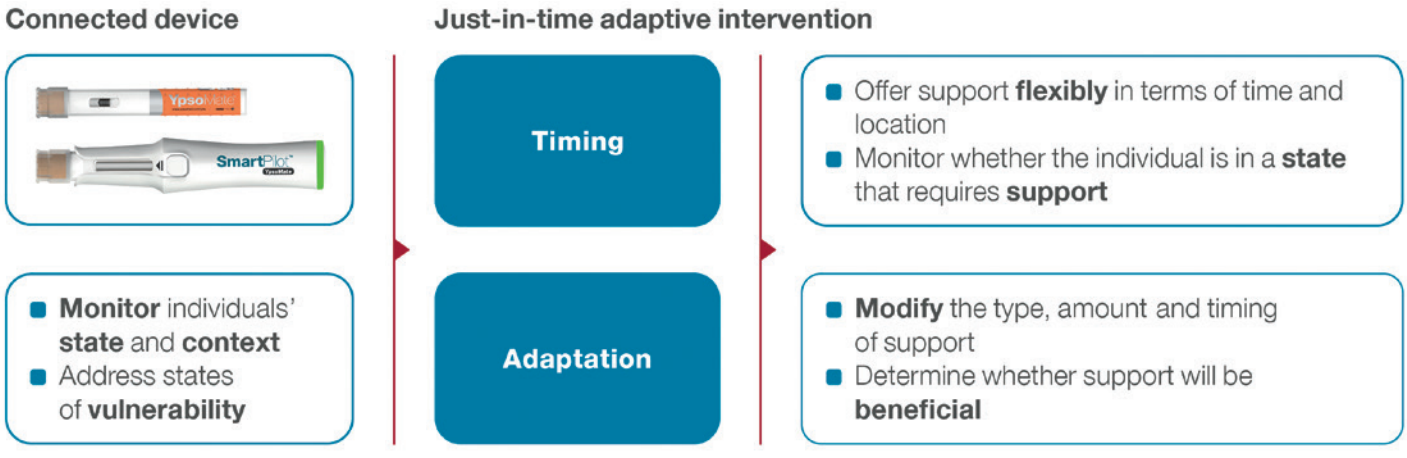

Figure 4: Smart connected devices as a basis for personalised digital health solutions.

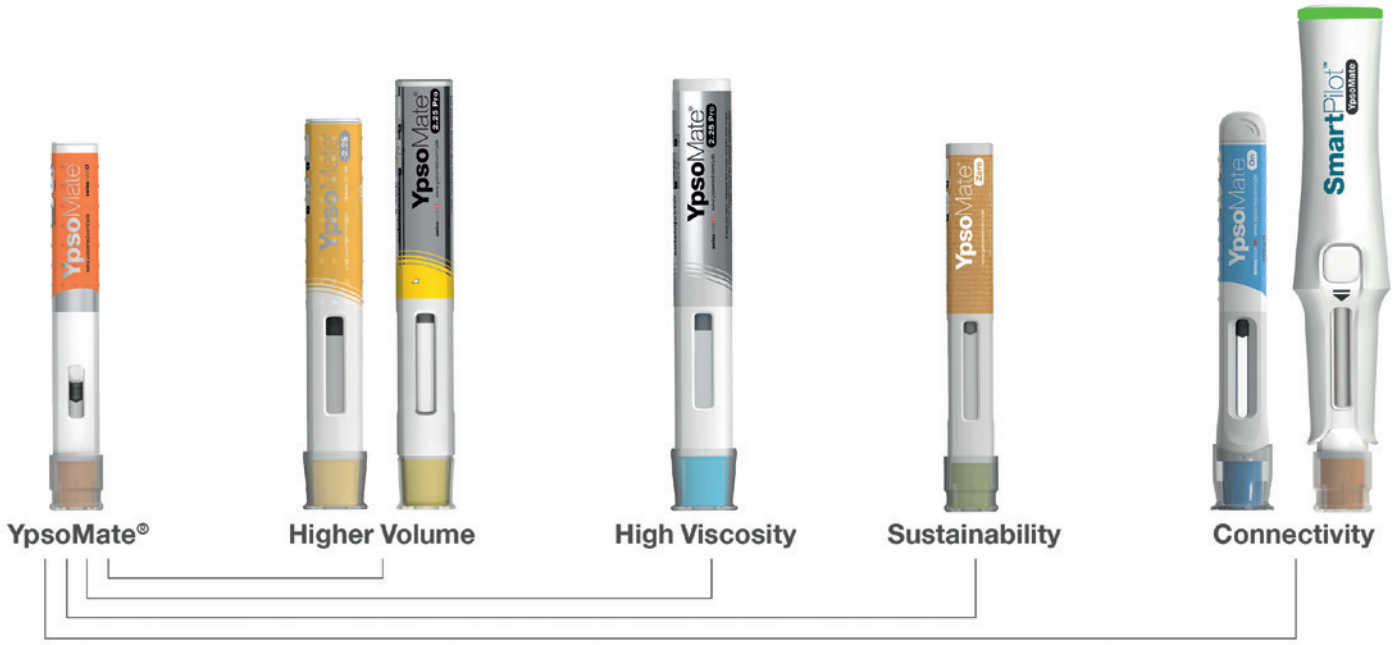

Figure 5: Evolution of the Ypsomed autoinjector portfolio.

lower the complexities of implementing a digital system and to design effective just-in-time interventions tailored to the specific needs of individuals. Joining forces between digital and device solution providers will be a winning formula to deliver substantial value-add 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 30 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases, and integrating these insights with 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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CONNECTING PATIENTS AND HEALTHCARE PROVIDERS IN THE AGE OF SELF-ADMINISTERED INJECTABLE DRUGS

In this article, Gemma Wood, Innovation Manager at Bespak by Recipharm, explores connected device development trends, the patient-centric benefits the technology has to offer and how, with the help of experienced manufacturing partners connected to key enabling technology partners, they can develop products that deliver improved patient outcomes.

Global growth in the use of parenteral biopharmaceuticals to treat chronic and age-related disease is expanding rapidly. In particular, the administration of biopharmaceuticals by global healthcare providers (HCPs) to treat chronic conditions, such as arthritis, diabetes and other autoimmune diseases, continues to drive global growth and development of injectable drugs. For this category of pharmaceuticals alone, the market is projected to reach US$856 billion (£683 billion) by 2030.[1]

This growth is supported by decades of combined drug and device innovation to support the safe self-administration of parenteral drugs. In the wake of the pandemic, the trend towards remote self-care to treat chronic diseases of all kinds is driving a similar demand for better, smarter and more effective ways for patients to self-administer their medications. Rapid innovation is occurring within the pharma industry to help care providers deliver better modes of self-care.

> "Pharmaceutical developers, device developers and digital health experts are continually seeking more effective ways of improving therapeutic outcomes."

To deliver better care overall and overcome the challenges related to remote parenteral drug delivery, drug developers are looking to integrate new ways to connect the patient, the combination device and the healthcare provider (HCP) via the cloud. However, integrating connectivity to device development adds complexity into product development strategy.

REMOTE PATIENT SELF-CARE TREATMENT MODELS TRENDING

To reduce the overall cost of healthcare and provide a better life balance for patients, especially for those with chronic conditions, HCPs have steadily moved patient care models away from administering drugs in clinical settings towards remote self-care models that put the patient in control of delivering their therapy themselves.

More recent events, such as the covid-19 pandemic, have accelerated this trend. During the pandemic, travel to clinics became more challenging. In addition, there was a desire to reduce the possibility of vulnerable patients becoming infected during visits to clinics.

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The pandemic highlighted the potential for a deterioration in outcomes when patients are unable to have face-to-face contact with care providers. As a result, pharmaceutical developers, device developers and digital health experts are continually seeking more effective ways of improving therapeutic outcomes.

There are few signs that healthcare's adoption of remote self-care will slow anytime soon. Key factors driving the uptake of self-administered drugs (such as topicals, inhalable compounds and injectables) include the rise in demand for combined, prefilled medical devices, developments in the biologics segment and rising technological innovation in delivery and automated dose control. Furthermore, the rise in the number of outpatient services and the growing prevalence of government-funded insurance is expected to further influence growth.[2]

DOSE COMPLIANCE CRITICAL TO BETTER PATIENT AND PAYER OUTCOMES

The therapeutic efficacy of a drug depends on its pharmacology, bioavailability and patient compliance. The negative effects of non-compliance, especially for chronic conditions, is well studied and remains one of the biggest impediments to delivering affordable, sustainable pharmaceutical-based healthcare successfully. In a recent brief, McKinsey noted that failure to adhere to prescribed-medication regimens is one of the principal reasons that patients do not achieve expected outcomes. Studies reveal 50% or more of patients with chronic illnesses miss doses, take the wrong dose or drop off treatment in the first year. A McKinsey study cited an estimated 125,000 lives are lost each year in the US alone, which drives additional healthcare expenditures of $290 billion as a result of non-adherence.[3]

Reasons for poor dose adherence and compliance are often associated with symptomatic aspects of the disease, negative side effects of the drug, dose frequency and usability of the drug delivery device.

For millions of patients who inject themselves frequently, there is a growing preference for "smarter" and "friendlier" ways to self-administer their medications. Connecting patients and providers with the drug delivery device via the internet has been hailed as a potential part of the solution to this challenge.

By allowing dose compliance data to be transmitted from an injectable device to a patient's own smartphone and/or an HCP's database, it is possible for both the patient and their HCP to monitor dose compliance remotely in real time. As such, data connectivity via the cloud is becoming a smarter way to identify any potential gaps in the quality of care that might arise through remote care and that could adversely affect treatment outcomes.

THE CHALLENGE OF DRUG CONNECTIVITY

Consequently, designing drugs and devices that ease administration and support patient compliance and adherence to drug treatments has become a major driver for improving chronic disease control and optimising the use of healthcare resources and costs. However, truly harnessing the benefits of connectivity for the patient and HCP entails more than simply integrating smart technology into the device. Questions need to be answered, such as reimbursement, data privacy and security, what kind of data to collect, how it should be stored and which stakeholders should be included.

"Truly harnessing the benefits of connectivity for the patient and HCP entails more than simply integrating smart technology into the device."

Questions around the nature of the device and the usability of the smart component of the device also need to be answered to ensure true patient-centricity; a device that can share data but becomes more complex for the patient to use is unlikely to offer the overarching benefits sought by including the connectivity in the first place. In addition, it is important to consider the value proposition – whether the benefits of connectivity for all stakeholders outweigh the cost of development and implementation into a device. This can be a particular challenge when considering single-use devices.

KEY CONSIDERATIONS FOR SUCCESSFUL CONNECTED DRUG DEVELOPMENT

Development of connected devices to meet HCP and patient needs is set to grow dramatically in the near term. Mordor Intelligence's recent report notes that, during 2022–2027, the market for connected devices is expected to register a compound annual growth rate (CAGR) of 40.2% during the forecast period.[4]

Behind this projected growth is the fact that so much of the world is connected by the internet. According to Mordor Intelligence, as of September 2020, Internet World Stats reported there were approximately 4.92 billion people, about 60% of the world's population, actively using the internet.[4]

Figure 1: Syrina® AS autoinjector device.

> "It is important for drug developers to consider both the potential value and the risks of connectivity when embarking on new injectable projects."

Therefore, there are several key considerations to bear in mind for any drug developer when embarking on a connected, injectable drug development project:

- Usability and patient-centricity (design and function)
- Desired patient outcomes and efficacy goals
- Information architecture and data-set requirements
- Reimbursement
- Device compatibility
- Data security requirements
- Software/platform management
- Cost/risk/benefit analysis
- Data security and risk.

OVERCOMING CONNECTED DRUG DEVELOPMENT CHALLENGES

The additional elements associated with developing and manufacturing connected delivery devices requires a network of technology partners with deep expertise in digital health.

Recognising this need, in 2020, Recipharm collaborated with Team Consulting (Cambridge, UK) to jointly develop a connected proof-of-concept for the Syrina® AS autoinjector device (Figure 1). This included a Bluetooth-enabled connectivity module within the device that can sense various functionalities. An application was developed to inform users that the device had been used successfully and when dose delivery was complete. The software also included reminders about subsequent prescribed dosing and is readily adaptable to include additional functionality where required.

Working with an experienced device developer and its network of digital health specialists provides the following benefits:

- Guidance on achieving therapeutic value and patient goals
- Design and delivering turnkey cloud-based system architecture
- Levering existing data infrastructures
- Clear, efficient commercialisation
- Market-oriented products
- Desired patient and payer outcomes.

It is important that adding electronic modules does not impact the design of the base device. This helps minimise design risks or duplicating manufacturing equipment and supports continuing development and production of the base device design when the connected requirements are not fully understood or in their infancy. With this in mind, it is important for drug developers to consider both the potential value and the risks of connectivity when embarking on new projects.

Experienced device developers and digital health partners can support pharma companies in their deliberations, helping them decide whether connectivity is right for their project, and assist them in developing a product that will truly transform healthcare for the patient.

CONNECTING PATIENT AND CARE FOR BETTER OUTCOMES

What does the future hold for connected drug products? Although the category is set to grow to unprecedented levels, not all injectable drugs, self-administered or not, will be or need to be connected. However, connectivity will continue to play an important role in maximising the quality of healthcare for patients, especially those with chronic conditions. For the treatment of these and other vulnerable patient groups, connectivity certainly may offer a better path to a healthier remote-care relationship with patients.

ABOUT THE COMPANY

Recipharm delivers drug/device combinations targeting inhalation and injectables. By providing expertise in the development of combined drug/device products together with commercial manufacturing, Recipharm minimises hurdles and accelerates time to market. Through its business unit, the company has implemented technology platforms to provide drug formulation development expertise and comprehensive analytical support, as well as manufacturing capabilities for a wide range of devices. Recipharm offers highly innovative design, development and manufacturing capabilities for injectable drug delivery devices to the global pharmaceutical market, offering a range of autoinjectors with its proprietary VapourSoft technology. Keeping the end user in mind, Recipharm produces autoinjectors designed to facilitate patient-friendly administration and overcome formulation challenges, particularly for high-viscosity formulations. Its customers include several of the world's largest pharmaceutical companies.

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ABOUT THE AUTHORS

Gemma Wood, Innovation Manager, currently leads the Bespak by Recipharm Innovation team in Cambridge (UK), and has over 22 years' experience in the management of injectable device developments. The Innovation team focuses on the identification and development of novel drug delivery technologies that address unmet market needs and create new opportunities for the Recipharm Group.

MEETING AN UNMET PHARMA NEED: PIONEERING THE WAY TO A CONNECTED FUTURE

In this article, Chelsea Williams, Manager of Digital Health, Nagisa Kobashi, Product Manager of Global Emerging Technologies and Digital Health, and Nils Weber, Global Head of Emerging Technologies and Digital Health, all at SHL Medical, discuss the digital transformation of injectables, where drug formulation and device are enmeshed within a connected ecosystem powered by patient data.

Covid-19 has proven to be a catalyst for significant change across many industries, and there can certainly be no doubt of the influence it has had on accelerating the digital future of healthcare.

The confluence triggered by the pandemic presented an opportunity for accelerated change, with long-discussed innovations in healthcare delivery quickly embedding themselves as part of the everyday patient experience. An example is the dramatic shift towards the use of telehealth – now a prevalent patient-clinician interface, having spiked during the pandemic at a use level that was a remarkable 78 times higher than the pre-pandemic period for office visits and outpatient care.[1]

But while the industry can celebrate such step-change developments, there remains some distance to go before it can be argued that healthcare's digital transformation is complete. There are many reasons behind this, of course, but culture arguably plays its part. Reid Hoffman, the co-founder of professional networking platform LinkedIn, famously pointed out that "Silicon Valley is a mindset, not a location" in reference to the fast-moving, disruptive, entrepreneurial culture present among many firms based in the technology sector's spiritual heartland.

> "Digital disruption and the potential for scaling concepts at speed must also align with the fundamental principles that underpin patient care."

In healthcare, there is certainly evidence of an appetite for the innovation this culture can unlock, but it is understandably tempered by an overarching responsibility for patient safety and improved health outcomes. Digital disruption and the potential for scaling concepts at speed must also align with the fundamental principles that underpin patient care. The stakes for adopting a Google-style "fail-fast" philosophy are simply too high.

SUPPORTING PHARMA ON THE ROAD TO INNOVATION AND INTEGRATION

Pharmaceutical companies can therefore find themselves in a situation where a digitally enabled future is coming ever more clearly into view, but they do not necessarily have an obvious path to get there. Connected healthcare is evolving fast and has great potential to answer unmet patient needs, but drug manufacturers themselves have unmet needs in terms of how to realise all the possibilities that continue to emerge.

SHL Medical acts as a guide for pharma partners facing such challenges. With a collaborative, innovative culture that has brought more than two decades of leadership in injectable drug-delivery devices, it is

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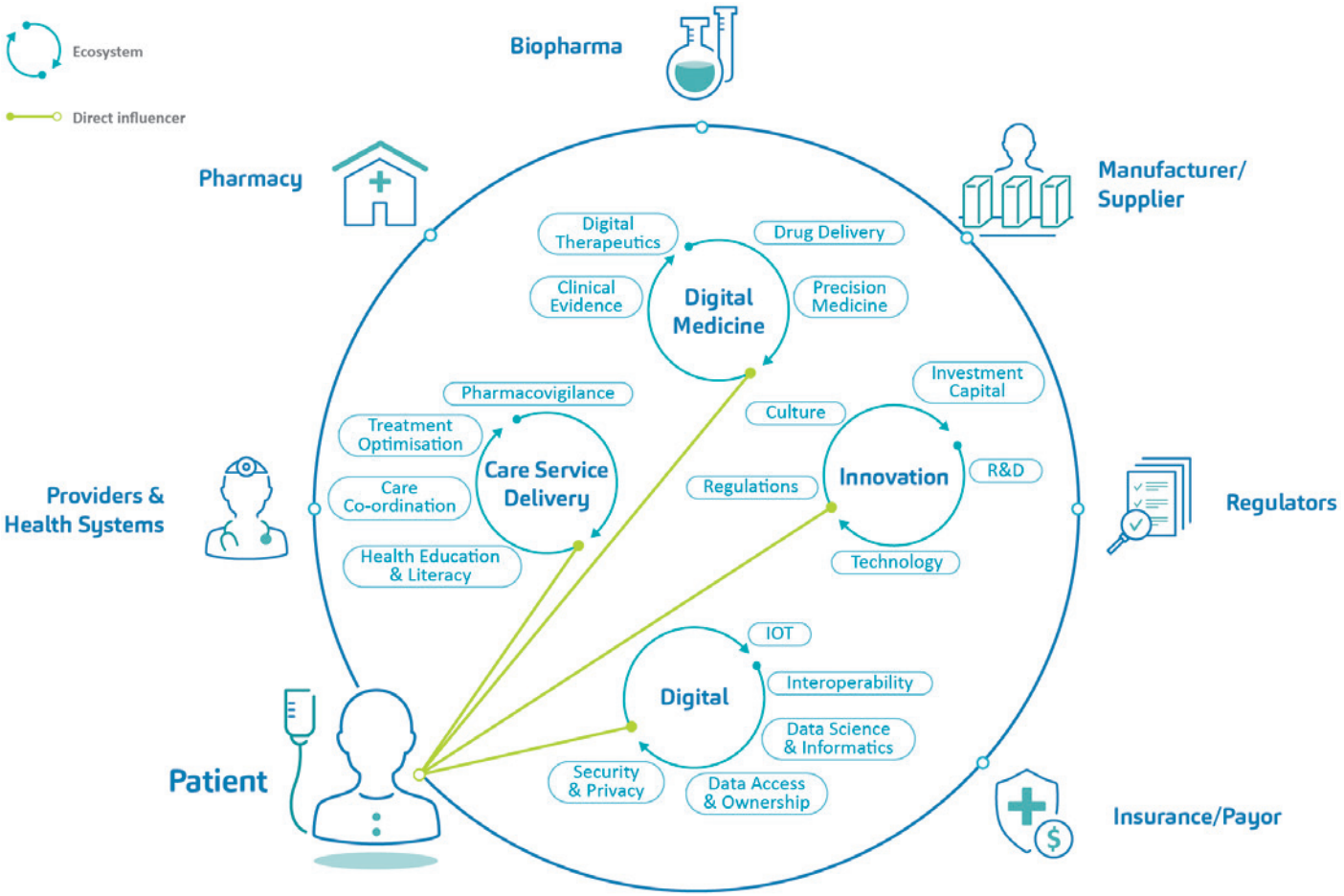

Figure 1: Components of a patient-centric digital health innovation ecosystem.

pioneering new digital healthcare pathways that will result in the creation of remotely managed, patient-empowered, data-rich platforms for the continuous care of patients with chronic conditions. The company's role as an enabler for pharma partners means it is focused on mapping therapies with connected devices as part of a digital ecosystem. Its offering is flexible by design, both of its ability to engage at any level desired by its partners and in its ability to integrate with third-party patient interfaces and systems for data capture and processing.

Digital ecosystems are characterised typically as a synergistic network of digital communities functioning as a unit and linked through the flow of information across stakeholders, institutions and digital devices.[2] In turn, Dr Gloria Iyawa *et al* noted that incorporating healthcare into the emerging digital network would create a digital health innovation ecosystem (DHIE), as seen in Figure 1, which incorporates components from care service delivery, digital health, innovation and digital ecosystems in administering patient-centric services.[3]

> "Patient centricity is a key element in the drive towards digital health."

Patient centricity is a key element in the drive towards digital health. With an increasing emphasis on self-management of conditions and shared decision making between healthcare providers (HCPs) and patients, such a model for digital healthcare lays the groundwork for patient-focused systems predicated on personalised, precise and co-ordinated care delivery. Applied appropriately, technology is enabling the delivery paradigm to shift away from providers and institutions and towards healthcare recipients and their home or care setting, facilitating the data capture that enables the treatment process to be augmented by ongoing monitoring and even predictive and preventative care. As patients embrace digital tools and services as key enablers in allowing them to become gatekeepers of their own health, this will lead to increased speed of technology adoption and, in turn, economies of scale.

PUTTING THE PATIENT AT THE CENTRE

While still in its infancy, the DHIE model has significant potential, and it is clear that the complexity involved will demand deep-rooted partnerships between digital device innovators, biopharmaceutical companies and healthcare providers to trigger exponential growth. Co-ordination, intent, engagement and collaboration are essential between stakeholders – and the broader the cohort of partnerships, the greater the likelihood of potential success.

SHL Medical is ideally positioned to leverage key competencies in line with potential partners, offering the right skills, technology assets and strategic vision to be a leader in healthcare delivery solutions, chiefly for injectable drug delivery. The company believes digital healthcare solutions must be friction-free at the point of use while also being aligned and integrated throughout the treatment chain. All stakeholders, from patients to HCPs and potentially payers, must be co-ordinated at strategic and operational levels to ensure the "oil" in the system – data – flows through the appropriate channels from its original source, the patient.

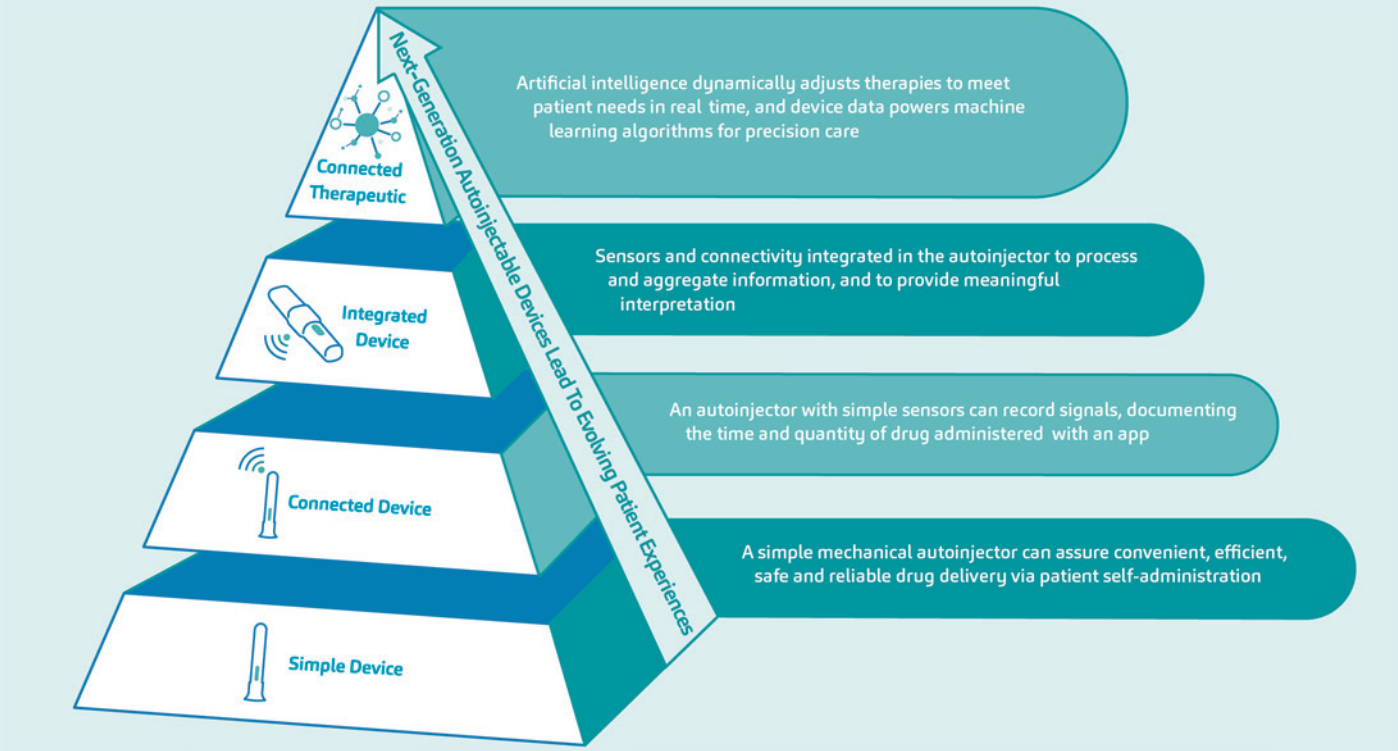

Figure 2: Cumulative value generation and implications of device complexity – evolution of the patient experience.

Medical device companies have previously approached digital health and digital transformation from a top-down, product-first perspective, akin to the "if you build it they will come" philosophy espoused in the film Field of Dreams. However, this resulted in a focus on the development of bespoke solutions with no guaranteed market or infrastructure to sustain the innovation and create economic value. The industry has since re-evaluated its strategies, instead favouring a bottom-up approach that starts with the patient – identifying their real needs and building solutions from that point of certainty.

This patient-centric approach to the design of new devices can be seen in the increased emphasis on digital strategies and investments by pharma companies, which are placing renewed attention on digitalising their portfolios.[4] Several analogue devices have graduated into the self-managed digital space to address unmet patient needs, including, for example, activity trackers, titration devices and even inhalation drug-delivery devices. In the case of connected self-injecting drug-delivery systems, innovation has the potential to enhance home-based treatment, reach unserved patient populations and support patients with adherence. Unlike other digital health technologies, however, the autoinjectable market has yet to determine the best approaches and avenues to provide meaningful and actionable data to patients.

> "The autoinjector has the potential to become the focal point of decentralised precision care for many chronic conditions, powering AI disease-management systems that impact overall patient care."

A framework for next-generation connected autoinjectors, shown in Figure 2, demonstrates the stages of technological transition from a simple device to connected therapeutic.[3] The ultimate stage in this evolution refers to the augmentation of biologic molecules through sensors and connectivity, exploiting the accessibility, personalisation and data outcomes associated with a digital therapeutic. Here, there is seamless measurement of the patient experience with increased levels of fidelity and feedback. But reaching this endpoint on the digital transformation pathway is predicated on securing the incremental steps that precede it, namely the development of the connected device and, subsequently, the integrated device. This approach – of setting and achieving realistic stepped goals within a transparent structure – supports the continuous improvement necessary for maintaining momentum and limiting development risk.

SHL Medical envisions the future of autoinjectors to have multiple components that will facilitate the harvesting of more – and more objective – data for use by patients, healthcare providers and payers. With each step, the technological capabilities of an autoinjector are expanded, graduating from simple adherence tracking via an add-on sensor to a feedback-loop device that can influence direct therapeutic management by the HCP. The ultimate step on this pathway is the evolution of an autonomous closed-loop system employing advanced data analytics and artificial intelligence (AI), such as those currently being explored in the diabetes space in relation to the artificial pancreas.

Through this design evolution, the autoinjector has the potential to become the focal point of decentralised precision care for many chronic conditions, powering AI disease-management systems that impact overall patient care.[4] It can inform a shift in the relationship dynamic between patients who are given greater autonomy and responsibility for their own healthcare and physicians overseeing home-led treatment predominantly from a remote position.

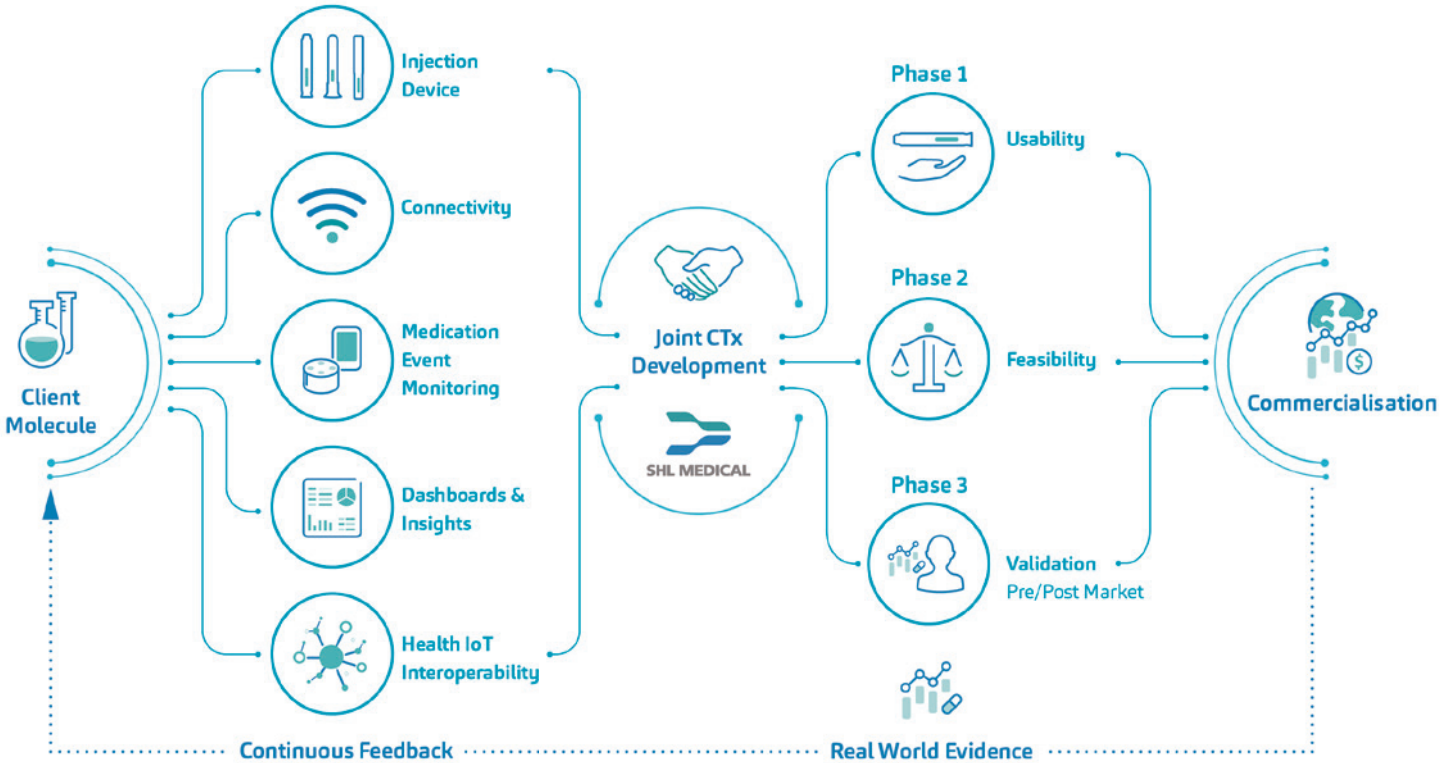

Figure 3: SHL Medical's conceptual connected therapeutics (CTx) innovation partnership framework.

A PARTNERSHIP APPROACH BUILT ON FLEXIBILITY AND INTEGRATION

Successfully transitioning to a co-development model depends highly on the device-pharma partnership, which should be established on the basis of co-creation and collaboration. SHL Medical has conceptualised the innovation partnership shown in Figure 3, which leverages SHL Medical's technological capabilities with pharma's clinical innovations. This adaptable framework builds on the foundations of the verification, analytical validation and clinical validation (V3) approach for determining fit-for-purpose biometric monitoring technologies.[5] Crucially, it enables the co-development of innovation partnership solutions in alignment with pharma objectives, but also in a way that keeps risks relatively low as they extend into the digital space.

In the drug delivery industry, there are concepts for hybrid mechanical delivery devices, such as diabetes pens or inhalers, which are complemented by digital add-ons. The innovation partnership provides a platform for legacy autoinjectors to mature into the digital space with connected features, interoperable capabilities and a supportive ecosystem to bring the co-developed solution cost-effectively from concept to market.

With digital health technologies evolving at pace, a fundamental aspect of this partnership model is the implementation of the theory within real-world collaborations that have productive outcomes. SHL Medical has identified that an attractive first step in implementing an innovation partnership is through the design and support of a clinical trial, where a connected device can be used to monitor and measure adherence accurately among candidates. By automating the immediate collection and delivery of robust real-time data, connected devices are a valuable enabler on the digital transformation journey while supporting the integrity of the trial in the context of the growing prevalence of decentralised, digitised trial environments. For pharma partners, this approach presents a self-contained vehicle for assessing the power of connected devices together under realistic timeframes, within rigorous conditions and with relatively low risk. This paves the way for further iteration as the partnership evolves.

As part of its work to support pharma partners in progressing their digital healthcare ambitions from concept to commercialisation, SHL Medical has also created connected device demonstration kits that are designed to help inject momentum into early-stage development projects. The contents of the kit encompass the device, interface and even study protocols, and it is made available on a shared-cost basis. They are designed to provide a practical, accessible route to conducting exploratory feasibility studies or mock trials, transposing the theory of digital transformation into real-world implementations that do not involve patients but can form valuable first steps on a journey to develop more sophisticated digital healthcare solutions in the future (Figure 4).

As technical complexity grows and the partnership is nurtured, co-exploration and integration with other health technologies is possible to build more layered platforms rather than independent connected products. An integral part of the DHIE, therefore, is the requirement for strong partnerships between medical technology and device manufacturers and their pharma counterparts, whose digital agendas need to cohere around pharmaceutical innovation. Collaboration should also address interoperability and privacy concerns – and ensure that the aim of digital transformation for each stakeholder group is to improve care and health outcomes for all.

FUTURE DEVICES FOR FUTURE GENERATIONS

For patients, the concept of an injection was transformed by the advent of autoinjectors, allowing self-administration in the comfort

Figure 4. An inset image of SHL Medical's demonstration kit, a proof-of-work in connected healthcare intended to facilitate the development of a digital health ecosystem – from theory into reality.

of their homes. We are now embarking on a new point of digital transformation for injectables, where drug formulation and device are enmeshed within a connected ecosystem powered by patient data. This opens the door to a range of new possibilities that can now begin to be realised through innovative collaboration.

This is both an exciting prospect for patients, who will be increasingly empowered in the self-management of their own health in their own homes, and an exciting opportunity for pharma companies, which have the potential to instigate such change through a commitment to innovation and collaboration with leading stakeholders across the industry who are aligned on this journey.

The Silicon Valley mindset is unlikely to govern decisions around healthcare. However, the fact that the unexpected catalyst of a pandemic provided a tipping point for significant digital transformation underlines the need for innovation to be twinned with momentum to affect change. It is down to device and pharma partners to grasp the digital healthcare opportunity together and take the next vital steps in building a connected future that promises so much for patients. This is where SHL Medical is leading the way – trailblazing efforts to make the drug delivery ecosystem smarter.

> "It is down to device and pharma partners to grasp the digital healthcare opportunity together and take the next vital steps in building a connected future that promises so much for patients."

ABOUT THE COMPANY

SHL Medical is a major solutions provider in the design, development and manufacturing of advanced delivery devices, such as autoinjectors and pen injectors. The company also provides final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe. With locations in Switzerland, Taiwan, Sweden and the US, SHL Medical has successfully built a strong international team of experts that develops breakthrough drug delivery solutions for pharma and biotech customers. These include advanced reusable and disposable injection systems that can accommodate high-volume and high-viscosity formulations – and connected device technologies for next-generation healthcare.

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Chelsea Williams is a Manager of Digital Healthcare at SHL Medical, focusing on digital healthcare innovation and healthcare service delivery. She brings nearly a decade of experience in healthcare technology services, from both health IT and government contracting industries. Prior to joining SHL Medical, Ms Williams provided support for large-scale projects for the Centers for Medicare and Medicaid Services and the Office of Medicare Hearings and Appeals in the US. She gained a master's degree in Global Health Program Design, Monitoring and Evaluation from the George Washington University (Washington DC, US).

Nagisa Kobashi joined SHL Medical as a Product Manager of Digital Health, working cross-functionally with the global emerging technologies and digital health teams, as well as with the global product management team. In this newly created role, Ms Kobashi leads product strategy for SHL Medical's digital health solutions and oversees leading customer projects based on the company's emerging digital health platforms. She has a master's degree in Human Movement Sciences from the ETH (Zurich, Switzerland) as well as a Swiss Federal Diploma as a marketing expert.

Nils Weber joined SHL Medical as its Global Head of Emerging Technologies and Digital Health. In assuming this new leadership role, he leads and manages various global teams that actively develop products outside the core business of autoinjectors. Mr Weber is entrusted with further developing the company's technological vision and strategy as well as managing the overall emerging technologies and digital health product and service portfolio. He holds a bachelor's degree in Microtechnics and a master's degree in Telecommunication from the EPFL Lausanne (Switzerland) and Eurecom (Biot, France). He also holds an MBA from the NYU Stern School of Business (New York, US).

SHL MEDICAL

Connected Health for all

We're innovating ways to make the drug delivery ecosystem smarter. As part of our digital health initiative, SHL Medical has worked over the years to build a comprehensive array of connected therapeutics platforms – all with the ability to become a part of any digital ecosystem. Connectivity is a step we're taking towards bringing value that enhances the quality of care across the entire continuum by improving patient outcomes and safety, increasing patient satisfaction, and elevating the maturity of digital health as we know it today.

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HOW DIGITAL UX IN CLINICAL TRIALS CAN IMPROVE MEASURES

In this article, Ben Cox, PhD, Head of Digital Design at Team Consulting, discusses the key challenges, principles and advantages of following a user-experience approach to digital health technologies in clinical trials.

In recent years there has been an increasing interest in decentralisation and the use of digital health technologies (DHTs) for clinical trials. These new tools, devices and apps are offering ongoing improvements to existing trials and have the potential to offer new methods for conducting better trials for the future.

> "One of the key advantages of DHTs with respect to clinical trials is that they allow more measurements to be taken at a subject's home, which can lead to an increased participation rate and access to more vulnerable populations, such as children or the elderly."

When conducting clinical trials, the aim is to measure more meaningful outcomes – but what exactly makes a meaningful product or experience? Increasingly, meaningful outcomes are a primary focus in clinical trials, referring to the aim of gathering data that are going to add value, such as by providing accurate insights into a subject's symptoms or health. The aim is for these data to lead to better outcomes – something that DHTs have significant potential to help with.

WHAT ARE THE OPPORTUNITIES FOR DIGITAL HEALTH TECHNOLOGIES IN CLINICAL TRIALS?

One of the key advantages of DHTs with respect to clinical trials is that they allow more measurements to be taken at a subject's home, which can lead to an increased participation rate and access to more vulnerable populations, such as children or the elderly. Take-home instruments and measurement devices also allow for increased data frequency and the ability to gain "real world" validity, with less reliance on more subjective reported data from subjects.

Digital biomarkers, such as wearables and apps, allow for more realistic measures to be captured from trial subjects, with more objectivity, frequency and efficiency compared with traditional trials. Not only can these measures provide far deeper insights, they also have the potential to improve subject adherence and retention and increase clinical capacity, with research showing a significant increase in willingness to participate in mobile or decentralised trials among participants.[1]

THE CHALLENGES OF DIGITAL HEALTH TECHNOLOGIES IN CLINICAL TRIALS

As well as opportunities, the adoption of DHTs presents several challenges for developers, sponsors and end users alike.

Navigating a Complex Multistakeholder Environment

There are already many players involved in clinical trials, and digital approaches often present their own complex landscape on top of that, with many stakeholders and users across organisations and regions, each with different needs and expectations. It is often the case that pharma companies looking to incorporate DHTs will partner with tech or digital health companies, introducing multiple systems and applications from multiple vendors. As such, introducing new tools and ways of working into a somewhat fragmented ecosystem can prove to be a real challenge for the industry.

Tolerability and Usability

In almost all contexts, users desire to complete tasks with a minimal amount of effort – clinical trials are no different.

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"In clinical trials, the most obvious user would be the subject or patient, however, a solution needs to work just as well for all stakeholders and teams involved in the work of the clinical trial."

Clinical trial teams are, however, often expected to work with multiple products and systems, and most are uninterested in becoming application experts. Subjects may themselves be required to manage different instruments and devices for extended periods of time in accordance with complex protocols, while remaining engaged throughout. Common user experience (UX) challenges that face connected health apps, including onboarding, engagement and retention, must therefore be addressed in the design of tools for clinical trials. The key is to develop products and systems that are both powerful and easy to use.

DEVELOPING MEANINGFUL PRODUCTS

In the broadest sense, digital products are designed to be useful to a user. However, the term "meaningful products" refers to the need for a product to resonate with people's needs and match their values. While this aspiration might be a stretch to fully realise in the context of clinical trials, the careful application of UX design tools and methodological frameworks can provide benefits to all stakeholders throughout the different stages of a study, ultimately helping to drive towards a more successful outcome.

The opportunities for DHTs are clear and unprecedented but their potential can only be fully realised if they are developed with all end users in mind. When designing a digital product, it is crucial to perform due diligence in understanding the user. Product experiences are only meaningful if they are created with the user in mind, meaning the priority should be on features and services that cater to user needs.

In clinical trials, the most obvious user would be the subject or patient. However, a solution needs to work just as well for all stakeholders and teams involved in the work of the clinical trial. One of the biggest decisions regarding a digital product or service development is actually one of the first ones, "What exactly is the problem (or problems) you are solving?"

Is the idea for the product something that rises internally from the developer's organisation, or is it based on some real evidence or user insight? What is the desired outcome? Does it lower user effort and save time or, in the best case, could it create new ways of thinking and working, and change someone's daily routine for the better? For a successful digital product or service, it does not matter how well designed and pixel perfect it is if it fails to offer some real tangible value to its user.

UX APPROACH TO DIGITAL HEALTH TECHNOLOGIES IN CLINICAL TRIALS

A UX approach to design involves developing a deep understanding of the end users and use context through research, organising information, wireframing and more, all with the goal of meeting user needs robustly and elegantly. It involves putting users at the centre of the design and development process, and establishing an iterative cycle of research, design and evaluation (Box 1).

TYPICAL PROJECT TIMELINE

There are a number of key activities when thinking about the integration of new digital tools and new ways of working in a clinical trial context. Typically, a small team of UX researchers and designers will work in close collaboration with a development and clinical trial team, spending anything from a few weeks to a few months working through these stages to reach a decision about what functionalities can be included in the design and start offering some real value to users.

"When it comes to user interviews, subject matter expert reviews and desk-based research, following an unstructured research approach may sound counter-intuitive. However, the aim here is to mitigate preconceptions and to uncover valuable unknowns."

HOW TO FOLLOW A UX APPROACH

Unstructured Research

When it comes to user interviews, subject matter expert reviews and desk-based research, following an unstructured research approach may sound counter-intuitive. However, the aim here is to mitigate preconceptions and uncover valuable unknowns. A structured approach to research can lead to bias towards certain users and certain problems. By following a freeform process, interviews can be conducted across

BOX 1: KEY ELEMENTS & PRINCIPLES OF A UX APPROACH

Research – Perform user research to understand user profiles, including capabilities, limitations, goals, expectations and tasks.

Understand Needs – Capture and understand all the critical needs of users.

Understand the Context – Understand the specific locations and conditions in which the solutions will be used.

Validate – Collaborate and continuously evaluate both the problem space and the solution (as it emerges) with stakeholders, users and subject matter experts.

Factor Complexity – Understand how the solution may integrate with existing workflows.

Examine Tools and Data – Explore the full range of tools, systems and data that may be used in conjunction with the solution.

Balance Innovation – Identify opportunities to innovate whilst being mindful of existing validated systems and established practices.

Design – Generate ideas and concept solutions based on user-derived evidence and prototype to bring concepts to life.

different levels of hierarchy in a clinical trial context to explore each user situation, enabling the researchers to fully interrogate the problem space.

It is important to ensure that all users have a seat at the table, ranging from site staff and subjects all the way up to global sponsor leads. It can also be important to consider the full trial lifecycle and all phases of the study. This can be a challenge given limited time and resources, so this is where subject matter experts can be invaluable for representing multiple user profiles. From here, workflows can be mapped, challenges and opportunities can be identified and user roles can be understood. This leads to user role definition.

User Role Definition

Personas are typically documented in UX projects, but when working on DHTs for clinical trials it can often make sense to take a more pragmatic approach and define user groups or profiles instead. This involves spending less time exploring how a user thinks or feels and focusing more on behaviours and goals in order to document profiles based on stakeholders' knowledge of the user (rather than direct research data). This approach allows for rapid identification of key differentiators between user roles and enables developers to implement measures that help to provide contrast between them. Examples of user roles could include editor, reviewer and viewer roles for study setup, with differentiated submitter and viewer roles for study data.

Task Modelling

Prior to mapping out user journeys, it is useful to build an understanding of the processes and tasks involved for each user group. Task modelling can provide a more flexible framework with which to consider the steps that is agnostic of the platform or interface that a user is interacting with. When setting up a digital tool in a new trial, there can be many different steps and several approaches, some sequential and some not, so task modelling helps to provide a clearer picture of these steps and workflows. It also helps to mitigate any bias the research and design team may develop regarding the way a certain interface works.

User Journey Maps

When solving problems for users, it is important to understand where the problems arise in their current journey. A journey map is a visualisation of the process that a user goes through in order to accomplish a goal. Building from task models, journey mapping can be used to highlight the unique steps in a user journey and record the potential frustrations or obstacles that users may encounter at a particular point.

Blueprints

Blueprints are well suited to helping with the integration of new tools in clinical trials, given the number of actors and the complexity of system interactions and data transfers involved. They are used to visualise the interactions between the end user and "back-stage" actors and systems for a specific user journey. This enables a clearer understanding of the product and provides a systemic view for capturing vital details that relate to other systems and data, as well as keeping the focus on the users who will be interacting with it at different stages in the process.

Landscape Reviews

In any product development, it is useful to understand what other developers are doing in the space. Landscape reviews provide insight into potential competitors and identify common features and problems they appear to be solving. This process can also help to uncover hitherto unrealised opportunities, as well as highlight potential overlaps and therefore mitigate the building of redundant features. For example, a common feature developers may wish to include is a messaging or communication system. However, this can often turn out to be burdensome for users who already work with multiple products, as it is another messaging system they need to check on top of the others that they are already engaged with. It is important to avoid overlapping with other systems and weigh up the benefits each feature will bring against the burden they will place on end users.

Feature Definition and Wireframing

Following confirmation of the research findings, inputs are taken for translation to a feature set that enables users to achieve their goals. This is the phase to dig deeper into the problem space, to create multiple different scenarios, outcomes and prototypes of the product or service and to gather feedback from key stakeholders. The design team should begin wireframing low fidelity screens and regularly share them with subject matter experts and technical stakeholders to make sure that they understand the problem and that the solution makes sense.

This is an iterative process, where the main goal is to learn something new from each hypothesis or prototype and improve

the solution based on learnings. The look and feel of the screens is less important at this stage, with the primary aim being to confirm what content needs to appear on each screen, as well as any screens that are unnecessary or could be consolidated. Once the team is confident that a desirable concept solves the problem, it is time to make a decision about the smallest set of functionalities that can be built and start offering some real value.

CONCLUSION

DHTs in clinical trials can provide benefits to all stakeholders throughout the different stages of a study and, ultimately, help drive towards a more successful outcome. Despite this, integrating new tools and new ways of working into a complex multistakeholder environment is challenging. In order to realise the potential benefits of DHTs in clinical trials and capture more meaningful measures, it is key to put users and stakeholders at the heart of the development and trial design process. By following a UX approach, developers can identify and validate problems – and develop more meaningful digital products to solve them.

ABOUT THE COMPANY

Team Consulting is a leading medical device design and development consultancy focusing on the pharmaceutical and healthcare industries. Team is an expert in drug delivery device development and works with companies both large and small across Europe, the US and beyond. Combining its expertise and experience in industrial design, engineering and human factors, Team develops medical devices from early concept through to commercial launch. Team is accredited to ISO 9001:2000 and 13485:2003.

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Ben Cox, PhD, is Head of Digital Design at Team Consulting. He works with a cross-functional group of designers, researchers and engineers to craft engaging and intuitive interfaces, and to optimise the user experience of medical devices. With a background in human factors and user-centred design, Dr Cox focuses on the user experience and interface from product vision to implementation. Previously, Dr Cox has worked in several design consultancies, as a clinical scientist and design engineer in the UK NHS, and has conducted extensive research for DePuy Johnson & Johnson. He has a BEng degree from Cardiff University (UK) and an MSc and PhD in Biomedical Engineering from the University of Leeds (UK).

A PATIENT-CENTRIC, CONNECTED INJECTION DEVICE FOR DECENTRALISED CLINICAL TRIALS – THE HUMAN FACTORS RESULTS ARE IN!

Here, Aurélie Pager, Senior Clinical and Human Factors Specialist, and Mircea Despa, PhD, Associate Director, R&D, both at BD, follow up on an article published in the December 2021 issue of ONdrugDelivery. BD has now completed a human factors study assessing the usability, acceptance and ease of use of its connected injection prototype for clinical trials.

The BD connected injection prototype by BD Medical Pharmaceutical Systems for use in decentralised and hybrid clinical trials addresses the needs of study sponsors, patients and clinical research organisations (CROs) for a safe, reliable, easy-to-use connected injection device that helps to overcome many of the challenges that arise during clinical trials. The basis of the BD connected prototype is an optional upgrade of the BD Ultrasafe Plus™ Passive Needle Guard.* The upgrade enables the device to automatically capture reliable, high-quality and time-stamped data from the injection event, with automatic data transmission to a cloud-based database of choice.

The challenges associated with clinical trials have been widely reported: growing trial costs and complexity,[1] increased cycle time to database lock[2] and non-adherence to protocol,[3] followed by dropout and data quality issues due to labour-intensive data transcription and complex integration processes.[4] Recruiting and retaining study participants also pose substantial problems[5–7] due, in part, to travel and time burdens when participants are required to get to and from trial sites.

The covid-19 pandemic has both accentuated these challenges and accelerated movement towards change, in the form of decentralised clinical trials.[8] Following the positive results of human factors testing, the BD connected injection device prototype indicates itself as a promising technological approach to facilitate more efficient and cost-effective clinical trials through injection event data capture and reporting.

> "Following the positive results of human factors testing, the BD connected injection device prototype indicates itself as a promising technological approach to facilitate more efficient and cost-effective clinical trials through injection event data capture and reporting."

BD is a world leader in injection devices, with billions of products produced each year. This connected injection device prototype is part of a larger focus at BD on patient-centric solutions. Its development aims to offer substantial benefits to the patient, healthcare and research communities alike. It represents the first step in bringing connectivity to a full range of BD drug delivery solutions.

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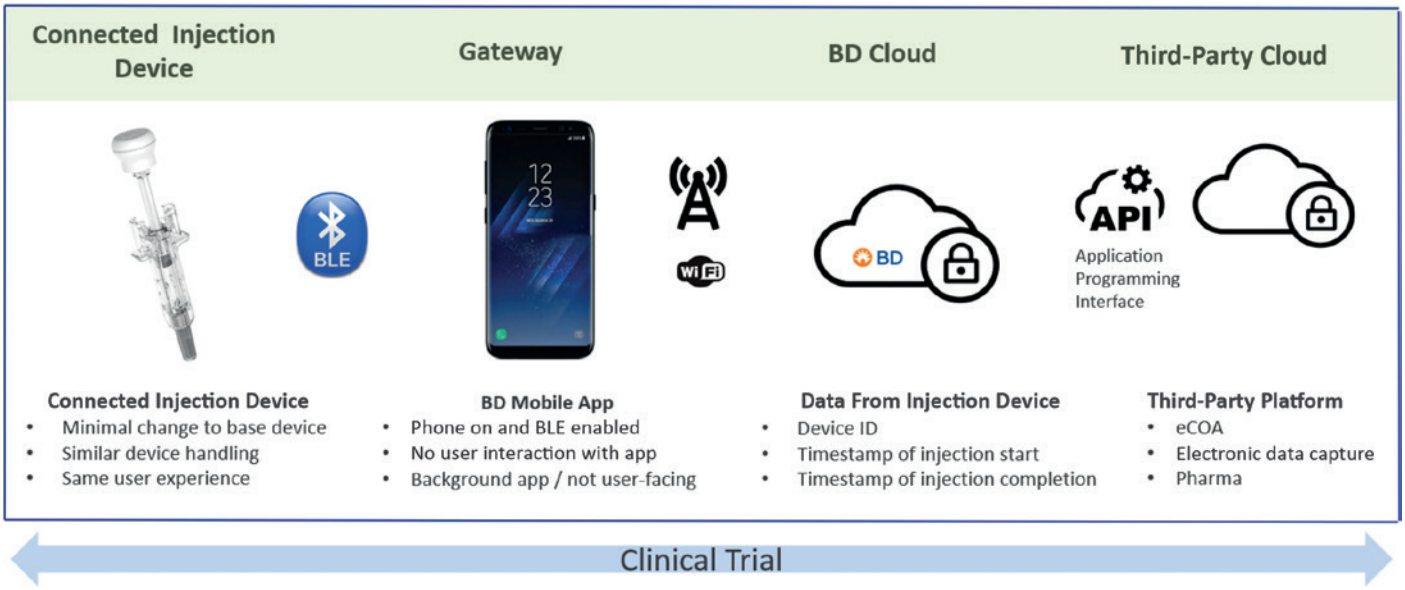

Figure 1: Contours of the BD connected solution. Informed by the research output, BD developed the solution architecture to match the needs of key stakeholders involved in clinical trials.

THE TECHNICAL SOLUTION: MEETING PROJECT OBJECTIVES

BD set out to create a connected injection device with minimal perceivable differences compared with the standard, non-connected injection device. In other words, the connected aspect would neither interfere with the device's functionality nor negatively impact its usability. With the BD Ultrasafe Plus™ Passive Needle Guard as the starting point, this meant integrating a wireless module (Bluetooth Low Energy) in such a way that it would go largely unnoticed by users – and in no way interfere or distract from the injection. To achieve this, the wireless module was integrated into the head of the injection prototype. This discreet module provides injection start and stop event data capture using a reliable, switch-based mechanism. Data emitted by the device, including the device unique identifier, is relayed to the cloud via an off-the-shelf smartphone device running a background app. The app functions as a "silent reporter", requiring no actions by the user. The only user task beyond the injection itself is to ensure the phone is powered up with sufficient battery level and in the same room where injection takes place.

Previously reported test results[9] confirmed that the connected version of the BD Ultrasafe Plus™ Passive Needle Guard does not modify device operation and closely aligns with the form factor and ergonomics of the base device (Figure 1).

BUILDING ON A USER-INFORMED DESIGN

The development of the connected BD Ultrasafe Plus™ Passive Needle Guard prototype was guided by quantitative and qualitative studies conducted among professionals in pharma, biotech, CROs and electronic clinical outcome assessment (eCOA) providers.[3] In the context of those studies, presentation of the connected solution concept resulted in participants identifying multiple possible benefits. First and foremost, participants identified the timely detection of deviations from protocol as the most valuable potential benefit. Other perceived benefits included the elimination of manual data entry, avoidance of transcription errors and enhanced data quality, and automatic data transfer.

Asked what data such a device should capture in the context of clinical trials, the study participants identified device unique identifier, start time of the injection and the time of injection completion. Participants emphasised that the connected solution should not entail additional burdensome steps, that the form factor and function of the connected solution should closely align with that of the base device, and that the user should not be required to handle or interact with the phone at the time of injection. These studies laid the foundation for the design of the BD connected device prototype for clinical trials.

Once the prototype was developed, the device underwent a series of lab-based mechanical tests[10] confirming that the connected solution was fully compatible with the base device. The evaluation confirmed complete dose delivery, successful triggering of the safety mechanism and equivalence in plunger activation force. The success of event capture and data transfer were also tested and found to be functioning as expected. The next step was to undertake a human factors study among user profiles corresponding to potential clinical study participants.

"The development of the connected BD Ultrasafe Plus™ Passive Needle Guard prototype was guided by quantitative and qualitative studies conducted among professionals in pharma, biotech, CROs and eCOA providers."

HUMAN FACTORS STUDY: DESIGN AND RESULTS

A human factors study was designed and executed to evaluate the functionality, usability, ease of use and acceptance of this connected version of the BD UltraSafe Plus™ Passive Needle Guard.[11] The study included both on-site and home-based simulated subcutaneous injections. This proof-of-concept study provided an opportunity to simultaneously gather detailed observations and user feedback on the handling and use of the device and assess the automatically captured injection data.

Study Design

The study took place during December 2021. The number of participants per user group was defined following human factors guidance,[12] with participants recruited from three populations:

- Healthcare workers (HCW) (N = 7):
  - Licensed and practising for at least two years, with experience with BD Ultrasafe Plus™ when possible.
- Naïve patients (NVP) (N = 8):
  - With chronic disease, when possible; if chronic disease, not receiving injectable treatment (oral treatment accepted); and not experienced with self-injection or with injections to others within the past 10 years.
- Experienced patients (EXP) (N = 8):
  - With chronic disease and without hand impairment; self-injection experience with prefilled syringes, syringe and vial or autoinjector; and experienced with BD Ultrasafe Plus™, when possible.

All participants undertook at least five simulated injections at the study centre, while participants in the two patient groups also performed two at-home injection simulations. Injection at the study centre took place over 45–90-minute sessions in a venue similar to a clinical setting and were video recorded. During those sessions, subcutaneous injections were simulated by injecting into a foam pad. At-home simulated injections took place with cut needle devices, by injecting into a cup or above a sink.

The data generated by the sessions were automatically collected into a BD database. In the case of an actual clinical trial, the data can readily transfer to a third-party platform, be it an eCOA tool, an electronic data capture system or directly to a dedicated pharma platform, via the use of application programming interfaces (APIs).

As shown in Table 1, all participants (n = 23) undertook at least three connected simulated injections on Day 0 at the study centre, with the HCW group also undertaking a fourth on Day 0. The two patient groups undertook at-home connected simulated injections on Days 3 and 6, with additional connected simulated injections at the study centre on Day 7.

Usability Confirmed

The usability of the BD connected prototype for clinical trials was confirmed in the study. For the initial in-clinic simulated injections, study participants were asked to do the simulations with no instructions or additional information available. Two incomplete simulated injections were observed during this first round of testing,

Day	Site	Who?	Total Planned Injections
D0	Study Centre	HCW (n=7) NVP (n=8) EXP (n=8)	84
D3	At Home	NVP (n=8) EXP (n=8)	16
D6	At Home	NVP (n=8) EXP (n=8)	16
D7	Study Centre	NVP (n=8) EXP (n=8)	32

Table 1: Overview of human factors study design with planned connected simulated injections.

committed by a single naïve participant who dismantled the device at cap removal, thus preventing the assessment of the following tasks. Use errors were seen mostly from the NVP and EXP groups related to cap removal and performance of the injection tasks. For all completed simulated injections, the entire dose was delivered and the safety guard was activated. After the initial injections, directions for use (DFUs) were made available to participants with no additional prompt or requirement to read them. For at-home simulations, specific instructions in addition to the DFUs were packaged along with the cut needle devices, the phones and the chargers.

Human Factors Study Results

Functionality results:

- Planned connected injections: 148
- Connected injections successfully completed: 146** (98.6%)
- Device failures: 0
- Cloud capture rate: 97%.***

Usability, ease of use and preference results:

- 23 participants (seven healthcare workers and 16 patients):
- 100% complete delivery****
- 100% safety activation****
- 93% of participants evaluated the connected prototype as easy or very easy to use*****
- 52% of the participants preferred the connected Ultrasafe prototype versus the standard reference product (30% of participants). The rest of the participants did not have a preference between the two products.

Key takeaways:

- BD Ultrasafe Plus™ Passive Needle Guard connected prototype performed as designed
- Excellent data capture rate, six-second median transmission time
- Zero new user risk identified
- No negative impact of connected plunger rod on users' preference (Figure 2).

GOING FORWARD

The human factors study discussed here indicates that the connected BD Ultrasafe Plus™ Passive Needle Guard prototype ensures reliable data transfer, enables near-real-time transmission of injection data and demonstrates similar usability results to the referenced standard product. With this first evaluation completed, the connected BD Ultrasafe Plus™ Passive Needle Guard prototype is ready for the next stage of development with the aim of being introduced in pilot clinical trials.

> "With this first evaluation completed, the connected BD Ultrasafe Plus™ Passive Needle Guard prototype is ready for the next stage of development with the aim of being introduced in pilot clinical trials."

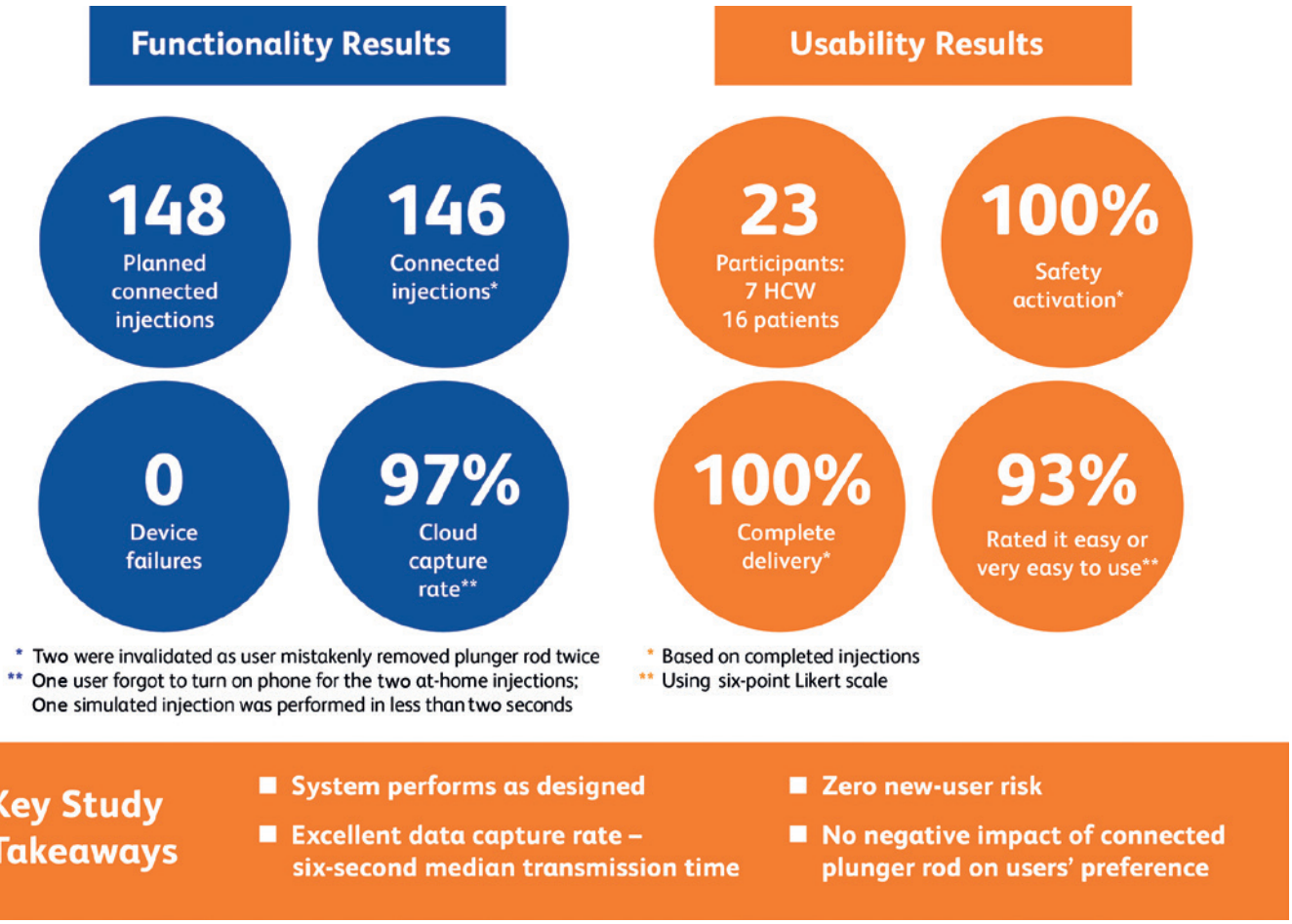

Figure 2: Human factors study at a glance.

BD is presently seeking partners wishing to make this connected solution part of their future clinical trials for a new drug product, using the BD Ultrasafe Plus™ Passive Needle Guard. Timely detection of deviation from protocol, the elimination of transcription and accompanying errors, and fewer queries of drug intake data are some of the potential benefits the solution can offer.

ABOUT THE COMPANY

BD is a large, diverse, global medical technology company. Its Medical Pharmaceutical Systems division is the world's largest syringe manufacturer. It offers prefilled syringes, self-injection systems, safety and shielding solutions, and needle technologies and associated pharma services.

**The connected injection prototype for the BD UltraSafe Plus™ is not a released product and is under development; some statements are forward-looking and are subject to a variety of risks and uncertainties.*

***Of 148 planned connected injections, two were invalidated because one user mistakenly removed the plunger rod twice preventing injection completion.*

****The cloud capture rate was affected by three user behaviours (during the at-home simulations, one user did not turn the phone on, and one on-site injection was done so fast that the device did not register it).*

*****Complete delivery and safety activation percentages based on completed injections.*

******Ease of use assessed using six-point Likert scale.*

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Advancing the world of health

FOCUS ON ADHERENCE TO EMBRACE DCT BENEFITS

Here, Bernard Vrijens, PhD, Chief Executive Officer and Scientific Lead at AARDEX Group, looks at the effect of decentralised clinical trials on medication adherence in clinical studies.

Decentralised clinical trials (DCTs) offer a multitude of benefits, from expanding access to increasing cohort diversity, but they can also serve to compound existing challenges, such as managing medication adherence.

> "The emergence of DCTs has resulted in huge advantages, such as increasing accessibility and diversity, while lowering the patient burden associated with poor recruitment and retention."

If the industry intends to squeeze every drop of potential out of these new ways of working, it needs a thorough understanding of the pitfalls as well as the advantages.

THE VALUE OF ADHERENCE

Poor medication adherence during clinical trials is a significant, long-standing problem with worrying, well-documented consequences. Studies have shown, for example, that 50% of patients across all trial phases admit to not following the dosing protocol.[1] This negatively impacts patient outcomes, leads to underestimations of product efficacy and can threaten study success, even to the point of study failure.

The emergence of DCTs has resulted in huge advantages, such as increasing accessibility and diversity, while lowering the patient burden associated with poor recruitment and retention. But it has also compounded the adherence issue.

DCT CHALLENGES

Fewer site visits can sometimes mean weaker clinical staff-patient relationships. This can impact on the patient's engagement with the trial protocol, which is a well-documented factor in poor medicine-taking behaviour.[2,3]

It could be argued that replacing site visits with home visits removes the so-called "white coat effect", which is defined as improved adherence to treatment around the time of clinic visits.

In addition, by facilitating a more diverse population, DCTs may actually reduce the number of adherent patients recruited. Study teams tend to have a selection bias towards those they know to have disciplined medication-taking behaviour, but broader inclusion remits, including the trend towards open recruitment via social media, can remove this site-imposed filter.

It is also worth noting that many commentators believe digitally enabled DCTs will lead to an increase in side-effect reports. The rationale is that many people attending a monthly site visit are likely to forget mild adverse events (AEs), such as nausea or diarrhoea, between visits. By contrast, when people are asked to log their health status daily, via an app, for example, they may be more inclined to report everything. This is invaluable data, of course, but sponsors and contract research organisations (CROs) need to be ready to receive the predicted additional reports and understand how AEs relate to adherence and dosing patterns.

Of course, variability in assessment translates to variability in clinical outcomes, but the move towards increased off-site assessments by a larger number of clinicians has the potential for lower standardisation of clinical evaluations. As such, it has never been more important for sponsors and CROs to understand the spilt between assessment-related and product-exposure-related variability in their trial data.

CONNECT TO ADHERENCE

Despite poor medication adherence during clinical trials being a problem for decades, it continues to be a stubborn challenge. Traditional methods, such as pill counts, blood sampling and healthcare provider

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"Combining connected drug packaging and powerful data analytics, for example, is objective, precise and, crucially, provides a holistic view of medication-taking behaviour."

(HCP)- or self-reporting, are simply not sensitive enough to tackle the problem.

For example, counting returned tablets is easily censored by participants; and it provides but a summary of adherence between site visits, not the overall understanding of treatment initiation and dosing patterns needed to meet the challenges of the DCT era. The same is true of monitoring drug or drug metabolites in blood, urine or hair, due to the white coat adherence affect, and all reports – self, site or HCP – are vulnerable to bias. All in all, these historic approaches tend to generate incomplete or inaccurate data.

Digital monitoring is different. Combining connected drug packaging and powerful data analytics, for example, is objective, precise and, crucially, provides a holistic view of medication-taking behaviour.

Electronic sensors in the packaging, whether it be connected inhaler, capsule bottle or prefilled syringe, records dose administration and other essential information, and automatically transmits it to the study team. A cloud-based platform then uses sophisticated algorithms to analyse medication-taking behaviour and flag any erratic dosing patterns.

This advanced approach is feasible, reliable and easy to implement, but, importantly, it is continuous. Providing an overall, real-time picture of drug-taking behaviour gives researchers all the information needed to make informed decisions.

Importantly, this advanced model of adherence monitoring is evidence-based. Studies have shown, for example, that it is 97% accurate, compared with 60% for pill count, 50% for healthcare professional rating and just 27% for self-report.[4]

RISK/BENEFIT PROFILE

There is no arguing that DCTs have the potential to make clinical research more representative, more efficient and more patient-centric.

But before diving into this new way of working, sponsors and CROs must first ensure they are aware of any potential threats to the collection of quality data and adjust their workflows accordingly.

By focusing on adherence, organisations can be sure they are working with the full data set, regardless of the impact of DCTs on the way studies run and people behave.

ABOUT THE COMPANY

AARDEX Group is a global leader in digital solutions to measure and manage medication adherence. With operations in Belgium, Switzerland and the US, AARDEX develops and markets digital solutions for adherence-enhancing strategies in clinical trials, research settings and professional healthcare systems. AARDEX is the central actor of a complete ecosystem that combines its MEMS® Adherence Software with a wide range of smart packages and devices that measure patient adherence across all routes of drug administration. AARDEX's vision is to continuously innovate in data-driven medication adherence solutions to enhance digital therapeutics and patient empowerment.

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ABOUT THE AUTHOR

Bernard Vrijens, PhD, Chief Executive Officer and Scientific Lead, AARDEX Group and Invited Professor of Biostatistics, Liège University, Belgium, holds a PhD from the Department of Applied Mathematics and Informatics at Ghent University, Belgium. Dr Vrijens currently leads a research programme investigating (a) the most common errors in dosing using a simple but robust taxonomy, (b) particular dosing errors that can jeopardise the efficacy of a drug and (c) the optimal measurement-guided medication management programme that can enhance adherence to medications and maintain long-term persistence. Dr Vrijens is also the co-author of seven book chapters, over 100 peer-reviewed scientific papers and named as inventor on six patents. He is a founding member of the International Society for Medication Adherence (ESPACOMP), and an active member of several EU- and US-funded collaborative projects around the theme of adherence to medications.

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TURNING CONNECTED DRUG DELIVERY PIPE DREAMS INTO REALITY

In this article, Mindy Katz, Vice-President, Marketing and Alliance Management, at Eitan Medical, discusses the benefits of integrating homecare technologies that are patient centric and connected.

Prior to the fateful month of March 2020, the introduction of hospital-grade medical devices and technologies into the home had been looming on the horizon. Catalysed by covid-19, the healthcare industry had to fast-track the deployment of remote care solutions, including telehealth, digital health and connected devices, to deliver care at home.

Unlike previous industry trends, the need for home-based care solutions was strongly influenced by patient demand, rather than by major players (providers, hospitals, payers, etc) within the healthcare sector. With hospitals overloaded and fear of contagion at an all-time high, people were hesitant to receive care in hospitals. In addition, hospitals were limiting the number of non-critical services being made available. This resulted in a greater need for homecare workers, as observed by the National Association of Homecare and Hospice,[1] which saw a 125% increase in February 2021.

Understandably, the implementation of homecare technologies and the subsequent trend towards developing patient-centric devices that would allow patients to "self-treat" brought about a behavioural change from providers and patients. This change will eventually see hospitals and clinics focus on providing critical care and enable patients to care for themselves independently in less-critical situations from the comfort of their homes. In particular, for patients with chronic conditions without acute incidents, home-based models of care can become the primary pathway for care delivery.

> "For more independent homecare treatments to succeed, providers will need to offer solutions that are patient centric and connected."

However, for more independent homecare treatments to succeed, providers will need to offer solutions that are patient centric and connected to ensure patient adherence and regimen upkeep, and to maintain open lines of communications with care providers, especially within the drug delivery space.

DIFFICULTIES OF HOME-BASED DRUG DELIVERY

Providers face unique challenges when shifting drug delivery treatments to the home. These difficulties can include the ability to accurately and remotely monitor patients, a lack of access to treatment logs, safety concerns resulting from not being notified of alarms and troubleshooting errors.

With direct and constant connection between patient and clinician in the hospital setting, healthcare teams can review treatment data, understand patient adherence levels and receive alerts and notifications in real time. By adding these capabilities to homecare-optimised devices,

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Figure 1: Eitan Medical's Sorrel drug delivery device is wearable, offering mobile drug delivery options.

> "To ensure long-lasting integration into the homecare environment, device manufacturers will need to increase the ease of use of devices."

there is the potential to improve patient care and ensure the efficacy of drug delivery regimens from a distance, instilling a sense of trust in home-based solutions for both providers and patients.

THE NEED FOR PATIENT CENTRICITY

Before even considering the doors that open with connectivity, medical device manufacturers need to develop solutions that are more patient centric to accommodate the move towards the home, allowing both patients and caregivers to become more independent in the care delivery process. This is especially difficult to achieve within the world of drug delivery, as these devices are more complex to operate and require more clinical protocol navigation.

To ensure long-lasting integration into the homecare environment, device manufacturers will need to increase the ease of use of devices. By adding features such as intuitive protocol instructions and embedded safety software, home-based patients will be better positioned for success. In fact, increased ease of use through human factors usability testing is now mandated by the US FDA,[2] which will hopefully reduce medication dosage errors and increase positive outcomes. Additionally, this empowers patients and caregivers who lack professional training to support and receive care with confidence (Figure 1).

INTRODUCING PHARMA TO THE MIX

Due to an increased understanding of the growing acceptance of, and affinity for, home-based patient-centric approaches, pharmaceutical companies are now encouraged to make drug delivery easier for patients to manage on their own. One of the main ways in which pharmaceutical companies can improve the drug delivery patient journey is by changing administration routes, mainly moving away from intravenous towards subcutaneous drug delivery, generally at a cost of reformulation and new regulatory filing. This change has the potential to create routes of drug delivery as safe as those administered in hospital settings,[3] but which allow more patients to self-treat in their own homes (Figure 2).

WEARABLES PAVING THE WAY

Simultaneously, the nature of injectable drugs is changing, with advancements in biotech resulting in a surge of biologics reaching the market. With higher viscosities and larger volumes than chemically synthesised drugs, these medications require an alternative delivery system to traditional handheld injectors. Wearable injectors address this issue, offering devices that accommodate larger-volume and higher-viscosity drugs.

Figure 2: Eitan Medical's Sorrel wearable drug delivery platform.

Figure 3: Eitan Medical's Sorrel wearable drug delivery platform in action.

> "By giving clinicians a clearer picture of patient status from a distance, they will be positioned to act quickly to ensure proper care delivery and compliance."

Moving forward, wearable drug delivery devices that are primary-container agnostic may be increasingly adopted, potentially providing flexibility for pharmaceutical companies and faster turnaround times for the development of one primary-container-based device to the next. The benefit is that this approach allows pharmaceutical companies to enter the homecare market faster and more efficiently with drugs that can be safely self-administered by the patient using a wearable drug delivery platform (Figure 3).

CONNECTING THE HOME AND THE HOSPITAL

With advanced connectivity capabilities, such as Bluetooth and near-field communication, being widely used, we are in the process of witnessing change within the healthcare sector. Now, clinicians will be able to access treatment data remotely, expanding the reach of care. With regards to wearable injectors, these smart, connected devices, combined with a series of user indicators including visual, audio and tactile, can help guarantee a safe, easy and successful self-administration experience.

By giving clinicians a clearer picture of patient status from a distance, they will be positioned to act quickly to ensure proper care delivery and compliance. Real-time remote patient monitoring enabled by advanced connectivity capabilities, beyond the capabilities of smartphones today, can be instrumental in maintaining the safety of patients at a distance, even for patients with complex situations.

AGGREGATING DATA FOR A MORE PERSONALISED EXPERIENCE

Additionally, analyses of aggregated patient data can enable caregivers to identify treatment patterns and make data-driven decisions to improve care optimisation. Of course, near-time gathered data allows for near-time medical interventions. This offers a more personalised experience for patients, which, considering co-morbidities and complex patient conditions, could have serious implications. This approach can be seen within the realm of oncology, with oncologists altering drug dosages and prescription plans to provide the care an individual patient needs more effectively.

From a big data perspective, connected drug delivery devices can offer pharma, providers, payers and patients a tremendous boost. In better understanding the actual usage of drug delivery devices, the industry can better prepare for the future of healthcare delivery.

COMING FULL CIRCLE WITH PATIENTS, PROVIDERS AND PAYERS

Understandably, providers, patients and payers are intertwined. The addition of connectivity allows for improved patient compliance, further ensuring that patients are adhering to their medication regimens at home. This built-in accountability will tell clinicians if their patients are properly abiding by their treatment plan. As a result, this confirmation can act as justification for

the expense of the treatment, closing the loop between medications prescribed and care delivered.

MOVING AHEAD AND STAYING CONNECTED

Integrating technologies for homecare that are patient centric and connected will help healthcare systems become more effective, giving them the ability to manage larger patient populations with the same resources. This also paves the way for increased patient comfort, lower hospital readmission rates and, ultimately, better outcomes. Looking ahead, we can expect homecare to continue becoming more connected and patient centric – the results of which will be industry-changing.

ABOUT THE COMPANY

Eitan Medical develops drug delivery systems, including wearable injectors and infusion solutions, that put patients at the centre of care, making drug delivery easier and safer. The devices are applied across the continuum of care, including hospital, ambulatory and homecare environments.

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ABOUT THE AUTHOR

Mindy Katz is Vice-President, Marketing and Alliance Management, at Eitan Medical, where she heads the company's alliance management, marketing and product management activities for the Pharmaceutical Solutions business unit. Her involvement in the company's early days influenced Eitan Medical's decision to pursue the wearable drug delivery market, resulting in the development of the Sorrel wearable drug delivery platform. To date, Ms Katz has held a number of positions within the group, including serving as Vice-President of Marketing and Director of Product at Sorrel Medical (before it rebranded under the Eitan Medical name) and, prior to that, as Program Manager at Q Core Medical (also now under the Eitan name), where she worked across multidisciplinary teams to build structured and collaborative partnerships between companies in the world of drug delivery. She holds a BSc in Biomedical Engineering from the Technion – Israel Institute of Technology.

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SUPPORTING PATIENTS ON THE ROAD TO SELF-CARE

In this article, Michael Earl, Director, Pharmaceutical Services, at Owen Mumford, discusses the importance of transitioning current healthcare models to embrace patient self-management and how advanced drug delivery device technologies, such as connectivity, can ease this burden on overstretched healthcare services.

The future of chronic illness treatment will rely on improved collaboration between healthcare professionals and patients to support effective self-management and self-administration of therapies. Patients need to be educated about their condition and its treatment if they are to take control of their own care, rather than being passive recipients. Efforts to improve the patient experience have led to developments in drug formulation, medical device design and patient-professional interactions. There is a trend towards easy-to-use injectable therapies for self-administration and the development of connected devices – providing patients with more independence and allowing healthcare professionals to monitor conditions between consultations.

The covid-19 outbreak increased the burden on global healthcare providers and, as a result, increased the difficulty of treating patients. In the UK, the 15 million sufferers of chronic diseases – who would normally take up 50% of GP appointments and 70% of bed days – were unable to receive the same level of attention, and aspects of care had to be modified to ensure patients still received the necessary support.[1]

While the worst of the pandemic may have passed, healthcare services must continue to adapt to deal with the difficulties of treating an ageing population that is increasingly susceptible to multi-morbidities and chronic conditions. By 2030, one in every six people worldwide will be aged 60 or over.[2] Enabling broader self-administration of medication is a key factor in helping prevent healthcare services becoming overwhelmed. Those in the industry recognise this, with a recent survey of over 3,000 clinicians across the globe finding that almost half (49%) believed that the majority of healthcare will be provided within patients' homes in 10 years' time.[3]

"By 2030, one in every six people worldwide will be aged 60 or over."

PATIENT SELF-MANAGEMENT – EDUCATION AND STANDARDS

Patients with chronic diseases already take on significant responsibility for their own treatment, with health maintenance, illness prevention, monitoring and condition management predominately performed outside a clinical environment. Under a shared-care approach, this is reinforced with appropriate support from healthcare professionals to help patients feel confident in their ability to successfully adhere to treatments and manage their own condition. For example, tailored support can provide reassurance for patients who have specific worries or phobias until they are able to overcome them.

The shared-care approach is receiving attention from healthcare authorities across the globe. In Europe, standards on patient participation in self-care practices were first established last year.[4] The standard will be an important guide not only for patients

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and healthcare practitioners but also the researchers and businesses that are involved in every facet of industry.

As a more detailed example, the UK NHS is making personalised care an important aspect of its long-term plan.[5] Health coaching, self-management education and peer support will be designed to improve the skills and confidence of patients and enable successful adherence to treatments. The NHS estimates that implementing self-management practices could see the need for GP appointments fall by 9% and emergency appointments by 19%.[6]

In the US, the American Medical Association has established a variety of resources aiming to improve dialogue between patients and healthcare workers, such as the "patient experience programme".[7] The programme collects patient feedback on all facets of care and uses it to update processes causing issues.[8]

Supported self-management is likely to lead to more engaged patients who are keen to adhere to treatments and make meaningful lifestyle changes, reducing the need for further interventions by healthcare professionals. In turn, this will reduce the burden on healthcare systems and free up valuable time and resources for use elsewhere. Patients with more awareness of their treatment, its duration and the range of possible effects will have greater confidence, improving health-related behaviours, as well as their overall physical and mental wellbeing.[9] A recent study found that diabetes patients who received education on self-management were 2.5 times more likely to engage with these practices. These patients are then 1.5 times more likely to manage glycaemic levels effectively.[10]

GAPS IN SELF-ADMINISTRATION SUPPORT

Successful self-administration of medication relies on clear guidance for the patient, as well as healthcare professionals having time to respond to queries, address concerns and discuss how the patient can integrate their treatment into their daily routine. However, this may be difficult for healthcare professionals to provide due to their busy schedules and the time-sensitive nature of appointments with healthcare professionals may discourage patients from raising issues they are facing.

A study of patients who have struggled with self-injecting showed that only 50% had received a visual demonstration of the injection process from a healthcare professional. As few as 13% were able to demonstrate the process themselves to a professional and receive immediate feedback.[11] Pharmaceutical and drug delivery providers are beginning to step in and fill the void to provide patients with information about their conditions and how to implement and maintain good, consistent self-administration practices. Additionally, adherence monitoring, helplines, assistance with payments and more are being provided – allowing for faster detection of any problems.

> "Pharmaceutical and drug delivery providers are beginning to step in and fill the void to provide patients with information about their conditions and how to implement and maintain good, consistent self-administration practices."

MEDICAL DEVICES – ADAPTING AND INNOVATING

While setting standards and providing education for self-treatment is important, it must be paired with the provision of drug delivery device designs that cater for increasing self-administration. Recognition of this has led to many companies moving away from traditional vials and syringes to focus instead on developing drug delivery devices that are easy to use and reduce the risk of needlestick injuries. This includes a host of devices, including prefilled syringes, pen injectors and autoinjectors. The challenge for the makers of these products is tweaking designs to keep up with innovations in the drug formulation world while still creating the best user experience possible.

In recent years, there have been widespread changes to the traditional design parameters of drug delivery devices. There is a growing trend towards higher subcutaneous injectate volumes with more devices accommodating 2.25 mL prefilled syringes – with 3mL (and greater) volumes a distinct possibility for the future. A significant factor contributing to this increase in drug volumes and viscosities is the pharmaceutical industry's effort to reduce injection frequency, thereby easing the burden on self-administration patients.

While this trend may alleviate one concern for patients, it can create new difficulties, such as increased hold times during administration, that may prove uncomfortable for some patients and impossible for others. Development of 34G needles, degradable micro-needles and thin wall needles are a few examples of how companies can accommodate greater volumes and flow rates without increasing pain on injection.

Continuing development of biologics and biosimilars, plus drugs with multiple dosages, may see pharmaceutical companies prioritise platform devices that can be easily adapted to accommodate a variety of fill volumes and ensure products get to market promptly. In the competitive pharmaceutical industry, supporting lifecycle management and improving the usability of a device can be a differentiating factor for companies attempting to maintain or increase market share.

CONNECTIVITY – A KEY TO THE FUTURE

Connectivity is another area of exploration for companies looking to make their drug delivery devices suitable for the future. A range of data can be gathered, from basic date and time of injection to more specialised information on drug temperatures and checking for expiry. This data can then be relayed to clinicians and/or patients, enabling them to make modifications to treatments if appropriate.

Following covid-19, a wider range of patients may be willing to engage with connected devices, as the pandemic forced less tech-savvy members of the population to use digital applications and gain experience of remote consultations with healthcare providers. In fact, medical device manufacturers such as Abbott (IL, US) are seeing a chance to market connected products directly to consumers. The company's "biowearables" line will monitor glucose, ketone, lactate and possibly even alcohol levels, allowing users to monitor aspects of their general health and make lifestyle adjustments before medical issues arise.[12]

"While there are a host of exciting possibilities associated with connectivity, it is imperative that firms prioritise simplicity in device design and ensure a patient-centric approach, otherwise any new innovation may be lost on many users and ultimately not provide the return on investment."

It is certainly conceivable that digital health could become popular in the consumer market and encourage more widespread personal health and wellbeing monitoring. This has already been demonstrated by the recent boom in smartwatches associated with the adoption of health features.[13] While there are a host of exciting possibilities associated with connectivity, it is imperative that firms prioritise simplicity in device design and ensure a patient-centric approach, otherwise any new innovation may be lost on many users and ultimately not provide the return on investment.

CONCLUSION

Creating a healthcare system that is better able to support self-management and self-administration has a host of benefits. An ageing population is likely to increase dependence on healthcare services, so freeing up valuable time and resources is crucial. Introduction of self-management standards and better training around self-administration of therapies must be supported by medical device design.

A user-centric approach must be prioritised, especially when introducing more complex elements, such as digital health and connectivity. The pharmaceutical industry can also pick up some of the burden of training users to relieve overstretched healthcare services. Future devices may ease these pressures, as smarter products allow better collaboration and help to keep people well informed about their own health.

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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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 its substantial medical devices business. Prior to that, he worked for a number of pharma, biotech and device companies. In a career spanning 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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