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CONNECTING DRUG DELIVERY

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

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YPSOMED SELFCARE SOLUTIONS

COVID-19: A CATALYST FOR IMPLEMENTING CONNECTED HEALTHCARE PRODUCTS?

Napoleon Monroe, Managing Director, New Directions Technology Consulting, analyses how COVID-19 is catalysing a wide range of reactions in healthcare. He says drug and device connectivity are essential to improving patient access to treatment – and patient outcomes – as well as reducing overall cost. Factors such as personal and population health – along with societal, technological, commercial, regulatory and legislative reactions – are interwoven in the changes. Mr Monroe argues that considering the possibilities for patient outcome improvement is critically important – and our outcomes, our lives and our companies depend on reactions to the catalyst.

Almost every assumption about healthcare made before COVID-19 is being reconsidered or upended. The speed of change in healthcare – including accelerated patient outcome assistance and product connectivity – is suddenly in the spotlight.

> "Patient and caregiver adoption has moved from 11% to 46% and providers are now seeing 50–175 times the number of patients via telehealth compared with before the pandemic."

Social distancing, restrictions on personal interaction and provider access limitations have forced immediate wide adoption of telemedicine – for limiting the spread of the disease, improving access to informed care, understanding individuals' health and contacts across a broad population, and promoting individual responsibility for self and family. The US Federal Communications Commission (FCC) granted US$68 million (£55 million) for COVID-19 telehealth programme applications as part of the $2 trillion Coronavirus Aid, Relief, and Economic Security (CARES) Act.

Once tried – and especially once services are expanded and improved – the adoption and growth of telemedicine is likely to be permanent. A report in May 2020 from McKinsey & Company, *Telehealth: a quarter-trillion-dollar post-COVID-19 reality?*, documents what it calls "the massive acceleration in the use of telehealth since the COVID-19 pandemic". Patient and caregiver adoption has moved from 11% to 46% and providers are now seeing 50–175 times the number of patients via telehealth compared with before the pandemic. Pre-COVID-19, total annual revenues in telehealth were approximately $3 billion. With further provider adoption, up to $250 billion of US healthcare spending could be virtualised.

McKinsey discusses five models (some elements of the models are already practised). Within the scope of the models, one can envision:

- Remote medication outcome assistance for diagnosis and adherence, compliance and administration
- Urgent care triage and treatment
- Virtual office visits enabled by remote patient monitoring, and digital diagnostics and therapeutics
- Near-virtual office visits, combining virtual access to physician consults with other entities for testing and specialty services
- Remotely delivered home health services for the elderly and disabled including personal, physical, behavioural and occupational assistance.

Healthcare systems around the world were – and still are – paying, directly and indirectly, for medications and devices which are often not used or are used improperly. Medication and device outcome

> "Telemedicine is a catalyst for breaking the legacy barriers."

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"The traditional wisdom that patients and practitioners would reject telemedicine was disproved."

assistance can benefit from these sunk costs when outcome assistance barriers are removed. Telemedicine is a catalyst for breaking the legacy barriers.

Effective COVID-19 prophylaxis and treatments will rely on medication adherence and compliance. Even a vaccine may require multiple doses or boosters. Therefore, medication adherence and compliance have received greater recognition in outcomes research. Connected products are being used to gather population data and improve individual electronic medical records and to reduce interpersonal and system communications failures.

Lockdowns have affected clinical trials of medications, which have been moved away from dedicated clinical trial sites. Connectivity enables more meaningfully distributed clinical trials – and the immediacy of connected products has sped up the process.

Psychiatry is another area now receiving far more attention as the effects on mental health related to COVID-19 become widespread. Psychiatric outcomes are extremely sensitive to medication adherence and compliance.

Many of these changes are predicted to outlast COVID-19. The traditional wisdom that patients and practitioners would reject telemedicine was disproved when there was no choice but to accept it. While face-to-face is rightly preferred, telemedicine is less costly for patients and many other stakeholders; and can suffice for many visits. Once telemedicine is adopted, regression to old systems will be difficult.

The following are just some examples of changes brought about by the pandemic:

- Practitioner shortages, acknowledged before COVID-19, became extreme and were eased by telemedicine.
- Temporary payment parity was granted for telemedicine consults related to COVID-19. While universal parity is not likely, a Bloomberg editorial predicts two-tiered reimbursement for medical office visit (OV) and telemedicine after the pandemic – full for OV and reasonable, but less, reimbursement for telemedicine.
- US Health Insurance Portability and Accountability Act (HIPAA) regulations were relaxed for providers with existing patient relationships acting in good faith. The need for rapid responses to the pandemic also sped up turnaround times and innovation.
- Nationalistic considerations grew.
- Many barriers to telemedicine were temporarily removed. Going back to prior restrictions will be difficult.
- In the US, Governors have issued waivers for practice across state lines for COVID-19, extending prior agreements.
- Automated product identity is now recognised as having greater importance in post-market surveillance due to accelerated trials; and adulterated, misbranded ineffective, recalled, stolen, counterfeit and diverted products, which are currently of great concern.
- Medication compliance is recognised as important in combating COVID-19 and ensuring readiness for any future pandemics.
- Building on opioid and fintech controls, payers have proposed means to limit fraud and abuse of telemedicine.

FUTURE SCENARIOS FOR US HEALTHCARE

Three model scenarios for US healthcare will predict how outcome assistance and connected combination products will be viewed in the future. In all scenarios, the US and state governments will remain the largest payer for Medicare, Medicaid, government employees and retirees. Deficits will demand that governments control costs. US healthcare stakeholders will have to rely more heavily on new applications of newer technology than in the past. Telemedicine and connected products will be more important to all stakeholders than before.

Scenario One

Some predict that there will be little substantive change to the fee-for-product service models. Haven (the two-year-old Amazon, Berkshire Hathaway and JPMorgan coalition) has tried to bringabout change but so far it appears that the fragmented stakeholder systems have shown little interest. There have been few announcements of progress from Haven – and Haven Chief Executive Officer Dr Atul Gawande announced his resignation in May 2020. The earlier 54-company Health Transformation Alliance as well as Walmart succeeded in chipping away at some costs. Nevertheless, stakeholder resistance and US post-COVID-19 unemployment – which has taken many more people out of the employment healthcare insurance pool – make it apparent that, ultimately, dramatic change will come no matter which political party is in power.

Scenario Two

Others predict mandatory price controls and allowing negotiation and importation. However, price controls are not enough, and are likely to be badly administered and will kill much valuable US innovation. Importation is not adequate and will be blocked based on national needs and large US volume requirements. Pharma will have fewer tools to differentiate and justify costs, meaning telemedicine and connected products will be more important to all stakeholders than in the past.

Scenario Three

Lastly, others predict a "healthcare for all" model. However, none of the proponents or opponents are yet willing to define the rationing which will go along with this effective state takeover of basic healthcare. Opponents are unwilling to consider the possibilities, acknowledge that disparities in health lead to further socio-economic disparities or discuss the current rationing. It is likely that the US will evolve into a German, Dutch or French style system for basic needs and a parallel private free market for anything beyond basic care.

In all three scenarios, telemedicine and connected drug delivery products will be used more to help improve patient outcomes and control total healthcare costs. As pharma and device manufacturers have the most knowledge about the drugs and devices they manufacture, a prescription for

"Pharma will have fewer tools to differentiate and justify costs, meaning telemedicine and connected products will be more important to all stakeholders than in the past."

a drug or device should qualify as an existing patient relationship to allow information exchange. Among the various stakeholders, connected product manufacturers, or their contractors, are the best positioned to assist with adherence and compliance.

Before COVID-19, there was great resistance to – and limited perceived need for – major change in US healthcare fee-for-service, in-person healthcare delivery. The fragmented nature of US healthcare presented significant barriers to change. Some issues in two categories were:

Great Resistance

Different stakeholders have put up great resistance because they thought:

- Changes to established fee-for-product and service models are threatening
- We might lose our advantages with changes through legislation or otherwise in our various legacy stakeholder models
- Reimbursing telemedicine would bankrupt payers
- There is limited or no payback for connected diagnostic devices or drug/device combination products

> "Among the various stakeholders, connected product manufacturers, or their contractors, are the best positioned to assist with adherence and compliance."

- Changes to improve outcomes would add cost for some stakeholders
- Connected products are not interoperable and are difficult for patients to use
- Adding patient outcome assistance would delay marketing and may add legal liabilities
- Any change from centralised, randomised clinical trial approval could jeopardise the entrenched approval and payment systems
- Patient privacy might be put at risk. We must abide by existing HIPAA regulations.

Limited Perceived Need

There was a perception of limited need among stakeholders, who believed, for example, that:

- Inertia in systems already in place is comfortable
- We can continue to merge, acquire, lobby, advertise, automate, add lower paid staff, and make others (and even ourselves) more efficient and keep on going
- Patients' opinions are uninformed and difficult to evaluate
- Payment for outcomes and closer post-market surveillance won't become broad-based realities
- We can continue to rely on the randomised control trial approval process to be paid.

POST-COVID-19 CATALYSTS

However, over the past few years even prior to COVID-19, many catalytic factors have emerged, encouraging healthcare stakeholders to take actions to promote better patient outcomes:

Health

As the population ages, we have experienced growth of known chronic diseases which still go undiagnosed, undertreated or untreated and, therefore, worsen. Some of these conditions even seemed to be moving towards better control – but new diseases and new treatments have been overlaid on those previously identified. The complexities of patients' comorbidities and treatment possibilities have made focus difficult. There is greater recognition of overall treatment costs and the costs of poor outcomes related to non-adherence and non-compliance. There is also recognition that medication use – and non-use – are valuable diagnostic tools.

Societal

Provider access has become increasingly difficult because of factors including provider consolidations, fragmented and overlapping healthcare bureaucracies, provider specialisation with limited numbers of generalists who must often function as gatekeepers, less generous employee insurance, contract workers not covered by employer insurance, and healthcare inflation outpacing wage growth for many years. In addition, the media has, for many years, highlighted the role of health disparities on outcomes. Pharma has also gained a far greater understanding of human and economic factor issues, and attempts to limit provider costs have made specialty products available for home administration.

Technological

Biologics, other specialty medications and remote diagnoses have become extremely important. Smartphones with sophisticated communications capabilities are ubiquitous and health apps are available and used by many patients. And healthcare product automated identity and data capture (AIDC) systems – including product serialisation barcoding systems – have been around since 2013, although adoption has proceeded slowly.

Predictions have been made that technology will open many more lasting possibilities for telemedicine – and investments in this area have been substantial. Stakeholders such as pharma companies and their suppliers, technology companies, providers, payers, medical device and consumer device companies, healthcare distributors and information companies have invested in smarter, simpler-to-use drug delivery and diagnostic devices, remote professional and personal software and hardware products, communications, security, analytics information gathering, analytics and processing.

Entities experimenting with advancing healthcare improvements have uncovered and addressed interpersonal and system communications failures. Blockchain and other security systems have also been developed outside healthcare to address security and privacy concerns. Nevertheless, as of early 2020, the digitisation and integration of healthcare information lagged other sectors of the economy.

Commercial

The last decades have witnessed huge growth of medication and device spending. Consolidations within and beyond healthcare stakeholder categories have gathered speed. Outsourcing to more specialised companies, often abroad, lengthened supply chains and created interdependencies. These actions provided economies of scale and growing market influence for larger companies.

In the last few years, new stakeholder combinations beyond legacy pharma stakeholders explored how to change existing modes of delivery – CVS Health/Aetna being one of the most striking.

Large pharma companies have focused on expensive biotech and other specialty products – leaving lower cost generics to others.

Cost savings related to "televisits" were recognised and published in some quarters. Tiered pricing proposals were floated to rationalise telemedicine and office visit encounters.

The period 2017–2019 saw prescription drug and device recalls, regulatory letters and back orders based on human factors, tightened regulatory restrictions and other causes. In 2019, a device tracker database for connected drug products became newly available. In 2019–2020, new stakeholder developer combinations realised the need to simplify and make products interoperable.

Coalitions actively promoted change and innovation. But change was slow in coming.

Regulatory and Legislative

Over the years 2016–2020, there has been slight relaxation of some US FDA regulatory requirements. The 21st Century Cures Act in 2016 encouraged patient data interoperability and accessibility, and many innovations. Limited compacts for licensure portability allowed some practice across state lines. In addition, complicated, antiquated HIPAA rules, which limited adoption of telemedicine, protected major suppliers and priced out smaller practices from buying telemedicine software, have been under fire.

Pharma has also developed more effective regulatory strategies for smart drug delivery products. Controls on billings were implemented to prevent overprescribing and professional abuse of controlled substance licences. Indictments were handed down and sentences imposed to limit fraud and abuse in billing. A 2019 Executive Order encouraged artificial intelligence, but by early 2020, medical data sharing was still opposed by some stakeholders.

The past is an invitation to future healthcare change and improvements. Ask how each of the aspects above are likely to change in the post-COVID-19 world, and it becomes self-evident that COVID-19 will prove to be a powerful catalyst for a connected future for healthcare.

ABOUT THE COMPANY

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

ABOUT THE AUTHOR

Napoleon Monroe, the sole inventor of the mMed medication-telemanagement patents, has been involved in the successful commercialisation of patents for decades. He spent more than 20 years at Survival Technology (now part of Pfizer), where he built up and managed its IP portfolio. There, he invented three medical devices that were patented and commercialised – two for autoinjectors and one for a transtelephonic peak-flow monitoring device. Mr Monroe also led teams that invented, prototyped, tested, commercialised and scaled up emergency pharmaceutical delivery systems, such as the original EpiPen, for treatment of anaphylactic shock, and the Antidote Treatment Nerve Agent AutoInjector delivery system, which still protects US and allied military and civilian personnel.

SENSORS ARE TOOLS – BUT HOW DO YOU MAKE THEM SMART?

In this article, Gaël Senée, Research and Development Engineer, and Arnaud Guillet, Business Development Director, both of Biocorp, explore the benefits of Mallya – a smart sensor that turns conventional injection pens into connected devices. They also discuss the crucial role Biocorp's connected prefilled syringe, Injay, could play in future COVID-19 vaccination programmes.

The digital revolution in progress over the last few years has had an impact on various aspects of everyday life, including in the medical field. One of the reasons is the increasing ageing of the population and the rise in the number of chronic disease cases, such as diabetes. According to the World Health Organisation, 425 million people were affected in 2017 – and this number may reach 629 million in 2045.

With the development of the Internet of Things and telemedicine, both doctors and patients are becoming increasingly digital. From the preventive stage to the onset of the disease, patients want better control of their disease and to live as normally as possible. This process may include more personalised follow-up, which can help avoid complications and emergency hospitalisations.

Several forecasts predict a global e-health market representing hundreds of billions of dollars by 2022–2023. As a result, connected healthcare is a booming market. It attracts more and more healthcare players who want to take advantage of it. Few people anticipated the potential of this phenomenon.

ANTICIPATION OF NEEDS

Biocorp was a pioneer. Since 2013, our teams have been working on the development of connected devices. Step by step, Biocorp developed a range of products that addressed unmet needs. These devices are intended to help patients to optimise the treatment of various pathologies. Examples include asthma, diabetes or the development of connected syringes for easy monitoring of injections.

> "Mallya is an add-on device – a smart sensor that turns conventional injection pens into connected devices."

The market for diabetes apps has exploded. Many patient-friendly smartphone apps have been created, allowing automatic data transfer from a blood glucose monitoring device or an insulin pump to a mobile phone via near-field communication (NFC) or Bluetooth. Despite this, one piece of the puzzle was still missing: the one allowing the automatic collection of insulin injection data from pen injectors. The Biocorp Mallya device fills this gap and is available for diabetes patients using disposable insulin pens for their daily treatment.

Mallya is an add-on device – a smart sensor that turns conventional injection pens into connected devices. It automatically records treatment information (selected dose, date and time of injection). Data is sent in real time to a mobile app thanks to Bluetooth technology. Mallya is currently the only device in its category that has been classified as a class IIb CE medical (CE0469).

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"The patient selects a dose by rotating the dose knob, then the pen is placed where the injection needs to be made, and finally the knob is pushed down until it reaches the end, in order to deliver the selected amount of drug."

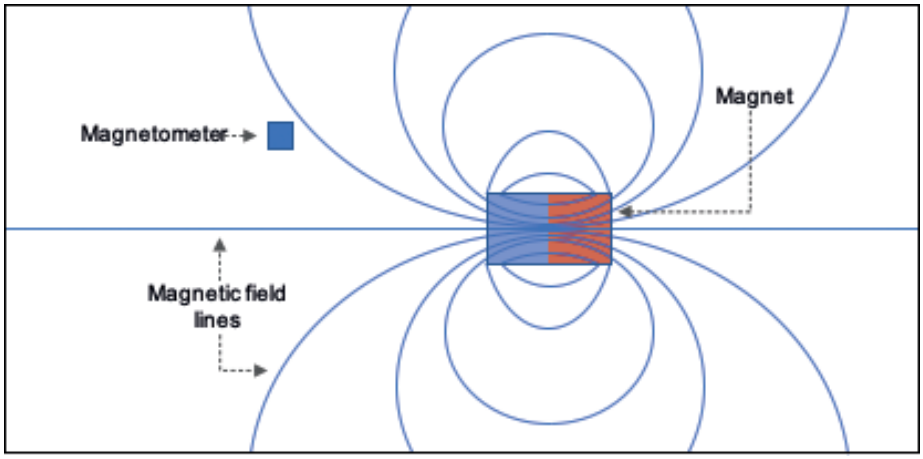

Figure 1: Several simulations and studies of the magnet positioning are made.

The use of such devices involves the processing and exploitation of health data. It must be shared, stored and secured – and be as accurate as possible, since it is the basis for medical monitoring. The stakes are high. Thanks to its technology, Mallya is able to record accurate information, which gives it a strong advantage in the field. The purpose of the Mallya device is to record and log any dose dialled by the patient. The accuracy of the dose determination and the reliability of the detection need to be ensured.

A MAGNETIC APPROACH

The device is made of two parts: a body, containing an electronic board that is clipped to the pen; and a plastic cap, with a magnet inside, which covers the dose knob of the pen. Mallya can be used on several pen platforms. Its usage generally consists of the same procedure – the patient selects a dose by rotating the dose knob, then the pen is placed where the injection needs to be made, and finally, the knob is pushed down until it reaches the end, in order to deliver the selected amount of drug. The knob proceeds through two phases: a rotation and a thrust. The magnet encased in the knob cap allows the device to follow these movements by acquiring magnetic field data. Processing this data will lead to the reconstruction of the magnet's track, and the determination of the dialled dose.

RAW DATA ACQUISITION

The Mallya device is designed with a custom-made electronic board, the choice of components for which is essential. Several magnetic sensors have been tested to find one complying with specific features (e.g. measurement accuracy, range of use, measurement noise, etc.). Magnets are obviously the key element when it comes to studying magnetism. Selecting the type of magnet, its direction of magnetisation, its dimensions and its grade are all different factors to understand and to take account of. According to the shapes and sizes of the platform pens, several simulations and studies of the magnet positioning have been conducted (Figure 1).

Each criterion noted above plays a role. The goal is to define a reference magnet, for which the magnetic field data acquired will be adequate over the entirety of the injection process. For example, under-dimensioned magnets will have a low field intensity, not fitting with the sensors' range of use, and sensitive to external interferences. An in-depth study is therefore needed. The magnets that are selected undergo several tests to check their conformity, both individually and regarding the batch they come from.

Processing magnetic field data requires handling of all the sources generating a signal in the area of the sensors. The magnet in the knob is the sole part we want the magnetometers to react to. However, external sources like the earth's magnetic field or any interference caused by a nearby device or object containing magnetic elements (such as a phone, a ring, a metallic part inside the pen, etc.) can impact the signal. Using two magnetic sensors simultaneously enables this issue to be tackled. By combining the signals, it is possible to ignore the disturbances of the external sources. However, this requires a more complex analysis and processing of the final data.

CREATING A MODEL AND AN ALGORITHM

During the manipulation of the pen, the knob's position will evolve in relation to the body of the Mallya device. This specific movement will help determine the dialled dose. In order to get enough data and measurements for this task, a magnetic test bench was conceived, on which a Mallya electronic board and a magnet can be placed. This allows reproduction of the magnet movements, without the pen obstructing the manipulation.

With measurements made at key positions, a model is developed. Note that this model depends on the platform pen. For each pen, the model needs to be adapted to fit its characteristic. The dose calculation algorithm revolves around two sets of data – one for each magnetometer. Associating these two sets results in a pseudo-field, which is averaged and smoothed for eliminating the measurement noise. This newly computed data consists of tri-axis co-ordinates (x, y, z), from which an angle and a norm can be calculated.

First of all, it is essential to determine the origin of the magnetic field measurement with precision – the overall offset due to several intrinsic deviations. In fact, when the knob is the furthest from the Mallya body, the intensity (i.e. the norm) of the magnetic field is the lowest. This is when the sensor is the most sensitive to these zero deviations. The accuracy of the angle calculation is greatly impacted by the intensity of the magnetic field. Determining the offset and negating it to each computed field increases this accuracy (Figure 2).

The idea is to roughly follow the magnet as it moves and revolves during the injection cycle. During the dial of the dose, the knob will rotate, thus the angle will change. Moreover, the knob is moving further and further away from the body, thus the norm

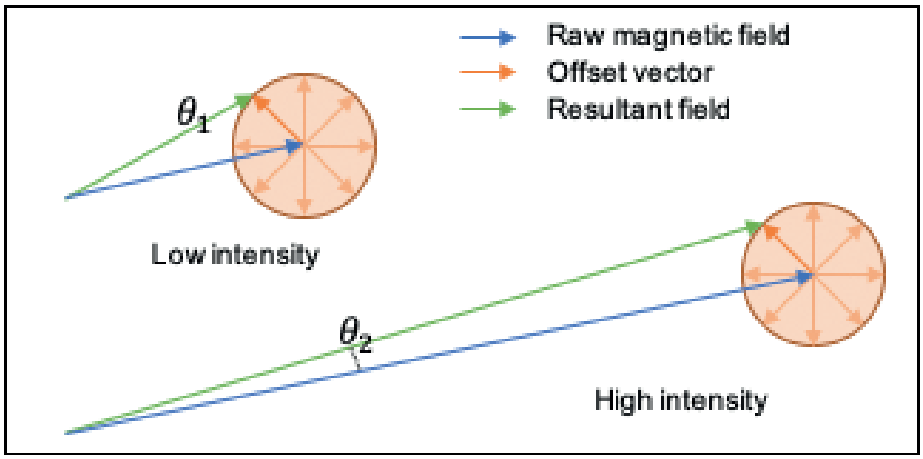

Figure 2: The impact of the overall offset on the magnetic field.

will decrease. When it is time to deliver the dose, the knob is pushed, without being rotated: the angle stays the same and the norm increases.

In short, analysing this couple of parameters allows us to track the positioning of the knob, count the number of full revolutions of the magnet and then determine which dose has been dialled by the patient.

CHECKING MODEL ACCURACY

Validating the accuracy of the model and the reliability of the algorithm relies entirely on testing. With the help of another custom-made testing bench, injections can be made over and over again. From these injections, several measurements are used to obtain training data. Retrieving them with a mechanical bench ensures that the process is repeatable and is not affected by the user's handling. The acquired signal is as neutral as possible. With specific tools, developed in-house, measurement constants and criteria are determined, analysed, learned and verified by the training data set – and used to complete the model. More injections are made, and a set of testing data validates the consistency of the overall model.

Controlling the reliability of the model on the test bench is not enough to validate the whole algorithm. Indeed, the device needs to be tested by users and patients doing real case injections. As previously mentioned, the pen and device being held by hand can lead to some interference and slightly distorted data, compared with the clean measurements made with the repeatable and straight-to-the-point test bench. The implementation of a few validation parameters, such as intensity and norm stability – or the detection of a rotation occurring during an injection – ensures that the device will not give the patient an incorrect piece of information. In which case, the user will be warned that an unexpected manipulation occurred.

THE RACE FOR A COVID-19 VACCINE

At the time of writing, a novel coronavirus (COVID-19) pandemic is unfolding across the world causing hundreds of thousands of deaths and hospitalisations and severe social and economic disruption. In this context, the remainder of our article will discuss the significant role connected injection devices can play in the global roll-out of a SARS-COV-2 vaccine.

The publication of the complete genome sequence of the SARS-COV-2 coronavirus in the Chinese Medical Journal on February 25, 2020 started a fierce race for the release of a vaccine, with nearly 150 projects involving pharma, biotech and institutional players, including J&J, GSK, Moderna Therapeutics and Inovio Pharmaceuticals. This wave has raised the expectation of a vaccine available for healthcare professionals (HCPs) and citizens within 12 to 18 months, maybe even before.

Given the unprecedented scale and stakes of this work, and the uncertainties related to the emergency context in which such a vaccine is being developed, it is absolutely paramount to run the vaccination campaign in the most secure and effective way. This means trace vaccines from the industrial filling line to the final administration, accurately identify patients and hold records, guarantee proper administration of the product, record vaccine information, run effective pharmacovigilance afterwards and manage any potential follow-ups if needed.

On the patient identity (ID) side, electronic health records (EHR) solutions have reached a mature stage in the US and can be leveraged if needed, even though

"In the context of a nationwide COVID vaccination campaign, Injay can provide extensive benefits."

there are no centralised federal database or standardised solutions at this stage. In Europe, patient ID can be supported in many countries by EHR national initiatives – e.g. the National Patient Summary in Finland, the NHS Care Records Service in the UK or the Shared Medical Record (DMP) in France – and the European Union has launched some initiatives to centralise patient information, including the European Health Data and Evidence Network (EHDEN) project involving 22 states, which aims to standardise around 200 million patient records across Europe in the coming years.

In the rest of the world, countries such as Australia, New Zealand and Singapore already propose advanced EHR solutions that can support a nationwide patient ID and vaccination tracking campaign. The patient ID options will have to be fully accessible by all stakeholders involved in the vaccination and patient monitoring (GPs, hospitals and clinics, vaccination centres, public health authorities, etc.), while guaranteeing authentication of every access to the system and complying with the highest standards of data security.

Beyond patient ID, Biocorp's Injay device can provide a reliable solution to guarantee full traceability, safe delivery and optimal pharmacovigilance for a successful COVID-19 vaccination campaign.

Injay is a standard prefilled syringe (PFS) featuring an NFC tag on the piston rod and a customised finger flange. The NFC tag contains key product information such as type of drug, concentration, batch number and expiry date – previously encoded by the drug manufacturer during assembly of the syringe. Once Injay detects a complete injection, the product information, stamped with a specific time and date, can be transferred to any device via an NFC reader. This solution is available for various PFS formats, including 1 mL short – the standard format for vaccines.

In the context of a nationwide or international COVID-19 vaccination campaign, Injay can provide extensive benefits:

- Optimal traceability of vaccine from the industrial filling line – product information and vaccine ID are encoded by the drug manufacturer or contract manufacturing organisation in the NFC tag of the piston rod directly on the assembly line.
- Patient identification – at point of care, HCPs can verify patient ID and check physiological data, treatment history and declared symptoms prior to injection, through the selected EHR solution.
- Easy treatment identification – HCPs can read the piston rod of the syringe to check the product reference and expiry date before injection.
- Simple and proper administration – Injay is seamless from a user perspective as it does not interfere with the traditional use of the syringe and injection process. Plus, the system detects that the piston rod is pushed down until the stopping point, which guarantees complete injection of the product. A mechanical feature also locks the piston rod in its final position, avoiding any reuse of an empty syringe.
- Simple and accurate reporting – after injection, the data (product reference, batch number, expiry date and successful injection) can be easily scanned and time stamped using standard NFC readers, and directly fed into the selected EHR solution. It avoids the need for manual entry by healthcare professionals, which saves significant time and guarantees exhaustivity and accuracy of reporting.
- Effective pharmacovigilance – with this new set of data available and a proper EHR solution enabling patients to report incidents, this solution can significantly improve pharmacovigilance.
- Thanks to the data provided by Injay, any incident reported by a patient can be linked to a specific product, batch number and administration date, helping authorities and healthcare companies to trace the issue easily and provide the appropriate response.

The introduction of Injay in connection with an EHR solution will not happen all at once on a global scale. It is expected to be a progressive process. The objective is to start this initiative in a few pilot countries and progressively expand to other geographies – eventually making it a worldwide standard for vaccination.

This initiative can play a role in a broader objective to accelerate the digital revolution in healthcare for the benefit of patients, HCPs, public health institutions and payers. The need to record, protect, access and share digital health data is more intense than ever at a time when a global pandemic of a novel virus makes physical access to doctors challenging, and decision making by public authorities is hampered by a shortage of meaningful information.

ABOUT THE COMPANY

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

ABOUT THE AUTHORS

Gaël Senée is a Research and Development Engineer at Biocorp. He first joined the team as an intern, and now works on connected devices. His main tasks are focused on data analysis, signal processing and technical studies around several projects. He studied at the École Nationale Supérieure d'Ingénieurs (ENSIM) engineering school in Le Mans (France), which specialises in acoustics, vibrations and sensors.

Arnaud Guillet is Business Development Director at Biocorp, in charge of finding partnerships and licence opportunities for Biocorp's range of connected devices. Previously, Mr Guillet worked for a healthcare consulting firm with a strong focus on connected health strategies for pharma and insurance companies and has additional past experience in the pharmaceutical industry (with Sanofi) and the insurance industry (with AXA). He graduated from HEC Paris, a major European business school.

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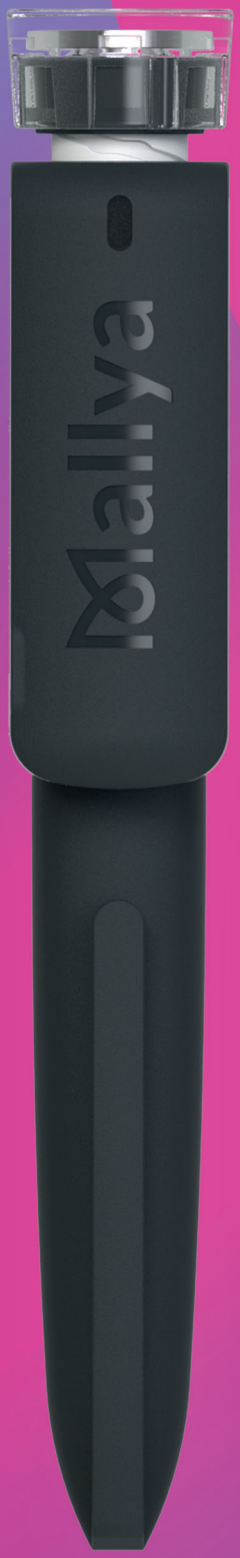
Mallya

Connected diabetes *



* Mallya automatically captures injection data (dose, date and time) and sends the information in real time to a companion software thanks to Bluetooth technology.

Mallya is CE-marked - medical device class II-b. Mallya is compatible with Solostar®, Kwikpen® and Flexpen®. Further information on www.biocorp.fr

BIOCORP

RISKS AND REAL-WORLD SOLUTIONS FOR CONNECTED MEDICAL DEVICES

In this article, Tom Oakley, Director of Drug Delivery Device Development at Springboard, discusses the risks surrounding the use of connected drug delivery devices – and the real-world solutions that have either been proved or are being trialled.

Modern medical devices, including drug delivery devices, are being connected to other devices and the internet at an increasing rate. Every organisation we have talked with that is developing drug delivery devices either has a connected device strategy in place or is forming one. An example application is a glucose sensor (perhaps integrated into a smart watch) which communicates with an insulin pump or injector pen to set or advise the correct dose (Figure 1).

It may become normal for high-value chronic diseases to have some sort of connected support story around them. This is already the case for some people living with diabetes, multiple sclerosis or growth hormone deficiency. For examples, see the Medtronic Minimed 670G (Figure 2) or Merck Serono's RebiSmart and easypod (Figure 3).

The potential benefits of connected drug delivery devices have been discussed a great deal in conference presentations and literature, and are summarised in Table 1.

We have all heard about the terrible adherence rates that beset much of the pharmaceutical industry – approximately 50% of all medicines are not taken as prescribed.[1] One of the most common justifications for developing connected drug delivery devices is that it will solve the problem of poor adherence, so let us look at this in more detail.

CAN CONNECTED DEVICES REALLY SOLVE POOR ADHERENCE?

Some people tout connectivity as solving the adherence problem. However, there are issues with this view. The main issue is that the people who are not adherent to their drug regime are also likely to be not adherent to using the connectivity features of their device. Those people would only be helped by connected devices which are completely automatic. For example, to be completely automatic, there must be:

- No installing apps on phones or computers
- No Bluetooth pairing
- No connecting to Wi-Fi
- No logging in or set-up
- Certainly, no entering data
- Ideally, no charging of batteries.

> "People who are not adherent to their drug regime are also likely to be not adherent to using the connectivity features in their app."

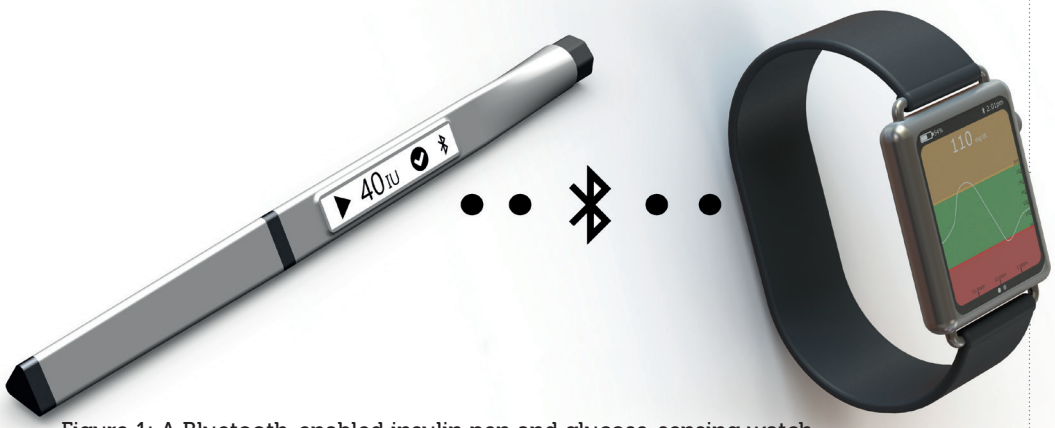


Figure 1: A Bluetooth-enabled insulin pen and glucose-sensing watch.

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Figure 2: The Medtronic Minimed 670G.

Figure 3: Merck Serono's RebiSmart and easypod.

If we look at fitness apps on smartphones, many of the popular apps have retention of only around 55% and that is after only one week.[2] We should not expect to increase adherence to medicines by using technologies which have lower adherence than medicines!

The best way in which connected devices can help with adherence is to understand who is non-adherent. Healthcare resources can then be directed to helping those people become adherent. I think that is where the true value of connectivity lies in addressing the adherence problem.

USABILITY RISKS

Usability (human factors) is already a major part of the device development process, and the regulatory bodies rightly expect it to be. Connectivity brings additional considerations. For example, there are:

1. Risks associated with additional user steps such as identification, connecting and recharging.
2. Risks with how we indicate status to the user. For example, does a flashing light mean "ready to use", or "low battery"?
3. Risk of disengagement as mentioned above.

The solutions are to:

1. Keep the requirements simple so that the solution can be kept simple.
2. Develop and communicate clear benefits to the stakeholders so that they are motivated to engage with (or at least not to frustrate) the functions around connectivity.

Patient	Carer	Carer
• Reminders • Training • Evidence for incentives • Hawthorne effect • Peer support	• Reminders • Training	• (Non)adherence data • Reduced costs
Healthcare professional	**Healthcare provider or regulatory authority**	**Pharmaceutical company**
• (Non)adherence data • Additional support for the least adherent • Adverse events	• (Non)adherence data • Adverse events • Clinical trial data (pre- and post-market) • Population trends	• (Non)adherence data • Adverse events • Clinical trial data (pre- and post-market) • Evidence for reimbursement • Market understanding • Product and training improvements • Increased sales by increased adherence

Table 1: Potential benefits of connected drug delivery devices for stakeholders.

3. Perform usability studies on diverse groups of people at each stage of the project. Diversity means across ages, genders, languages, cultures, technology skills and those with comorbidities and issues such as visual impairment.

RISK OF PUTTING CRITICAL FUNCTIONALITY INTO ELECTRONICS AND CONNECTIVITY

Electronics and connectivity are complex and therefore have more opportunities to fail compared with more traditional mechanical devices. There have been several drug delivery devices where recalls were issued due to failures in the electronics, which could have been avoided with a different device strategy. Examples of risk management strategies include:

1. Using a separate add-on to provide the connectivity so that the core critical functionality is not affected.
2. Build the connectivity into the device, but in a way that the critical device functions do not depend on it. Therefore, the connectivity functions could fail but the patient still receives their dose safely.

RISKS WITH SECURITY OF SUPPLY

The current COVID-19 pandemic has underlined the importance of security of supply. The electronics required by connectivity mean that supply chains can be more complex and less transparent than those for mechanical components (such as plastic injection mouldings and their raw materials).

For example, at a company that I used to work for, a colleague had designed a printed circuit board with a given memory chip. During component selection, he had selected a component which had two independent manufacturers. Following an earthquake in Japan, the first supplier was unable to supply for a few months. My colleague contacted the second supplier and they were also unable to supply. Both suppliers purchased the silicon wafer from a mutual second-tier supplier that had gone offline due to the earthquake. In electronics there is a need to be more vigilant against such "diamond" supply chains.

Another risk is that the production lifetime of components in the electronics industry is very short compared with the lifetime of medical devices. It is not uncommon for an electronic component to "go end of life" whilst the medical device is still being developed. The main strategies for mitigating the end-of-life risk are:

1. Engage with suppliers that understand and support the long timescales associated with medical devices so that they can:
   a. Guarantee minimum supply lifetimes
   b. Support engineering change processes
   c. Support any reverification or revalidation that is required.
2. Conduct full supply chain audits
3. Ensure supply chain diversity (such as dual sourcing) and disaster planning
4. Buy and store enough stock to allow enough time to change if necessary.

RISKS WITH CYBERSECURITY

Connectivity, either to the internet or to other devices, brings with it the risks of hacking and malware. We have already seen exploits in the public such as:

- Demonstration of hacking of pacemakers[2]
- Demonstration of hacking of insulin pumps[3,4]
- Hospital infusion systems with a security vulnerability allowing remote control[5]
- Insulin pump hacking over the air[6]
- Recall of insulin pumps due to cybersecurity risks[7].

The regulatory authorities are developing guidance and requirements in the cybersecurity space, such as:

- Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (draft 2018)
- Postmarket Management of Cybersecurity in Medical Devices (final 2016)
- Cybersecurity for Networked Medical Devices Containing Off-The-Shelf Software (2005).

The main strategies to mitigate cybersecurity risks are to:

1. Minimise the "attack surface" of the device and the infrastructure supporting

it. For example, the device should have as few vectors as possible through which an attacker could infiltrate the system.
2. Minimise the amount of data collected and transferred.
3. Use good practice such as encryption for storage and transmission of data.
4. Use internal and external "red teams" which are dedicated to testing the effectiveness of a security programme by emulating the tools and techniques of likely attackers in the most realistic way possible.
5. Keep up to date with, and ideally contribute to, international standards, regulatory working groups and industry groups on the subject.

RISK OF DATA SILOS

Multiple organisations are developing diverse devices, server software and data models to create the connected ecosystem, and they will introduce barriers to the outside world to ensure security as described above. An obvious disadvantage of this is that data will be locked away in "silos" so that:

- Devices will not communicate with each other properly
- Devices will not communicate with other organisations' server infrastructure or web portals, etc
- Stakeholders will need to use and maintain multiple systems to manage their conditions.

We must make a concerted industry-wide effort to ensure interoperability. To this end, there are guidance documents and standards on interoperability, such as:

- FDA Medical Device Interoperability strategy[8] and guidance[9]
- UL 2800-1 Standard for Medical Device Interoperability[10]
- Health Level Seven International standards.

However, some stakeholders have decided that the industry is taking too long to provide interoperable devices and are taking matters into their own hands. For example, some people with diabetes and their family members have started the #WeAreNotWaiting movement where they are connecting various devices such as insulin pumps and continuous glucose monitors on their own without regulatory approval.

RISK OF REGULATORY CHANGE

Regulatory authorities are adapting to the rapid pace of development and working on their requirements. The subject is too large to cover in detail here, but the main areas of change are:

- Interoperability
- Cybersecurity
- Data protection
- How to regulate medical devices which are based on non-medical platforms such as consumer smartphone operating systems.

RISK OF ENVIRONMENTAL IMPACT

Like almost everything in life, we should look at the benefits versus the risks and harm caused. Products such as ventilators typically have a lot of electronic components and they are not very easy to reuse or recycle. However, if we are going to use electronics for anything, I would suggest that the sustenance of human life is the best use. We should put our efforts into first removing electronics from musical birthday cards rather than from medical devices.

Nevertheless, we should do what we can to minimise the environmental damage caused by our actions. Sensible guidelines include:

1. Add electronics only where necessary
2. Create long-lasting devices. These could either be devices with a long use life or reusable devices
3. Implement return-to-manufacturer schemes as GSK has done for its inhalers
4. Design products for ease of disassembly to help with recycling processes.

RISK OF BUSINESS MODEL

The drug delivery industry is different from others, such as consumer products or automotive because in those other industries:

- An individual person chooses the product
- The individual pays for it
- The individual gets the benefit.

On the other hand, in drug delivery:

- The healthcare professionals play a big part in choosing the drug and devices
- The payer is often an insurance company or national healthcare system
- The patient gets the primary benefit.

Therefore, the business models to support connected drug delivery devices are different from those in consumer industries. In some cases, the pharma company is paying for the connectivity and infrastructure so that they can protect their market share of drug sales. In others, we have seen new business models, such as:

- Development of predictive algorithms that can identify patients at risk of adverse events before they occur. This can save large costs in the healthcare system. An example is the collaboration between Amgen and Humana which analyses real-world evidence from Humana's members with data from wearable devices, apps and smart drug delivery devices.
- A Fitbit-based rewards programme where patients can earn US$1,500 (£1,200) per annum, by UnitedHealthcare and Qualcomm.
- Deployment of a connected ecosystem to provide the full patient portal which protects sales of drugs in competitive environments. An example is Merck Serono's web-based software platform, MSDialog for people with multiple sclerosis.

We are seeing many different business models being developed and tested so it will be some time before leading business models emerge.

SUMMARY

We have discussed some of the main risks around deploying connected drug delivery devices, including:

- Expecting connectivity to solve adherence alone
- Usability
- Critical functions
- Cybersecurity
- Data silos
- Regulatory change
- Environmental impact
- Business models.

For each set of risks, there are real-world solutions that have either been proved or are being trialled. Connected drug delivery

devices are here already; they are here to stay and they are likely to become more common. By managing the risks well, we can bring distinct benefits to the various stakeholders.

ABOUT THE COMPANY

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

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ABOUT THE AUTHOR

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

ON drugDELIVERY

2020/21 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Jul 2020	Novel Oral Delivery Systems	PASSED
Aug 2020	Industrialising Drug Delivery	EXTENDED Jul 24, 2020
Sept 2020	Wearable Injectors	Aug 6, 2020
Sept/Oct 2020	**NEW TOPIC – INAUGURAL ISSUE!** Drug Delivery & Enviromental Sustainability	Aug 20, 2020
Oct 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
Nov 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
Dec 2020	Connecting Drug Delivery	Nov 5, 2020
Jan 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
Feb 2021	Prefilled Syringes & Injection Devices	Jan 7, 2021
Mar 2021	Ophthalmic Drug Delivery	Feb 4, 2021
Apr 2021	Pulmonary & Nasal Drug Delivery	Mar 4, 2021
May 2021	Delivering Injectables: Devices & Formulations	Apr 1, 2021
Jun 2021	Connecting Drug Delivery	May 6, 2021
Jul 2021	Novel Oral Delivery Systems	Jun 3, 2021

Elcam
Drug Delivery Devices

MEETING THE CHALLENGES OF COVID-19

In this article, Beo Arana de Martinez, Customer Service & Marketing Assistance, and Ilan Shopen, Marketing & Business Development Director, both of E3D – Elcam Drug Delivery Devices, discuss the effects that the COVID-19 pandemic has had and is still having on patient populations, how the healthcare industry has intensified activity to fight the virus, and – using the example of the FlexiQ eMU-P connected autoinjector – how connected devices that facilitate self-injection and remote monitoring, are coming into their own.

Based on the authors' blog articles, "Meeting the challenges of COVID-19", and, "The Day That COVID-19 Dies", that originally appeared on the E3D Web Page in June 2020.

Can you imagine that one day the coronavirus will be history, a creepy story to tell your grandkids? Anxiety is becoming more prevalent as the crisis stretches on, as are negative feelings such as uncertainty and loss of control, which prevent us from understanding that this difficult time will soon become a chapter in the history books.

In the healthcare industry, the story we'll tell is a different story. COVID-19 brought the world to a standstill but, since then, the healthcare industry has been motivated by the challenge of how to stop the virus spreading, find a cure and develop a vaccine. It's at times like these that we truly see the importance of the healthcare industry maintaining routines and providing the essentials to healthcare systems, as well as focusing on how the "day after" will look – the day that COVID-19 dies.

Today, the call to stay home still reverberates around the world. The effects of the virus continue to be felt worldwide and many people have stopped their usual visits to healthcare practitioners due to fear of infection. The need for safe and easy-to-use homecare solutions has been brought into strong focus, as has the need for online connectivity to enable healthcare providers to keep track of patient health remotely.

This crisis has made it clear that the trends towards homecare, improved patient compliance and quality of care utilising self-administered therapy, and a growing awareness of the environmental impact of products as well as the associated costs, will drive the development of solutions that meet these needs.

Home care integrates patient care with the various activities of daily living. A balanced approach to tomorrow's healthcare involves developing solutions that enable as much patient care as possible in a home environment. This requires an approach that is not only limited to clinical need, but also takes a more holistic view of patients' lives and an understanding of their physical and emotional environments.

It's here that E3D's FlexiQ eMU-P (Figure 1) provides the perfect homecare solution. It comprises an electro-mechanical multi-use driving unit, prefilled syringe and disposable cassette, enabling home self-administration. FlexiQ eMU-P is part of E3D's Flexi-Q family of mechanical autoinjector products, which also includes Flexi-Q PFS, Flexi-Q DV, FlexiQ mMU-Pand Flexi-Q eAI.

"The FlexiQ eMU-P allows physicians to monitor adherence through the connectivity system incorporated in the autoinjector."

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Figure 1: E3D's FlexiQ eMU-P connected autoinjector enables self-administration of drug dosages at home.

Designed for ease of use and with patient safety in mind, it prevents needle-stick injuries before and after use. Since the device is self-administered at home, monitoring dosages is extremely important. Users receive audible signals at the start and end of the injection process and a viewing window also allows progress and completion of the injection to be visually monitored. But crucially the FlexiQ eMU-P also allows physicians to monitor adherence through the connectivity system incorporated in the autoinjector.

In any self-administration device, safety is a key consideration, especially when it comes to verifying that drugs are administered in the correct dosage and at the correct time. It's also vital to ensure that the administered drugs are suitable for use by verifying the temperature, expiry date and any other relevant information. FlexiQ eMU-P's noiseless operation is a key feature, as is the rechargeable battery which ensures the device can be used for at least 30 injections before recharging.

CONCLUSION

COVID-19 has demonstrated how much our lives are dependent on others. Our needs and desires have to be balanced with our responsibility to the world around us, not only as individuals but also as companies and countries. The pharmaceutical industry has to contribute its part to this global effort.

In summary, when the coronavirus pandemic is behind us, a greater emphasis will be placed on three existing trends that drive drug delivery system development, in addition to increasing the commercial value (and lifecycle) of drug products. Those trends are:

- improved patient compliance and quality of care
- growing awareness of production footprint and associated costs
- increased use of self-administered, connected drug therapy

It's unsure when the world will return to business as usual. At E3D, the work has never stopped and throughout the crisis, we continue to focus on refining and developing homecare solutions to ensure that patients are able to administer treatments safely from the comfort of their homes.

ABOUT THE COMPANY

Elcam Drug Delivery Devices (E3D) portfolio encompasses a wide range of injectables produced in the company's manufacturing facilities in Europe, the US and Israel. These devices include single-use and multi-use, spring-powered autoinjectors designed for 1 mL and 2.25 mL prefilled syringes; wearable injectors for bolus, high-volume and viscous drug delivery; electromechanical and mechanical "smart" injectors with wireless connectivity; autoinjectors for viscous formulations; emergency-use injector devices; and injectors with both automated and manual reconstitution for lyophilised products.

POLYMERIC EMI SHIELDING: PROVIDING A MORE SECURE FUTURE FOR PATIENTS

In this article, Marnik Vaes, Business Development Manager; Leen-Pieter Deurloo, Senior Business Development Manager; and Martin Sas, PhD, Lead Scientist, all of SABIC, discuss the role of polymeric electromagnetic interference shielding in providing a more secure future for patients in a connected world.

Driven by the need to reduce costs, healthcare systems around the world are currently undergoing a paradigm shift – from treating acute and chronic conditions in hospital and intensive care settings to a remote point-of-care approach. This transformation requires medical device manufacturers to integrate data recording functions into their products that enable remote patient monitoring and ultimately improve patient outcomes at lower treatment costs. This is the promise of connected devices.

> "Shielding can be a complex issue to solve, as the majority of connected medical devices interact directly with wireless infrastructure or via a consumer device."

Of course, medical devices must also be demonstrably safe when used as designed, in combination with other therapies and in a range of environments – from home to hospital. Devices that require direct contact with patients – even simple skin contact – must also be biocompatible and function without interfering with, or impairing, basic immunological functions or causing injurious, negative physiological, allergic or toxic reactions.

Connected devices are challenged with an additional safety consideration – interference with the main content stream of the radio signals produced can potentially adversely affect device performance. This is caused by the phenomenon known as electromagnetic interference (EMI) or radio frequency interference (RFI). EMI is caused by the tendency of electronic devices to generate strong electromagnetic "noise" during operations. EMI has been a challenge in radio-based communications since the work of Guglielmo Marconi approximately 150 years ago. It remains a challenge for electronics, packaging and compliance engineers to this day.

The principal area of concern – and the focus of this article – is EMI caused by non-ionising radiation. ElectroMagnetic Compatibility (EMC) standards and testing ensure that electrical devices are able to operate safely in close proximity with a minimum level of RFI. The solution to managing EMI is shielding, which can isolate the devices from their surroundings and from the signals of other devices. In simple terms, shielding involves creating a form of Faraday cage around sensitive components within the device, usually using a metal encasement or similar solution.

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However, shielding can be a complex issue to solve, as the majority of connected medical devices interact directly with wireless infrastructure or via a consumer device – for example, a smartphone or other handheld device. They rely on a range of radio frequency (RF) bands with differing of signal power levels and operate in a range of communication modes. These include short-range wireless communication technologies such as near-field communications (NFC), Bluetooth, WiFi, ZigBee and the low-power version of these wireless communication protocols from industrial, scientific and medical (ISM) and short-range device (SRD) licence-free bands. All create a need for shielding against EMI. Figure 1 identifies the power performance for common wireless devices.

In general, RFI becomes significant at frequencies above 30 MHz, with typical levels of radiated emissions in units of electric field strength. Consumer electronics and healthcare-related EMC standards classify corresponding devices into a number of categories, according to their intended use environment. They also define immunity levels and limits to radiated RFI across a wide frequency range. Figure 2 summarises some of these limits in comparison with the radiated power levels of certain wireless technologies.

RF Device	Radiated power	Power level	Medical devices and adjacent	Electric Field strength	Electric Field strength level
BT Class2	2 mW	3 dBm	body-worn devices and implants	0.3 V/m	110 dBµV/m
BLE					
laptop WiFi module	10 mW	10 dBm		0.7 V/m	117 dBµV/m
BT Class1	100 mW	20 dBm	low power wireless devices – wearables and monitoring devices	2.2 V/m	110 dBµV/m
WiFi router					
cellular phone	250 mW	24 dBm	WiFi and cellular network based devices	3.5 V/m	130 dBµV/m
5G small cell	500 mW	27 dBm		5.0 V/m	134 dBµV/m
4G base station	20 W	43 dBm	4G base station devices (not applicable)	30 V/m	150 dBµV/m
5G MIMO base station	100 W	50 dBm	not applicable	70 V/m	157 dBµV/m

Figure 1: Typical RF power performance for common wireless devices expected to interfere with healthcare environments.

> "Increasing miniaturisation and the growing engineering complexity of connected devices, along with the demand to make them lighter and less intrusive, is posing challenges and highlighting design limits."

Shielding effectiveness (SE) indicates the capacity of the material to act as a shield against internal or external EMIs, providing protection from damaging electrical devices. It is determined by the material's overall conductivity level, wall thickness and target frequency range.

Conventional approaches to providing EMI shielding have relied on metal enclosures, usually using aluminium alloys; this method currently accounts for more than half the market. However, increasing miniaturisation and the growing engineering complexity of connected devices, along with the demand to make them lighter and less intrusive, is posing challenges and highlighting design limits. Weight becomes a greater consideration, with even the lightest aluminium alloys likely to be unsuitable – not to mention costly. In addition, the increasing complexity and sensitivity of these devices, combined with reductions in design space, could render them more susceptible to interference. Clearly, other solutions are needed to meet these evolving demands.

Some manufacturers have explored alternative approaches for providing shielding, such as metal coatings, vacuum metallisation and conductive paints on plastic enclosures. While these methods can be effective, they are less so than metal

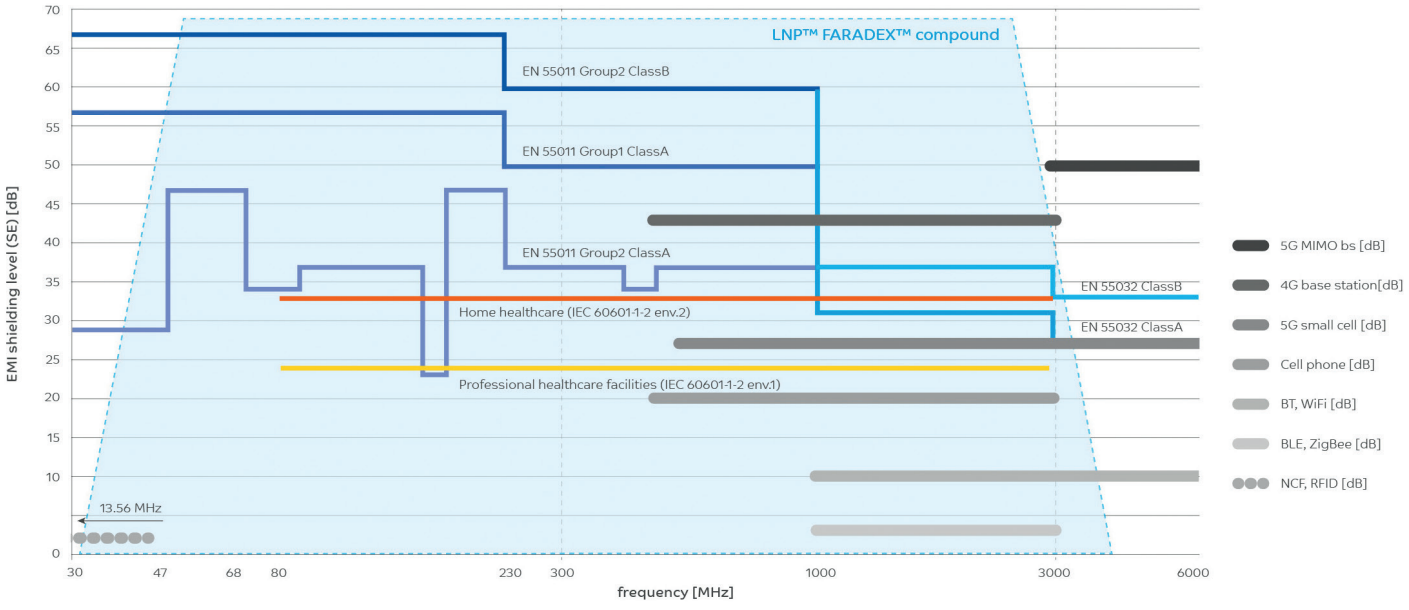
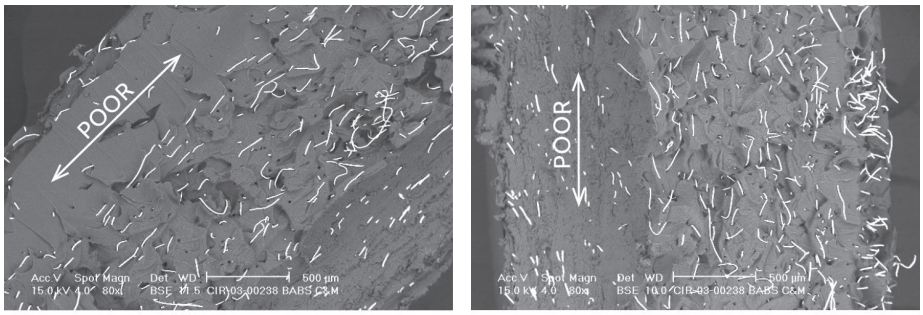


Figure 2: EMC-radiated emissions limits in terms of SE in dB based on EN 55011:2016, EN 55032:2015 and IEC EN 60601-1-2:2015 with examples of wireless technologies radiating RF power levels. Range of LNP FARADEX compound shielding effectiveness is highlighted.



Near gating area | Near end of flow path

Figure 3a: SEM analysis conducted by SABIC illustrates inferior dispersal of conductive fibres in moulded parts (PC resin).

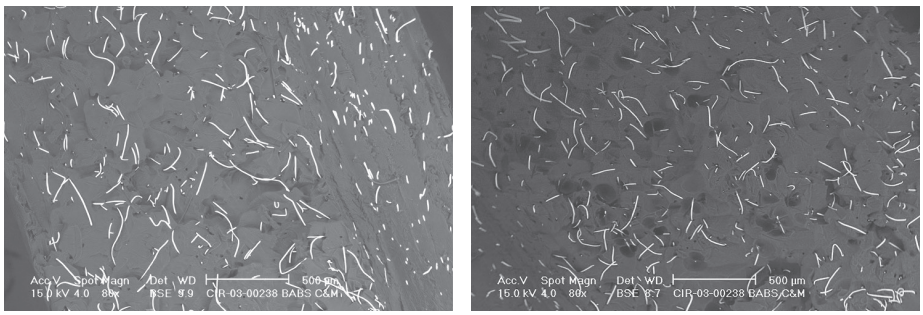


Figure 3b: SEM analysis conducted by SABIC illustrates good dispersion of conductive fibres in moulded parts (PC resin).

"The optimal dispersion of conductive fibres in the moulded part is critical to achieving maximum shielding performance."

enclosures and rely on secondary processes to the plastics following initial production. These steps add to the system cost and complexity – and increase the overall environmental footprint of the products. In addition, not all thermoplastics may be suitable for such secondary treatments.

The ideal solution, therefore, is to use a polymer that can provide EMI shielding as an integral property of the resin. This ensures a high degree of shielding and, by reducing the need to accommodate secondary treatments, allows greater flexibility in design. LNP FARADEX compounds, developed by SABIC's Specialties business, provide EMI shielding performance as an embedded, intrinsic property of the resin and the moulded part.

"The demand for connected medical devices will continue to grow rapidly for the foreseeable future, driven by the pressing need to constrain spiralling healthcare costs."

The optimal dispersion of conductive fibres in the moulded part is critical to achieving maximum shielding performance. SABIC has conducted extensive moulding studies to optimise fibre dispersion by selecting appropriate injection moulding conditions. Figures 3a and 3b demonstrate how SABIC's processing expertise can provide insights into material performance. Figure 3a shows poor dispersal of the fibres; the left-hand side of both images show a resin-rich part. Figure 3b shows the optimised fibre versus resin concentration after taking advantage of SABIC's processing knowledge to maximise the Faraday cage effect.

As well as simplifying the process of providing shielding, LNP FARADEX compounds offer a number of additional benefits, as summarised in Figure 4. Without the need for secondary processes, the material offers manufacturers considerably wider design freedom. Medical devices can be manufactured using more complex 3D shapes, offering greater comfort and convenience for patients. The material performance properties may also help to improve device development efficiency,

CHEMISTRY THAT MATTERS™

INNOVATION FOR PATIENT SAFETY

SABIC's healthcare business is driven by our passion to support our customers and improve patient experiences and outcomes.

Leveraging our global capabilities and creating new collaborations, we develop advanced materials and technologies that help drive innovation for the next generation of medical devices.

Bulk Shielding method	Weight reduction	Relative cost	Shielding effectiveness	Recyclability	Waste generation	Design flexibility	Comments
Conductive Compounds LNP™ FARADEX™ Compounds	●	▲	▲	▲	●	●	Design sensitive, limited shielding ability around apertures and joints, part thickness dependent.
Plating methods Electroless & electroplating	●	■	▲	■	■	▲	Masking limitations, waste disposal, EHS issues, tooling and fixture costs.
Conductive spray coats Paints, zinc arc	●	▲	▲	■	▲	▲	Masking limitations, adhesion to plastics.
Metalization Vacuum, cathode sputtering	●	■	▲	■	▲	▲	Tooling, fixtures, masking limitations, EHS, waste disposal.
Metal enclosures Die cast, foils, stamped sheet metal	■	●	●	●	●	■	Weight, size & lack of design freedom for complex geometries.

● Most positive ▲ Moderate ■ Most negative

Figure 4: Comparison of key features for the different shielding methods.

by enabling the design freedom associated with the use of plastics versus other materials. Additionally, LNP FARADEX compounds provide the opportunity to reduce both the weight of the final device and its assembly costs.

In healthcare applications, patient safety remains a primary concern. Therefore, all plastics intended for use in medical devices that come into contact with the skin must be certified as biocompatible and undergo a range of tests – most notably the Biological Reactivity Testing (USP Class VI) and ISO 10993 "Biological Evaluation of Medical Devices" – to ensure that they fulfill the correct parameters.

To address demand for a biocompatible material that also provides EMI shielding, SABIC has developed a new healthcare grade LNP FARADEX NS003XXW compound, which has been pre-assessed for biocompatibility according to ISO 10933. For those manufacturers considering switching from a metal, or metallised approach, to a polymer, the LNP FARADEX NS003XXW compound also offers the benefit of SABIC's management of change policy, which provides medical device manufacturers with surety of supply and formula lock.

The demand for connected medical devices will continue to grow rapidly for the foreseeable future, driven by the pressing need to constrain spiralling healthcare costs. It will also be driven by advances in technology, both in the health parameters measured and the technology that can perform the monitoring.

In such a dynamic environment, a biocompatible plastic with inherent EMI shielding properties, such as SABIC's LNP FARADEX NS003XXW compound, can provide device manufacturers with a cost-effective material solution, enabling improved accessibility for a greater number of patients and – because the devices can be lighter and more convenient to use – can increase their acceptance. In addition to product development, SABIC also brings its in-depth materials and processing expertise to assist manufacturers throughout all stages of the product lifecycle, including design, prototyping, moulding techniques and post-production quality control.

For those device manufacturers seeking to position themselves at the forefront of the expanding connected medical device market, SABIC is interested in collaborating to address the requirements for both EMI shielding and biocompatibility in a single material – the LNP FARADEX NS003XXW compound.

ABOUT THE COMPANY

SABIC is a global leader in diversified chemicals headquartered in Riyadh, Saudi Arabia. It manufactures on a global scale in the Americas, Europe, Middle East and Asia Pacific, making chemicals, commodity and high-performance plastics, agri-nutrients and metals. SABIC supports its customers by identifying and developing opportunities in key markets such as construction, medical devices, packaging, agri-nutrients, electrical and electronics, transportation and clean energy. SABIC has more than 33,000 employees worldwide and operates in around 50 countries. It has 12,540 global patent filings, and significant research resources with innovation hubs in five key geographies – the US, Europe, Middle East, South Asia and North Asia.

ABOUT THE AUTHORS

Marnik Vaes is an experienced business development manager for SABIC's Specialties business in Europe, collaborating along the value chain to drive innovations in medical device platforms for multinational healthcare original equipment manufacturers. He has more than 20 years of experience in a range of application development and commercial roles, delivering petrochemical solutions to customers in the healthcare industry. Mr Vaes holds a Master of Industrial Science from the University of Leuven (Belgium).

Leen-Pieter Deurloo is the senior business development manager for SABIC's Specialties business in Europe. He is responsible for delivering high-performance compounds and copolymer solutions for customers in a range of sectors, including healthcare, telecoms and mass transportation. He has more than 35 years of experience in a variety of technical and commercial roles within the plastics industry and is currently specifying electrical conductive materials for applications in the petrochemical industry. Mr Deurloo holds a BSc in Chemistry from the HMLS Breda (The Netherlands).

Dr Martin Sas is a lead scientist for SABIC's Specialties business, managing projects and activities for electrical applications of high-performance polymers. He has more than 15 years of experience in a range of technical roles, including research and development lead engineer for sensor development in the automotive industry – and, in the semiconductor industry, for application design of embedded systems and micro-electromechanical systems (MEMS) sensors for automotive, healthcare and consumer electronics products. Dr Sas holds an MSc in Mechanical Engineering and a PhD in Applied Physics from Slovak Technical University (Slovakia).

SAI SHANKAR, ADAM SHAIN & MARCUS BATES, APTAR PHARMA

Sai Shankar, Vice-President, Global Digital Healthcare Systems, Aptar Pharma, has 15 years of product development and business strategy experience in the pharmaceutical industry. He joined Aptar in April 2017, having had previous roles at Allergan and Sanofi, where he worked in packaging engineering and development.

Adam Shain is Global Business Development Director for Aptar Pharma's Digital Healthcare team and is responsible for driving the new business agenda with pharma, payers and hospital network partners to reinforce the division's leadership in the digital healthcare space. Adam previously worked for Promius Pharma, a subsidiary of Dr Reddy's Laboratories, where he was instrumental in the development, commercialisation, and launch of many of its branded combination products.

Marcus Bates is Director, External Partners Connected Devices, at Aptar Pharma and has spent nearly 20 years working in the world of drug delivery devices and connected health. He has worked for two industry-leading companies in a range of roles and is currently responsible for the implementation of the supply chain for Aptar Pharma's connected devices business, as well as leading business development activities in Europe.

In this interview, Sai Shankar, Adam Shain and Marcus Bates discuss the full potential of connectivity, coronavirus as a potential accelerator of adoption, and the place of connected drug delivery systems within Aptar Pharma's broader offering to industry.

Q What is the full potential of connectivity in drug delivery devices, and what are the main barriers that are currently holding connectivity back?

SS The first and most obvious benefit that connectivity can bring is to improve adherence. This is the current focus of many digital health companies. Secondly, beyond adherence, connectivity can have a positive effect on drug usage technique – improving the ways patients interact with their drug delivery systems. Third, as we collect more data we develop a better view of what the patient journey looks like with regard to things like drug interactions, understanding side-effect profiles, and documenting quality-of-life outcomes. The key is to look at the patient journey, the workflow that they currently have, and the challenges both in the use of the drug, understanding the use case for the drug, and really bringing patient education as a differentiator.

It's important to remember that between doctor visits there are multiple things happening with a patient's treatment on a monthly, weekly and even daily basis. Connected drug delivery systems allow us to create regular micro-engagements with patients between their visits to the doctor, based on their behaviour, their drug usage, their adherence etc. It's also possible to collect data on their responses to the micro-engagements so we can focus in on which incentives work well, and which do not. Companies are creating incentives around, for example, giving adherent patients coupons or other benefits. Some patients who are becoming non-adherent will respond well to being nudged in this way and will go back to their dosing regimen. Others will not respond, so other incentives need to be considered, for example having a nurse practitioner call them or having a doctor send them a note. This is using connected drug delivery systems to apply behavioural science and implement patient education to achieve what I would call health literacy.

> "The key here is to avoid being overbearing and constantly reminding people that they are unhealthy, but instead to help them build healthy habits."

Beyond the patient, connected healthcare can be applied in the wider healthcare ecosystem, for example, to improve objective data gathering. Currently much of the information available to medical practitioners comes from the patient, such as patient-reported outcomes. Device-reported outcomes are more objective. With both patient- and device-reported information available, doctors will be better equipped to make sound decisions.

Most of what I've described so far applies to chronic treatments. However, connectivity has a crucial role in acute indications too; for example, rescue meds for migraines, antipsychotic drugs, or seizure medications. In these cases, ensuring that the patient has the drug on them when it's needed is crucial. Connected devices benefit from the fact that digital technology can be "always on". Increasingly people are "always on" with regard to work, with smartphones, e-mails and news alerts coming through, but we're not "always on" when it comes to our health. A connected device for acute or episodic treatment can be "always on", so it can be located if lost, and remind patients if they forget to take it with them. The key here is to avoid being overbearing and constantly reminding people that they are unhealthy, but instead to help them build healthy habits.

Data from connected devices is also being applied to begin to make predictions using surrogate data. For example, in asthma, if a connected device records a patient increasing their rescue medication usage or, conversely, if you start linking rescue usage to the number of days a patient has or has not taken their preventer drug, then it's possible to begin to predict a potential exacerbation. So usage data becomes a surrogate measure for use in clinical analysis.

Further than using surrogate markers, connected devices might also be able to incorporate actual diagnostics too. For example, inhalers that measure and report lung function daily whenever the patient inspires their drug can detect a drop in the lung function, enabling a more robust prediction.

Bringing diagnostic tools into the picture, combining that with drug usage and patient outcomes data, really allows us to reach an end-to-end connected solution – a so-called "Holy Grail". With a centralised platform to crunch the data, it's possible to provide truly valuable, life-saving insights to the patient, as well as to their care providers and doctors.

AS Thinking about the potential of connected drug delivery systems to deliver value across the ecosystem – to healthcare companies, healthcare providers, patients – the power that we generate by having more information around a disease state and around medication utilisation is well recognised. That said, we must always remember that just because you can connect something doesn't mean that you should. It's not about collecting any and all data.

One of the biggest challenges right now, and one of the biggest barriers to adoption, is a perceived risk that adding connectivity might make things less convenient, adding extra medication utilisation steps for the patient, extra tracking that's not wanted, or requiring the doctor to do more because of the way that the data is being integrated and fed back to them.

Sai mentioned behavioural psychology, and this is a critical aspect. We really have to make their connected device a part of the user's daily life. People today want or even need their smartphones with them all the time, and rarely forget them. We need to have that level of engagement with healthcare and connected devices in order to reach their full potential, doing things like warning about exacerbations and acute episodes before they happen.

MB Another barrier to the adoption of connectivity arises from the fact that pharma companies might feel that if they have successful products out there, why modify the platform. If it's working, then why change it?

Especially when it comes to engaging with insurers and payers, demonstrating the business case and demonstrating the value becomes very important. What is the return that's going to be achieved from adopting a connected platform? Of course, the only way to really demonstrate this is through gathering significant amounts of real-world evidence. And to do this a product has to be out there, has to be commercialised for a significant amount of time. So therefore, someone has to take the plunge. Then it is possible to say, confidently, that by having this connected feature, for example a connected add-on for a pMDI, we have actually reduced the amount of times that the patient has to take their reliever, or we've reduced the number of times that this patient has to go back to their physician or has to go into the emergency room.

Q **How has the COVID-19 outbreak impacted Aptar Pharma and to what degree has COVID-19, and the associated lockdowns, affected attitudes towards and perceptions of connected healthcare and digital health across different stakeholder groups?**

MB As the pandemic unfolded, Aptar Pharma was quickly identified in numerous countries as being an essential business that needed to stay open. We were designated Critical Infrastructure status in the US, for example. Innovative problem-solving being one of our strong suits, the teams at Aptar rapidly started coming up with solutions and we have subsequently filed various coronavirus-related products with the US FDA as well as in Germany.

AS One of the projects is a decontamination solution for the N95 mask that, so far, we have filed both with the US and the German authorities. We took an existing technology that we were using on other projects and created a personalised solution for healthcare workers' masks.

On the injectables side, we have a large number of new projects related to the numerous vaccine developments that are underway right now. And we also have partners developing nasally delivered coronavirus-related products.

Arising from the COVID-19 crisis, we are seeing an acceleration with regard to digital health and connectivity, caused by the fact that that people weren't able to go and see their doctor and were forced to be at home. Across the ecosystem of platforms, companies and providers, those offering telemedicine services through their apps, for example, have seen an acceleration in the market. We might well find that, in this respect at least, coronavirus leaves us possibly five years ahead of where we would have otherwise been.

SS Telemedicine has clearly taken off in the wake of the coronavirus crisis. I don't want to overplay the role of drug delivery devices in the telemedicine space, but to enable telemedicine, you need other systems to come into play, such as patient monitoring, for which you need connected devices and other services based around them. I believe we're at an inflection point now with regard to remote patient

"We have connected solutions across five different delivery routes that we're offering to the market today."

Figure 1: Aptar Pharma's connected device portfolio.

monitoring services, and devices become significant. The combination of diagnostics and drug delivery devices that are fully connected brings about remote end-to-end patient care. So, although COVID-19 is obviously a negative reason, I would say it has certainly moved connectivity in drug delivery in the right direction.

MB This accelerated adoption is certainly apparent in the UK. It was clearly stated in a recent webinar organised by the NHS that the digital journey on which they had already embarked was now on "fast forward".

Q How do connectivity and digital health fit within the broader context of Aptar Pharma's industry offering?

SS Our start point for connectivity was to ensure that, for our current portfolio of drug delivery systems that are in the market today, we are able to offer connectivity where that makes sense. We don't believe in bringing connectivity for the sake of connectivity because that does not add value. We want to offer connectivity where it's going to improve patient lives and outcomes.

We offer connectivity across our entire respiratory line. We are doing the same across our ophthalmic, dermal, and nasal drug delivery lines (Figure 1). In dermal for example, when you think of diseases like atopic dermatitis or even skin infections, having a clear dosing regimen and complying with it makes a huge difference to your health. With poor adherence you could have a therapy extend out over six months, which could have been done in 14-21 days.

The latest area where we've added a connectivity offering is around autoinjectors, focused on injectable products across the spectrum of indications, anything from oncology to immunology. In addition to improving adherence, connected autoinjectors can improve technique, helping to avoid wet injections and incomplete injections, for example. Our connected autoinjector solution, made possible through our acquisition of drug delivery training device and patient onboarding world leader Noble (Orlando, FL, US), trains the patient as they're taking the drug.

We have connected solutions across five different delivery routes that we're offering to the market today.

Q Can you describe some of the recent partnerships that Aptar Pharma has entered into that are helping to expand the company's digital ecosystem and connected offering?

MB When putting together a complete global offering for digital health there's significant value to be had by partnering with external companies, whether it be through collaboration, or whether through investment or full acquisition. It's impossible to truly innovate and provide a world-leading digital health solution looking only inwards. Digital health and digital medicine encompass a very wide range of capabilities; functionalities that mean one needs to look outwards, to the experts in each particular sub-area. And this is what Aptar Pharma has been doing for the last five years or so.

Back in 2018 we partnered with digital respiratory company Propeller Health (Madison, WI, US), and we made an investment in Silicon Valley-based Kali Care for an ophthalmic product. We've continued to go out and find the partners we need to complement our capabilities and to build truly end-to-end connected solutions. This includes elements such as full back-end solutions and data analytics.

On the hardware, the actual connected device element, we've built our own in-house capability whilst leveraging external partners for manufacturing. We've identified chosen partners at a component level. The objective there is to ensure we get the best costings for key components and to make sure that we are front and centre when it comes to then equipping our devices with our component partners' most recent, next-generation products and solutions.

The most recent investment that we announced was in April 2020, with Sonmol, a digital health company based in Shanghai, China, to co-build the ecosystem of connected healthcare devices and services for China, and to collaborate on device development and manufacturing for local and global markets. Sonmol's focus is on data and software development for China. There are different requirements and different needs in each part of the globe.

"The investment in Sonmol will really open up the Chinese market. Clearly, having a local presence makes a huge difference, not only for building relationships with pharma companies, but also for interacting with other stakeholders such as hospitals and doctors."

With Sonmol, we've identified a specific part of the digital health world that they reside in, which complements us, certainly in the respiratory space. We believe that together we can offer a very compelling solution in China.

SS We believe the investment in Sonmol will really open up the China market, allowing us to further deploy our connected device solutions. Clearly, having a local presence makes a huge difference, not only for building relationships with pharma companies, but also for interacting with other stakeholders such as hospitals and doctors.

In India, we made an investment in a start-up called Navia Life Care. They were our deployment partners for our first connected product launch in India, initially as part of our launch for respiratory products, but we are also able to expand to other therapeutic areas. We have two partnerships across the European and US markets covering clinical-stage deployments as well as commercial. The idea is that in any given market, if there's a requirement from our customers to deploy a digital solution, we're able to deploy our digital ecosystem.

AS One of the reasons we put so much emphasis on partnerships at Aptar Pharma when it comes to digital solutions is that we're aware that this is a very fragmented space. I believe it will still be fragmented in 10–15 years' time, and these open partnerships are really going to drive the success of digital healthcare. You'll see companies working not only with their traditional customers and suppliers, or electronic component suppliers, but also partnering with big tech companies, or even working with competitors. That is quite a change for Aptar Pharma, which has its core areas such as pulmonary and nasal. Digital healthcare is a big space and success for Aptar Pharma and for all the companies that wish to participate in this space will come from that fluid ability to work with each other.

[Continued on Page 34...]

"Success for Aptar Pharma and for all the companies that wish to participate in this space will come from that fluid ability to be able to work with each other."

Building a Connected Devices Eco-System for Digital Medicines

As Pharmaceutical companies around the world look to address the challenges of non-adherence to improve patient health outcomes, they turn to Aptar Pharma.

Today, we are leveraging decades of manufacturing excellence and proven device design to offer the widest portfolio of connected solutions and diagnostic tools across all our delivery routes. Complemented by our partnerships with leading digital healthcare platforms and key stakeholders in healthcare delivery models, we are building a connected device eco-system for digital medicines.

To see how you can move towards a connected future, contact with **Sai Shankar**, Vice President, Global Digital Healthcare Systems, at Aptar Pharma on **+1 847 800 6058** or email **sai.shankar@aptar.com**

Delivering solutions, shaping the future.

Aptar pharma

[...Continued from Page 32]

Q How is Aptar Pharma positioned to help its pharma partners deliver to stakeholders the benefits and value that connectivity promises?

AS We really see ourselves as an integrator in digital healthcare across multiple therapeutic areas. Some other companies focus on one or two specific disease areas, for example asthma and COPD or diabetes, and build everything up from there. But Aptar Pharma's business is vast, covering a multitude of delivery systems that we provide for pharmaceutical products which touch upon maybe 50 or 60 different disease states.

We're driving value for all the customers and all the different patient services that we support today. Creating this integrator approach in digital health means that we can build a customised solution encompassing all of our customers' needs. We can bring in partners whenever required, and we can interact with pharma, payers, hospitals, and all stakeholders. Our strategy in digital healthcare is to really open ourselves up to being able to provide solutions in parallel and in combination for the customers with whom we're already working.

MB We've identified partners across different global locations, and we have manufacturing capability dotted around the world to ensure that we are able to provide the right solution in the right location. We are currently able to manufacture connected devices in Asia, Europe and North America for global deployment while meeting all local regulations.

> "We really see ourselves as an integrator in digital healthcare across multiple therapeutic areas."

SS Our model helps us pivot to the requirements and needs of the customer across multiple therapeutic areas and, geographically, worldwide. We can operate in markets that are highly cost-sensitive, like India and China. For example, I believe we are the first company to have offered a digital health solution in India for respiratory. That was a commercial launch with Lupin, which I would say was quite an achievement from our perspective. And at the same time, we've also a strong proven track-record of being able to offer solutions in the European and US markets. There are very few companies who can state that they offer digital health solutions effectively across these markets and this breadth of therapeutic areas successfully, and Aptar Pharma is one of them.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across a wide range of delivery routes including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. 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. (NYSE:ATR).

Aptar pharma

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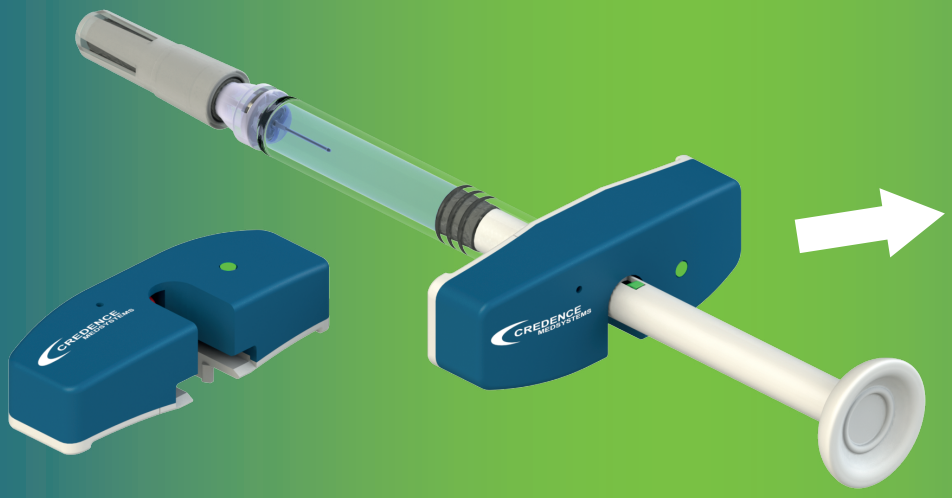
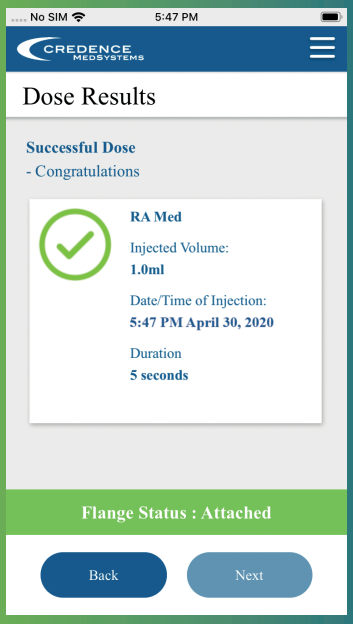
CREDENCE MEDSYSTEMS

CREDENCE CONNECT™

AUTO-SENSING INJECTION SYSTEM

Bringing connectivity to any prefilled syringe





Remote monitoring for clinical studies
Automatic capture of injection data
Real-time user feedback
Reminders, instructions & guidance
Reusable flange for sustainability & comfort

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These products have not been evaluated by FDA

CREDENCE MEDSYSTEMS

THE AWARD-WINNING CREDENCE CONNECT™ AUTO-SENSING INJECTION SYSTEM

In this article, John Merhige, Chief Commercial Officer of Credence MedSystems, explores the benefits provided, questions raised and challenges presented when bringing digital connectivity to a prefilled syringe – and explains how connectivity that is universally applicable to any existing prefilled syringe platform adds value throughout the ecosystem, both including and beyond the "compliance business model".

When the team at Credence MedSystems performed its first brainstorming sessions that resulted in the award-winning Credence Connect™ Auto-Sensing Injection System, it leaned heavily on the company's philosophy of delivering *Innovation Without Change*. The challenge was to produce a highly innovative system that would deliver value across the drug delivery ecosystem, while achieving broad compatibility of the technology with existing processes and prefilled syringe systems.

> "The application of digital connectivity in drug delivery devices continues to be a very important topic, especially so in light of the coronavirus pandemic's impact on remote clinical trial monitoring and the greater acceptance of telemedicine."

The application of digital connectivity in drug delivery devices continues to be a very important topic, especially so in light of the coronavirus pandemic's impact on remote clinical trial monitoring and the greater acceptance of telemedicine. The business case supporting connectivity is evolving rapidly to include applications in clinical study and commercial use. After being introduced at this year's Pharmapack conference in Paris, France, the Credence Connect received the Best Innovation in Drug Delivery Devices award. This honour reflects the value that the Connect can deliver across the drug delivery ecosystem to users, biopharma manufacturers, payers, providers and contract research organisations (CROs) by bringing connectivity to any prefilled syringe.

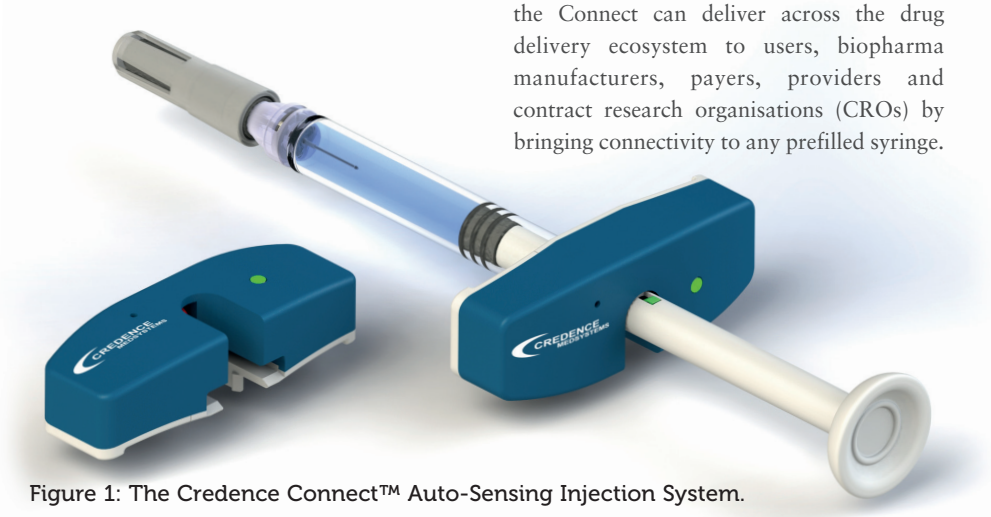

Figure 1: The Credence Connect™ Auto-Sensing Injection System.

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THE CREDENCE CONNECT AUTO-SENSING INJECTION SYSTEM

The Credence Connect (Figure 1) incorporates automatic monitoring of critical injection data and real-time user feedback into a reusable ergonomic finger grip. By embedding the "connectivity engine" in a comfortable grip that enhances usability, the Connect transforms any prefilled syringe into a connected delivery system via a ubiquitous ergonomic feature that users already prefer to use. The reusability minimises the environmental footprint, which is especially important when electronics are included, and helps biopharma companies meet corporate sustainability and cost objectives.

The automatic or "passive" function of the system allows the seamless capture and communication of injection information without requiring any additional actions by the user to verify administration. The Connect uses Credence's proprietary technology to measure the distance travelled by the plunger rod during the injection. The volume injected is determined based on the known syringe configuration and fill volume.

> "The user can track the progress of the injection by viewing a counter or meter on an associated app."

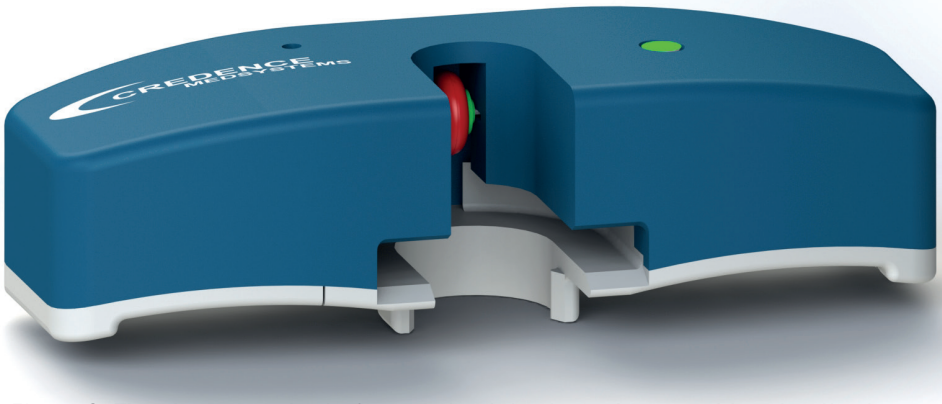

Figure 2: The elegant method of measuring injection volume enables visualisation of injection progress and broad applicability to prefilled syringes.

This elegant, straightforward method of measuring injected volume allows progress of the injection to be captured as the injection occurs and, critically important, provides the user with real-time feedback on the injection. The user can track the progress of the injection by viewing a counter or meter on an associated app; the meter increments as the injection occurs and the meter pauses when the injection is paused. This real-time feedback system empowers and reassures the user – an important aspect of supporting proper administration.

If the appropriate dose volume has been injected within the predetermined time duration, the injection is marked as a success. If too little volume is injected – or if the injection is not completed within the predetermined time – the injection is marked as a failure. Either way, the injected volume, time and date of administration, and duration of injection are recorded in dose history (Figures 2 and 3).

The Credence Connect links to an app on a smartphone via Bluetooth Low Energy. Credence has developed a demonstration app, although the Connect will be able to integrate with customer-specific or third-party platforms. The app provides the opportunity for further important interaction with the user, including reminders and alarms, instruction and guidance – and, of course, the feedback and dose history previously mentioned. The app also provides the medium for an information exchange amongst members of the healthcare ecosystem that can deliver value and enable innovative new business models. Features and benefits of the system are summarised in Table 1.

THE ROLE OF CONNECTIVITY IN THE DRUG DELIVERY COMMUNITY

There is ample discussion and debate in the drug delivery community about the role digital connectivity can play and the

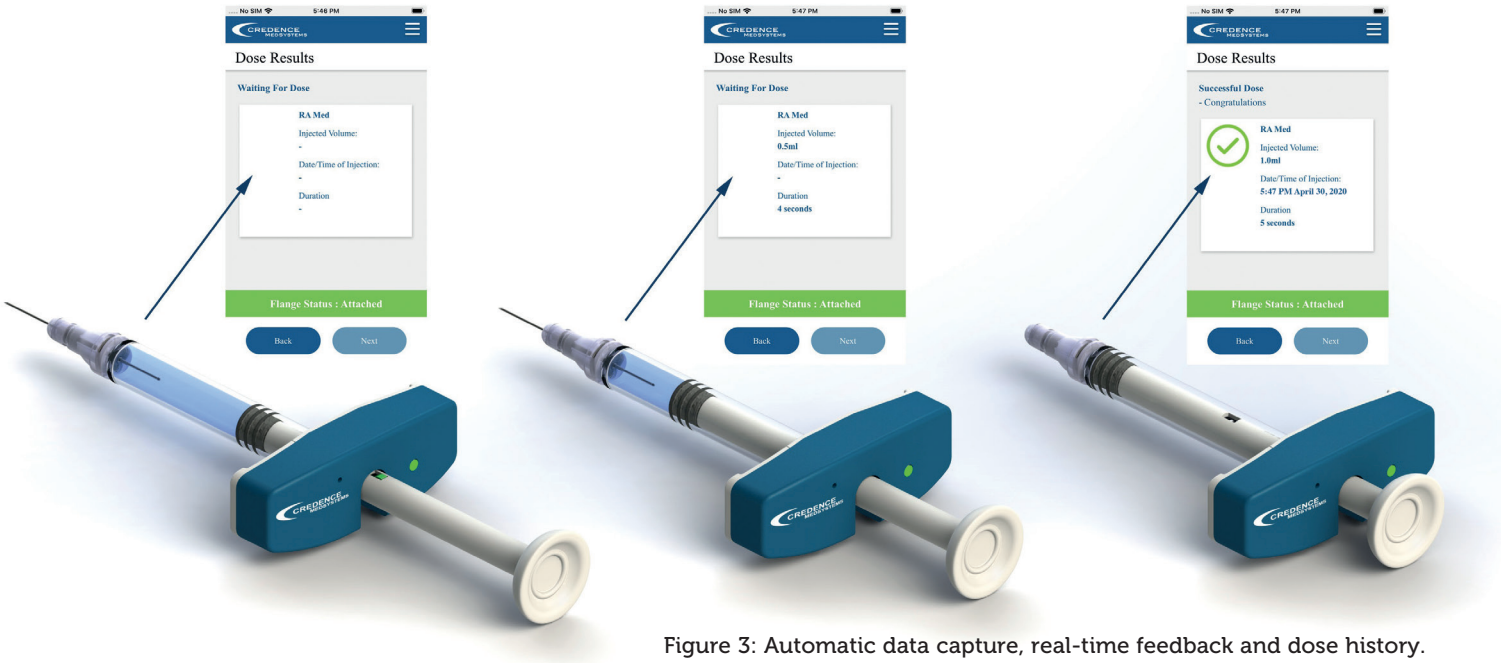

Figure 3: Automatic data capture, real-time feedback and dose history.

business case that supports it. Those value and business drivers differ in a clinical study application compared with the commercial use setting. Still, the discussion seems overly weighted on what can be described as "the compliance business model" for the commercial use setting.

Discussions around the compliance business model are accompanied by oft-quoted statistics describing poor patient compliance and the resulting economic impact. For instance, the WHO reported in 2015 that chronic disease patients in developed nations exhibit adherence of approximately 50%[1] and that avoidable costs associated with this poor adherence range up to US$290 billion (£235 billion) in the US alone.[2] The idea is that connectivity can help improve compliance, which should lead to better outcomes and therefore reduce healthcare spending. This is of course logical but leads to a series of questions.

Will connectivity result in improved compliance? Perhaps a better way of framing this question is: What should a system provide to users to motivate engagement and retention so that compliance improves? What will then be required to demonstrate that improved compliance results in better outcomes and reduced spending? And, further, will this wonderful result provide the proper motivation for pharma manufacturers to pursue widespread implementation? While some claim that increased compliance is not a driver for pharma, others identify a major opportunity to recover lost revenue that results from non-adherence. The opportunity to recover that lost revenue is significant – estimated to be $637 billion in 2015.[3]

Certainly, other challenges exist when it comes to the implementation of connectivity. A non-exhaustive list includes: privacy and security issues; potential distrust of the pharma industry; new usability requirements and the potential for increased complaints; the infrastructure that will be required to support digital systems; the conflict that arises between the rapid pace of technology development juxtaposed with the slow pace of pharma/device development; regulatory challenges; and many, many others. These challenges provide ample opportunity for sceptics to present obstacles – but these obstacles are certainly addressable if the upside in doing so is compelling.

The challenge lies in the fact that the compliance business model will take time to play itself out. This allows sceptics to ask whether developing digital connectivity is the act of developing technology solely for technology's sake. But compliance is not the only value driver of connectivity. Too often in our industry, the value that can be obtained is abandoned due to the challenge of implementing innovation due to the fear it involves too much change. It is the role of the innovative entrepreneurs amongst us to advance technology so that its implementation is manageable and its value is too compelling to be ignored. This brings us back to Credence's guiding philosophy of enabling *Innovation Without Change*, and the Connect's universal applicability to existing prefilled syringes.

Feature	Benefit
Automatic or "passive" data capture	Eliminates additional actions by user
Real-time transmission and feedback	Enhanced usability and feedback; promotes compliance; remote monitoring for clinical trials
Reusability	Environmental sustainability and cost containment
Ergonomic design	Enhanced usability
Universal applicability	Facilitates implementation for pharma in clinical studies and commercial use
Method of injection measurement	Reliability and universal applicability
Multiple modes of user communication	Enhanced usability
Guidance, feedback and injection history	Enhanced usability; promotes compliance
Enables communication within the drug delivery ecosystem	Patient support; promotes compliance; new innovative business models
Captures important usability data	Informs patient care for improved outcomes

Table 1: Features and benefits of the Credence Connect Auto-Sensing Injection System.

VALUE-ADD FROM CREDENCE CONNECT IN CLINICAL TRIALS

Stepping away from the commercial use setting for a moment, there is clear value the Credence Connect can bring in the performance of clinical studies. As CROs move towards a risk-based approach to data collection and methods of addressing the inherent flaws of manual journaling, there has been an ongoing trend towards remote monitoring. This trend has been made more acute by the recent pandemic as CROs search for methods of enabling decentralised studies. The Connect can enable more efficient performance of these studies and allow CROs a differentiated offering to their pharma customers so that studies can continue to be executed in the "new normal" of social distancing.

> "The most significant element in the clinical study value equation is the potential impact the Connect can bring to clinical study success."

But the most significant element in the clinical study value equation is the potential impact the Connect can bring to clinical study success. The cost to develop a drug is well debated but undeniably large, with estimates ranging from $1 billion to $3 billion.[4] While the cost of clinical trials that support US FDA approvals is a modest portion of that overall expense, with a median cost of $19 million,[5] a failed study jeopardises the full development expense and the revenue that could have come from approval.

The Connect can: promote proper compliance via benefits such as real-time feedback, reminders and injection guidance; enable targeted intervention in cases of non-compliance; and, collect dose history that can justify data inclusion/exclusion decisions. These can all allow the results of the study to be a true measure of a drug's safety and efficacy, as opposed

to a potentially misinformed result due to poor or unknown compliance. Further, the universal applicability to existing prefilled syringes will allow pharma companies to perform studies with the Connect as soon as their preferred prefilled syringe configuration is ready for implementation.

VALUE-ADD IN THE COMMERCIAL SETTING

Returning to the commercial setting, the ability of the Connect to capture opportunities will be contingent on delivering enough ongoing value to the user to promote engagement and retention. This is the case whether the opportunities come from driving improved compliance or from other innovative business models that are made possible. The real-time feedback, reminders, guidance, instruction and dose history that the Connect provides are all part of that user value.

Beyond these, facilitating user access to support groups via social networking platforms and relevant education can prove to be compelling drivers of retention. Tangible rewards for good compliance, in a mutually agreeable exchange between users and payers, can drive retention and achieve economic benefit for both parties. As we migrate towards outcome-based healthcare, this value applies to provider networks as well. Another well-discussed topic is the integration with electronic health records and the visibility that can bring to providers – but overburdening healthcare professionals needs to be considered.

Opportunity also exists for a mutually beneficial exchange between users and pharma manufacturers. Pharma spends significantly on patient outreach and direct-to-consumer advertising, the latter reaching $9.6 billion in 2016.[6] The Connect can provide insight into the daily relationship users have with their medications and an understanding of true use patterns, allowing pharma to embed insights into drug and delivery device development.

It also provides a platform for targeted messaging directly to user cohorts with education regarding common comorbidities and associated therapies, as well as messaging from third parties. This user cohort outreach will need to be executed in compliance with the EU General Data Protection Regulation 2018 (GDPR), the US Health Insurance Portability and Accountability Act 1996 (HIPAA), and other relevant requirements, and be offered to users with the appropriate incentive to motivate user acceptance. Nonetheless, the value is significant in its potential impact on the business model supporting connectivity.

SUMMARY

Implementing digital connectivity into drug delivery devices is not a simple endeavour and the business models supporting it continue to be discussed. It is critical to understand the value opportunities that exist both in the short term as well as the long term, and the role that can be played in both clinical trials and ongoing commercial use. It is equally critical to understand that any change brings obstacles but that the right technology can reduce those obstacles and facilitate implementation to achieve value throughout the ecosystem.

The Credence Connect Auto-Sensing Injection System has been designed in line with the company's philosophy of *Innovation Without Change*, to allow universal functionality with conventional prefilled syringes and to employ an elegant method of injection measurement that enables automatic data capture and real-time feedback to the user.

Credence MedSystems has a history of successful collaboration with its pharma customers and within the greater supply chain serving them, and we look forward to continuing that approach for the successful implementation of the Credence Connect in clinical studies and commercial uses alike.

AWARD WINNER

Credence MedSystems received the 2020 Pharmapack Best Innovation in Drug Delivery Device Award for its Connect™ Auto-Sensing Injection System, at Pharmapack (Paris, France, February 4-5, 2020).

ABOUT THE COMPANY

Credence MedSystems is an innovator of drug delivery devices that solve unmet market needs. Its Companion family of syringes includes proprietary needle retraction technology in Staked-Needle and Luer formats, and its portfolio has expanded to include Dual Chamber configurations, metered dose applications, connected devices and other novel systems.

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ABOUT THE AUTHOR

John A. Merhige is Chief Commercial Officer at Credence MedSystems. Previously, he was Vice-President, Market Development at Sanofi BioSurgery. Mr Merhige came to Sanofi upon its acquisition of Pluromed in 2012, which he joined in its early stages and where he was a member of the executive management team. He led the commercial activities at Pluromed, which developed and commercialised rapid transition polymers for cardiovascular and other surgical procedures. Prior to Pluromed, he founded Prelude Devices to target early-stage medical device technologies for development and commercialisation. Mr Merhige is a member of PDA, MassMEDIC, MassBio and has served on the board of directors of the MedDev Group

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UNLOCKING INSIGHT FOR PATIENT SUPPORT PROGRAMMES WITH CONNECTED DRUG DELIVERY

Neil Williams, Director of Front-End Innovation and Head of Connected Health, and Andrew Tubb, PhD, Director, Connected Health, both of Phillips-Medisize, discuss how insights delivered by a cloud-based connected health system help patient support programmes to monitor and improve medication adherence.

Patient care continues to move out of the hospital and doctor's office and into the home. This trend has rapidly accelerated with the COVID-19 crisis, as more clinicians have begun offering remote online and telemedicine care. In recent examples, a virtual care provider experienced a 900% increase in patients using telehealth services earlier this year, while one hospital reported that its video visits went from 200 a week to more than 12,000.[1]

This "new normal" places even greater emphasis on the ability to remotely monitor a patient's treatment regimen and effectiveness outside the four walls of a healthcare facility. A connected health system offers tremendous potential to capture timely, accurate data on a patient's at-home medication usage and health status – and quickly intervene as necessary.

Connectivity is already available in select home health sensor-based monitoring products, such as wearable blood pressure monitors and glucose meters designed to collect digital data. Alongside this, a rapidly growing field is emerging – connectivity in drug delivery solutions like inhalers, injectors, patch pumps and infusion devices. Data from these devices give new insights into actual device and medication usage and behaviour that help healthcare providers (HCPs) and patient support programmes (PSPs) to monitor and assist patients in correct device use and management of medication and dosage. The latest technology incorporates connectivity in legacy mechanical drug delivery devices (i.e. injection pens and inhalers) in a cost-effective manner, while newer electromechanical devices offer embedded connectivity capabilities.

> "Connected health systems offer an opportunity to amplify the value of patient support programmes."

A comprehensive, connected health system typically consists of three main components: a connected patient drug delivery device; digital interfaces for patients (i.e. engagement app on a smartphone) and PSPs/HCPs (web-based portal or dashboard); and a secure cloud platform that facilitates the transmission of digital patient data, so that it can be readily viewed and acted upon (Figure 1).

ENABLING PSPS TO BE EVEN MORE PROACTIVE

Connected health systems offer an opportunity to amplify the value of PSPs. These are generally third-party programmes, sponsored by a pharmaceutical company and

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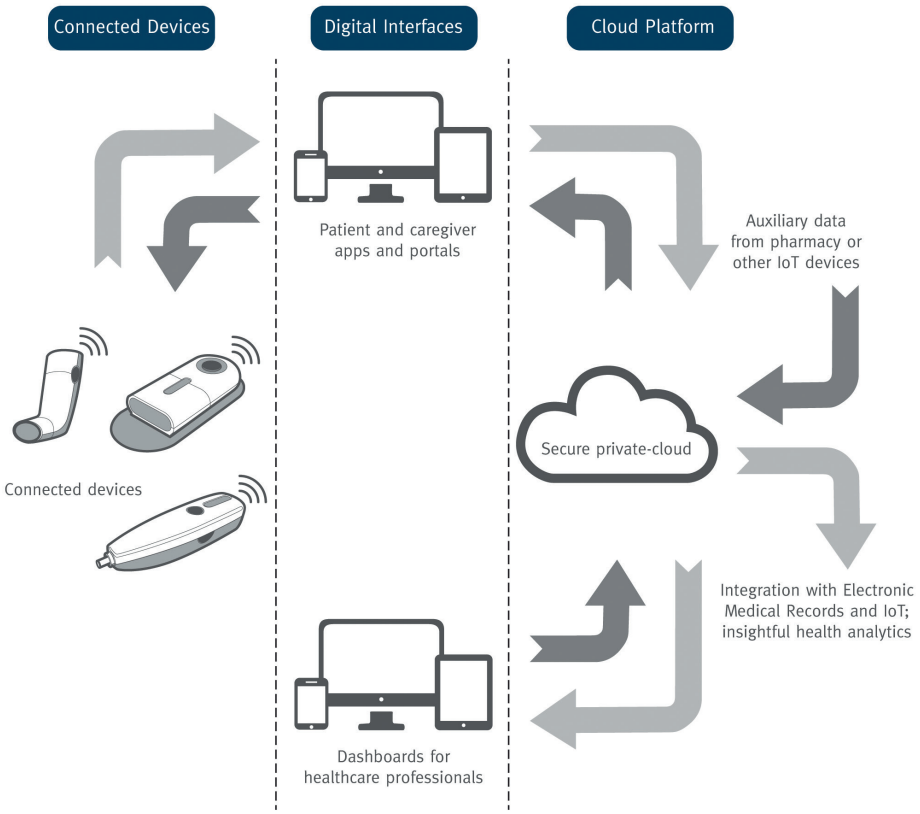

Figure 1: The Phillips-Medisize Connected Health Platform is designed to advance the digital health ecosystem and better support patients and healthcare professionals.

functioning separately from the commercial team. Typically, core staffing includes nurses and other clinicians with specific responsibilities to educate and support patients in self-managing their condition and adhering to their prescription treatment.

Poor adherence continues to be a widespread healthcare challenge. Up to 50% of medications are not taken as prescribed[2] and 33% of US hospital admissions are due to poor medication adherence.[2] This not only has a negative impact on patient outcomes but it also results in a large cost burden on the healthcare system overall.

HCPs and PSPs alike lack the objective, real-time or detailed visibility into a patient's health behaviours and status that would enable the most effective interventions. Whether care is delivered face to face or remotely, much time is spent trying to establish the patient's health behaviour and status in order to guide decision making and next interventions accurately. In many cases, PSPs follow standard scripts and pathways when communicating with patients but without sufficient health data insight to tailor support to the individual. As a result, a patient's behaviour, medication use or health status may change without the PSP or provider being aware – thus missing the most optimal points to intervene and make a more meaningful impact on the patient's health.

> "Analysis and learning from pooled/population data can deliver valuable insights that can then be turned into new decision and intervention points."

Today's advanced connected health systems support PSPs by bringing together data from drug delivery devices, patient-reported outcomes (e.g. from apps) and other sources such as home monitors and patient wearables. The different sources of patient information, along with records of the PSP follow-up and intervention, are protected in a secure cloud platform. They are presented to PSP clinicians in customised web portals and dashboards that help to pinpoint and prioritise patients based on their adherence behaviour and health status, such as patient-reported outcomes. As a result, PSP staff can more readily identify outliers, intervene earlier and steer patients toward behavioural changes with personalised and targeted supportive interventions.

FUTURE TRENDS DRIVING CONNECTED HEALTH SYSTEMS

There are four main trends shaping the future of successful medication adherence with connected drug delivery:

1. **Behavioural insights** – we'll see a greater shift towards understanding more about what motivates patients, so that we can define and implement successful interventions.
2. **Scalability** – there will be a movement from small pilot studies to large global programmes and shared infrastructure where we can start to benefit from economies of scale. This will help implement connected health solutions at a lower cost base, so that they can be used more broadly in the market.
3. **Integration** – as healthcare continues down the path of digital, medication adherence data will be shared from proprietary systems to leading electronic medical record systems, allowing HCPs to view this data from anywhere.
4. **Analytics** – this is going to be a key driver for connected health systems going forward. We'll see a trend in how patient data is used more effectively to understand patient behaviours tied to drug performance and even the relationship between taking medication and improved health outcomes. This will guide more tailored and personalised care delivery at both the individual and patient population levels.

TARGETING HIGH-RISK AND CHRONIC CONDITIONS

A connected health system facilitates personalised care by unlocking data that alerts PSPs to changes in individual patient behaviour that warrant action. At a more abstract level, analysis and learning from pooled/population data can deliver valuable insights that can then be turned into new decision and intervention points, on an individual patient level as well as for specific patient populations.

"Connected health systems enable PSPs to target care, to focus attention on the patients who need it most with the right intervention at the right time, ultimately streamlining costs and improving the effectiveness of care protocols."

For example, at a population or sub-group level, are changes in treatment adherence correlated with the appearance or worsening of medication side effects? Or are such changes linked with not seeing expected outcomes within a certain time period? From such insights, flags for intervention can be hypothesised and then tested – e.g. to trigger behavioural nudges or other interventions when patients in certain stages of therapy miss treatment by a pre-specified number of days or if the time at which medication is taken becomes variable or strays outside defined limits. This data can also be used to pinpoint which patient groups are at a lower risk and which are at a higher risk, and direct them down different care pathways.

Overall, connected health systems enable PSPs to target care, to focus attention on the patients who need it most with the right intervention at the right time, ultimately streamlining costs and improving the effectiveness of care protocols. Individuals who suffer from chronic conditions are prime candidates for PSP support enabled by connected health. Medication adherence and persistence play an essential role in the long-term management of chronic and often debilitating diseases such as asthma, diabetes, multiple sclerosis (MS) and many others. Data captured from connected drug delivery devices gives the PSP a window onto actual patient health behaviour to guide their interventions.

As a case in point, Phillips-Medisize collaborated with Bayer to develop a connected system for patients with MS, where adherence to long-term disease-modifying drug treatment is especially challenging. This is an example of how a user-friendly, connected drug delivery device and system can enable a PSP to support patients and manage medication adherence. In light of the telehealth trend, today's PSPs and HCPs in general have a timely opportunity to leverage digital data to monitor and measure patient behavioural changes remotely. This, in turn, can guide PSPs with measurable insight that advances more accurate patient risk identification, recommended changes to a prescription drug regimen, a higher level of personalised care and, ultimately, healthier outcomes (Figure 2).

Figure 2: Phillips-Medisize collaborated with Bayer to help bring medicine into the digital age with the BETACONNECT solution.

ABOUT THE COMPANY

Phillips-Medisize, a Molex company, is an end-to-end provider of innovation, development and manufacturing solutions to the pharmaceutical, diagnostics, and medical device market segments. Backed by the combined global resources of Molex and its parent company Koch Industries, Phillips-Medisize's core advantage is the knowledge of its people to integrate design, moulding, electronics and automation, providing innovative, high-quality manufacturing solutions.

ABOUT THE AUTHORS

Neil Williams is Director of Front-End Innovation and Head of Connected Health at Phillips-Medisize. Previously he was with Medicom Innovation Partner, which he joined in 2015 and which was acquired by Phillips-Medisize in 2016. One of his key roles is to evolve the company's third-generation connected health software platform. Having started his career in the clinical setting, working in the critical care faculty with a leading NHS University Hospital, Mr Williams moved into industry where he has focused for many years on healthcare IT including medical devices, clinical decisions support, health analytics and care pathway design.

Andrew Tubb, PhD, is Director, Connected Health, at Phillips-Medisize. His main focus is developing innovative connected health strategies and solutions for customers, to improve patient outcomes and strengthen competitiveness. Dr Tubb's background prior to Phillips-Medisize includes 13 years in global marketing with Sanofi and seven years consulting in pharma and medical technology. He is particularly interested in integrated care products and services that bring together medication, drug delivery technology, connectivity, services and behaviour change.

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an Aptar pharma company

APPLYING CONNECTIVITY TO ENHANCE THE TRAINING STANDARD OF CARE FOR SELF-INJECTING DRUG DELIVERY DEVICES

In this article, Erin Miller, Marketing Co-ordinator at Noble, looks at how connectivity can be used to enhance training to help address the challenges of accuracy and non-adherence when patients self-inject their medications.

The Internet of Things (IoT) and connected devices have transformed our everyday lives, from web-connected televisions and smart kitchen appliances to fitness trackers and home security systems. Similarly, connected medical devices are poised to revolutionise healthcare and drug delivery.

The medical technology industry designs and manufactures more than 500,000 different types of medical devices – including wearable external devices, such as insulin pumps and blood glucose monitors, and implanted medical devices, including pacemakers and defibrillators. These devices have proven instrumental in helping the healthcare industry achieve better patient outcomes and lower healthcare costs – and create new ways to engage and empower patients.[1]

THE INTERNET OF MEDICAL THINGS

This vast number of connected medical devices has given rise to the Internet of Medical Things (IoMT). Think of it as a connected digital health ecosystem of stakeholders that includes medical device companies, original equipment manufacturers, healthcare IT systems, networking technologies and end users that, together, can remotely connect patients to their healthcare providers (HCPs) and transfer medical-grade data over a secure network.

The in-home segment of the IoMT market includes personal emergency response systems (PERSs), remote patient monitoring (RPM) and telehealth virtual visits. RPM comprises all home monitoring devices and sensors used for chronic disease management, which involves continuous monitoring of physiological parameters to support long-term care in a patient's home in an effort to slow disease progression; acute home monitoring, for continuous observation of discharged patients to accelerate recovery time and prevent re-hospitalisation; and medication management, to provide users with medication reminders and dosing information to improve adherence and outcomes.[2]

> "Nearly half of patients who self-inject receive no training on how to do so properly."

BENEFITS OF IoMT AND CONNECTED MEDICAL DEVICES

Connected medical devices and IoMT applications represent the future of healthcare for patients, pharmaceutical

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companies and HCPs, playing a vital role in the remote tracking and treatment of chronic illnesses and delivering a range of benefits that include improved drug management, enriched patient experiences and enhanced patient outcomes. Connected devices also create market differentiation and enable value-based contracting.

> "When training is incorporated into the standard of care, patients experience significant improvement in their performance. They become more confident and less likely to abandon their treatment."

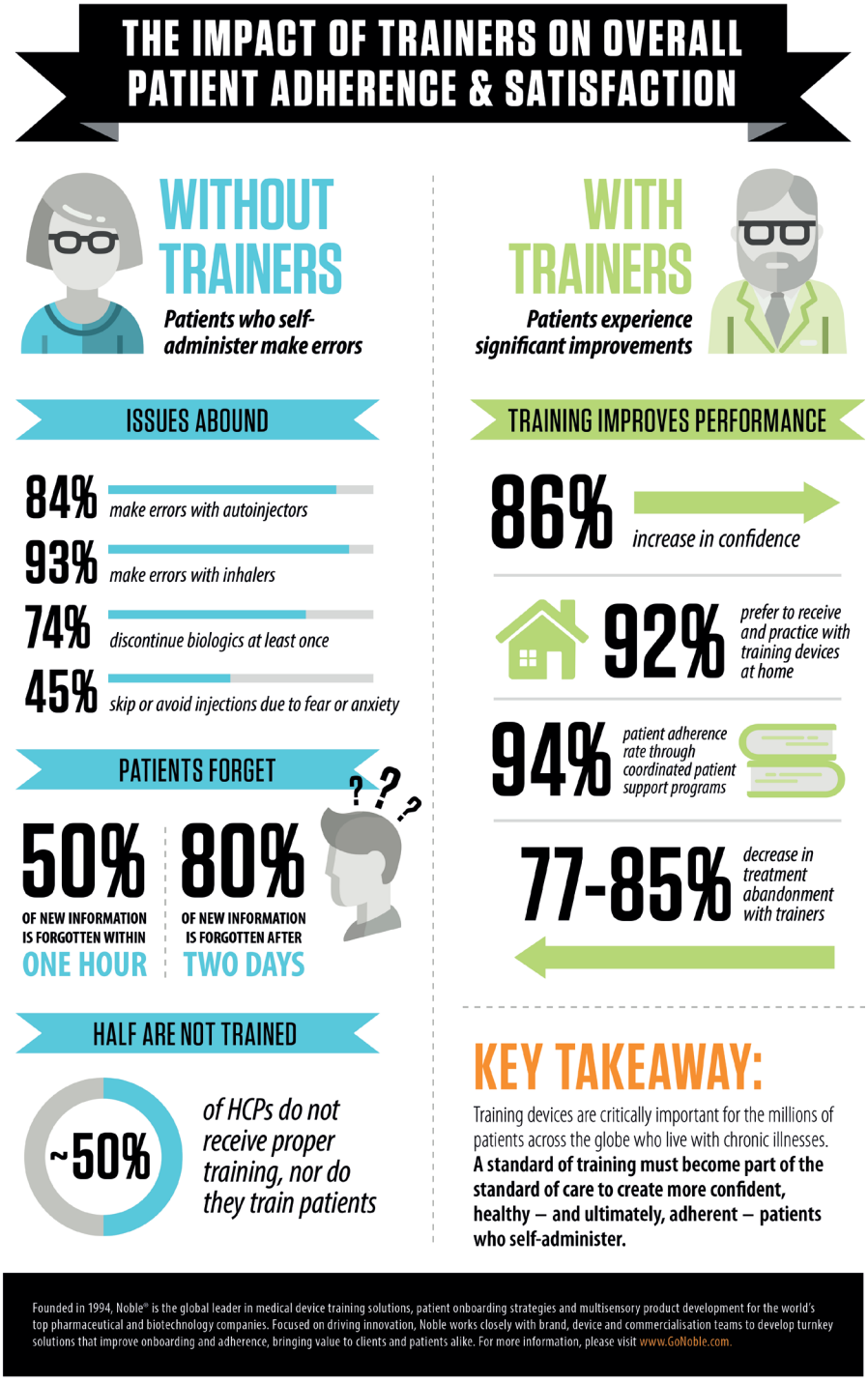

Figure 1: Patient statistics with and without training devices as support.

The potential of connected medical and drug delivery devices to help control healthcare costs and increase patient access to care is supported by an October 2019 study of trends in remote patient monitoring. It revealed that 88% of surveyed providers are investing in RPM solutions as a clinically effective, early symptom management tool to remotely monitor unstable, high-risk patients with chronic conditions which, in turn, supports value-based care implementation.[3]

THE INJECTABLES SEGMENT OF IN-HOME MEDICAL DEVICES

When it comes to the injectables segment of in-home medical devices – which includes autoinjectors and prefilled syringes – patient adherence and satisfaction have long been common concerns due to the lack of adequate training. These concerns are especially true for patients with chronic conditions such as arthritis, diabetes, Crohn's disease and multiple sclerosis who must self-inject their own medication.

Nearly half of patients who self-inject receive no training on how to do so properly, according to a recent study conducted by Noble, an Aptar Pharma company, which explored the impact of trainers on overall patient adherence and satisfaction. The study revealed numerous issues when patients self-inject their medications without training:

- 84% make errors when using their autoinjector devices
- 74% discontinue their biologic medication at least once
- 45% skip or avoid their injections due to fear or anxiety.

Conversely, when training is incorporated into the standard of care, patients experience significant improvement in their performance. They become more confident and less likely to abandon their treatment. The findings of Noble's study include (Figure 1):

- 86% increase in patient confidence when self-injecting their medication
- 92% of patients prefer to receive and practise with training devices at home
- 94% patient adherence through co-ordinated patient support programmes
- 77–85% decrease in treatment abandonment with trainers.

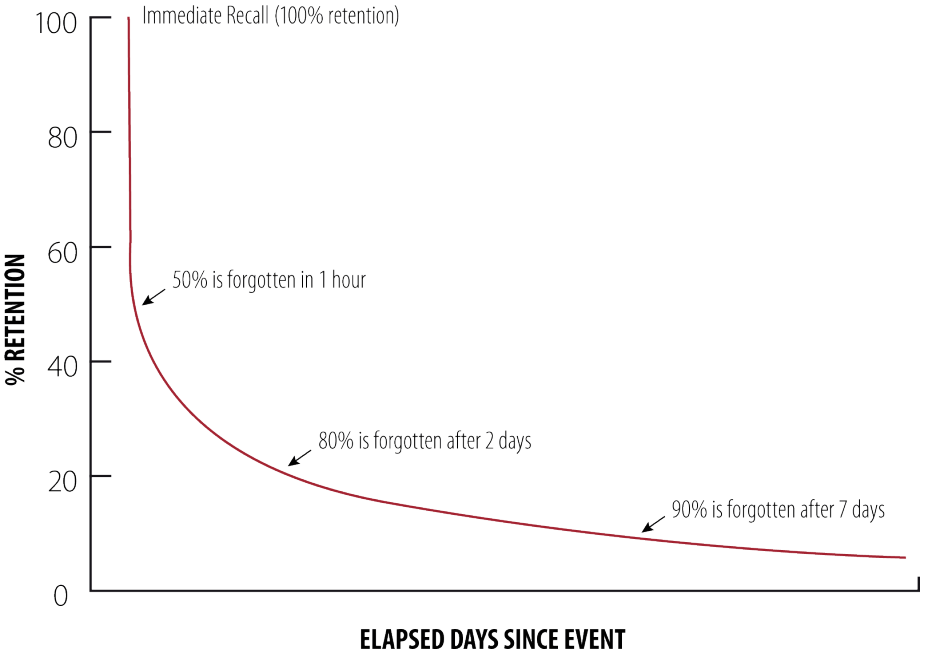

Figure 2: The forgetting curve theory.

Compounding this situation is the growing acceptance of telemedicine as a safe and convenient alternative to the traditional methods of care delivery, prompted by the COVID-19 pandemic. A national survey conducted in mid-March 2020 explored how Americans perceive telehealth in the new era of coronavirus and how it might impact their approach to telehealth in the future. Nearly 60% of respondents indicated that COVID-19 made them more likely to consider using telehealth services in the future. Yet more than 40% expressed concerns about the ability to get proper treatment or diagnosis in a virtual setting.[4]

IMPACT OF THE FORGETTING CURVE

A significant factor in the high percentage of device usage errors reported in the Noble study is the low rate at which patients retain information that their HCPs provide when prescribing self-injecting medications. Working against these patients is the forgetting curve theory that suggests retention and recall degrade over time without practise and repetition. This theory hypothesises that 50% of new information is forgotten within one hour, 80% is forgotten after two days and an astounding 90% is forgotten in a week (Figure 2).[5]

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

THE COST OF NON-ADHERENCE

In addition to the human cost of non-adherence on patient outcomes, there is also a significant business cost to the life science industry. Pharmaceutical companies lose US$637 billion (£518 billion) in revenue annually due to non-adherence to medications for the treatment of chronic conditions, according to a research paper co-authored with Capgemini and HealthPrize Technologies. Boosting adherence can provide unparalleled benefits to both patients and shareholders.[6] While the lost revenue is significant to pharmaceutical companies, it does not capture the full financial impact of non-adherence as it does not account for lost revenue to insurance companies and time and expenses incurred by HCPs.

HealthPrize Chief Executive Officer Tom Kottler called medication nonadherence the "final frontier", where pharmaceutical companies can simultaneously generate significant top- and bottom-line growth, improve outcomes and create substantial savings for the healthcare system. Mr Kottler added, "While pharmaceutical companies have historically focused on the physician as their customer, with the consumerisation of healthcare and a focus on bringing products to market to treat more complicated chronic conditions with smaller patient populations, more attention needs to be paid to patients and their behaviours that could improve outcomes and reduce health care expenses."

APPLYING DEVICE CONNECTIVITY TO TRAINING STANDARD OF CARE

Noble has long been an industry leader in the development of training devices and onboarding solutions for patients living with chronic illnesses who self-administer their drug therapies. The company manufactures autoinjectors, prefilled syringes and on-body, nasal and respiratory trainers that mimic the exact feel, force and function of true drug delivery devices.

These training devices take on even greater importance as in-home and self-managed care become more routine. Incorporating connectivity into the process can further improve adherence and confidence by:

1. Providing an augmented training experience with highly relevant and personalised content
2. Empowering the patient with interactive feedback to help guide them through the injection experience
3. Refining follow-up training and intervention based on user data.

Currently, Noble is in the early-stage development of a connected, intuitive and user-friendly training solution – called AdhereIT – for patients who self-inject using an autoinjector. It combines an autoinjecting drug delivery device with information technology to improve adherence and create a more engaging experience for patients who self-administer their prescribed therapeutic treatments.

AdhereIT is a reusable integrated device that pairs autoinjectors used by patients for at-home drug delivery to a software application via Bluetooth technology to provide immediate feedback about whether the injection was performed correctly. The training platform also allows HCPs to monitor their patients' therapeutic performance via a dashboard and provides biopharmaceutical companies with valuable non-patient-specific adherence behaviour information.

HOW THE NOBLE DEVICE WORKS

Patients face heightened anxiety during their first biologic injection and every time the next injection approaches.[7] AdhereIT allows patients to regain control of their therapy

regimen while easing the anxiety associated with self-injecting.

AdhereIT works with either an autoinjector training device or actual drug delivery device to detect the beginning and end of an injection session. Users place the AdhereIT device on the injection site and insert the autoinjector. Once the injection begins, the AdhereIT light will "breathe" green followed by two green bursts to signal that the injection is completed. AdhereIT will "breathe" red when a wet injection occurs, indicating that the user removed the autoinjector before the full dose was delivered (Figure 3).

Noble's design features clear, easy-to-understand visuals and haptic feedback, including:

- Real-time feedback to train users on correct self-injection
- Data that is stored and wirelessly sent to a mobile app
- A standalone design that does not need to be incorporated into the drug delivery system.

CONCLUSION

Training devices are critically important for the millions of patients across the globe who live with chronic illnesses. A standard of training must become part of the standard of care to create more confident, healthy – and ultimately, adherent – patients who self-administer their medications.

Connected drug delivery devices can support this standard of care and improve patient health outcomes by addressing the challenges of accuracy and non-adherence. This is a compelling value proposition for all stakeholders – patients, care providers, pharma companies and payers.

ABOUT THE COMPANY

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

Figure 3: Noble's AdhereIT 360 base with novel packaging.

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ABOUT THE AUTHOR

Erin Miller, Marketing Co-ordinator at Noble, an Aptar Pharma company, supports marketing and advertising efforts at Noble through copywriting and editing as well as content creation for Noble's print and digital communications platforms. She holds a bachelor's and master's degree in public relations.

A new way to connect with patients.

The AdhereIT® solution offers design flexibility to accommodate various autoinjector platforms. This allows for greater speed to market and lower development costs.

AdhereIT® enables brands to:

Track product usage to offer insights into patient behavior and better meet their needs.

Reduce costs by improving patient adherence, helping patients stay on therapy longer.

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Improve patient therapeutic experience through device features and app-based tools and resources.

ADHEREIT
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CONNECTED DEVICE DATA NEEDED TO MAKE HOME CARE THE STANDARD

With home care on the increase as a result of the coronavirus pandemic, Andrei Yosef, PhD, Chief Executive Officer of Sorrel Medical, looks at the crucial role played by connected home care medical devices and the data they generate.

The coronavirus pandemic has shocked healthcare systems around the world. The immediate task of finding appropriate short- and long-term solutions for COVID-19 has put the pharmaceutical and drug delivery industry in the spotlight as companies race to develop, test, approve and manufacture both treatments and vaccines. However, to paraphrase Churchill, a crisis should not be wasted. The pandemic presents an opportunity for drug developers, medical device manufacturers and regulators alike to reconsider how we treat patients and where care can be improved.

One silver lining that has emerged from the current situation has been the growing awareness of home care and its benefits. The seeds of this shift had been planted long ago with an increase in technology-enabled mobile health solutions. Last year even saw major tech companies like Apple begin to publicly explore the role they can play in patient-centric healthcare outside the hospital setting.

However, COVID-19 may prove to be a watershed moment for home care. It has forced hospitals and healthcare services to adopt new practices in favour of keeping patients at home – either because of the resource strain incurred from the pandemic or because immunocompromised patients risk too much by going to hospital. In doing so, it is helping patients grow accustomed to – and even prefer – remote health solutions and gives medical professionals access to the technology required to treat patients from afar.

The crisis has also given us a much better sense of where home care falls short. A doctor can listen to a parent describing a baby's symptoms but, without advanced connected devices, cannot check their ear to look for an infection from afar. They can give a patient a prescribed medicine but cannot track dosing and ensure adherence as they can in hospital. More complicated treatments such as chemotherapy are also problematic away from the watchful eyes of clinicians due to sensitivities in dosing and administration – and the harsh side effects of many of these treatments.

> "While the coronavirus pandemic has brought the need for home care to the fore, we must now overcome the opacity of the current home care reality."

Innovation addressing these and other gaps could help us reap the benefits that home care provides to patients while also reducing the burden on hospitals. The key to that innovation is connectivity that both produces and communicates data to healthcare professionals, allowing us to understand home care more thoroughly and with greater transparency than our current capabilities allow.

THE TROUBLE WITH HOME CARE DATA

A significant advantage to hospital care compared with current home care is in the data collection possible in a hospital environment. In a hospital, a doctor knows exactly how a patient's care is progressing. All details are recorded in an electronic health record (EHR), infusions are recorded by infusion systems – which are often integrated with the EHR – and machines are constantly monitoring vital signs. Hospitals, therefore, are perfect for data collection due to the controlled environment and the many assessments that patients undergo (Figure 1).

At home, the situation is markedly different. Patients are left on their own, or with the support of a family member, creating questions of adherence and accuracy in self-reporting. Even when the patient

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"With more data streaming from a patient's home to the hospital or pharmacy in real time, clinicians can more easily assess what the patient needs remotely – and intervene only when necessary."

is supported by a home care agency or a professional care giver, interoperability and reporting issues create gaps in the transition of data from the home to the hospital. For doctors, this becomes a treatment challenge, and for healthcare systems it slows the transition to home care environments.

As such, patients remain in the hospital for extended periods due to the need for continuous monitoring of treatment – or move to less-than-ideal home care settings, in which clinicians are often left in the dark regarding the patient's status and compliance with treatment. While the coronavirus pandemic has brought the need for home care to the fore, we must now overcome the opacity of the current home care reality.

Figure 1: Hospitals are ideal for gathering and analysing real-time patient data for clinical decision support.

CONNECTED DEVICES ARE KEY

Point-of-care EHRs serve as a positive example of what can be done with increased data. A 2014 study[1] showed that the implementation of point-of-care EHRs helped to decrease the number of days to make Medicare claims, and increased clinician productivity. Furthermore, it helped clinicians "in their provision of home care and communication among team members". The point-of-care EHRs were able to collect and organise data that were consistently being produced in a way that allowed for it to become actionable.

That model can be used for other aspects of home care. For instance, home infusion is currently wandering a data desert. Most studies on home infusion are retroactive and rely on patient self-reporting. It is therefore very difficult to design new home-infusion products that truly meet patient needs (Figure 2).

With more data, key questions that drive innovation could be addressed. These include rates of adherence for infusion solutions; whether demographic factors such as age influence patient adherence; whether types of devices or drugs affect adherence; and whether caregiver or family involvement increases adherence.

Figure 2: Connecting home infusion can help garner the data needed for improved home care focused technology innovation.

HOME CARE DATA ACCESS AND IMPLICATIONS

Garnering the data on the above-mentioned parameters can impact how willing insurance companies are to support home care, the design of new drug delivery devices and which patients can be sent home for treatment. The accumulated data we amass over time could help determine whether a patient should go home for chemotherapy treatment or whether they should remain in hospital where, on one hand, they can be kept under closer supervision but, on the other, they are at greater risk of hospital-related complications.

Beyond innovation, increased data can streamline home care standard operating procedures. As we move to a greater reliance on outpatient care, we simultaneously create an increased need for house calls to deal with various patient safety situations that may come up over the course of treatment. These calls are expensive and time consuming. With more data streaming from a patient's home to the hospital or pharmacy in real time, clinicians can more easily assess what the patient needs remotely – and intervene only when necessary.

Substantial gaps in our knowledge of home care have real policy implications as well. Many governmental analyses are based on studies that only look at narrow aspects of home care and fail to account for private households.[2] Consequently, legislators are left in the dark as to how best to support home care. This has also meant that more recent home care reimbursement policies from the Centers for Medicare & Medicaid Services have fallen short of industry expectations – and infusion industry organisations and their related patient advocacy groups are pushing for governmental bodies to revisit these policies. By collecting data on compliance and patient outcomes, we can also better support legislators in developing policies that adequately meet the needs of both providers and patients.

THE PATH FORWARD

Fortunately, we do not need to invent new technology to begin addressing home care challenges. To develop better medical solutions that serve patients in the home, we simply need to connect existing devices to the Internet of Medical Things. With an increased data flow, we can understand key aspects of patient behaviour in ways that were previously impossible. This connection does not need to be incorporated into existing EHRs, which already face challenges of interoperability. If application programming interfaces are open, different types of analyses and integrations with existing medical data can be achieved.

"By collecting data on compliance and patient outcomes, we can also better support legislators in developing policies that adequately meet the needs of both providers and patients."

After accumulating data over time, today's connected devices can be further customised to address the different patient challenges that will be discovered. Materials can be developed for patient groups that need specialised training for certain treatments – and doctors can have a better sense of who should be sent home and who needs to stay in hospital. It would open up new possibilities for home care, with all its associated benefits.

CONCLUSION

The global pandemic has put the concept of home care on the minds of not only the medical community but also many patients and non-medical professionals. This moment should be used to push for more data-focused home care solutions. By connecting our home care medical devices, we can improve patient outcomes, reduce hospital costs and help doctors focus on their most critical patients. The future of health is home care and the way we get there is through connected home care devices.

ABOUT THE COMPANY

Sorrel Medical is a medical device company focused on prefilled wearable injectors. Sorrel is one of three privately held companies operating under the Eitan Group, all in drug delivery devices, including Q Core Medical, Avoset Health and Sorrel Medical. The joint experience shared amongst Eitan Group's three companies includes commercialisation of drug delivery products across the continuum of care, multiple US FDA approvals, market presence in over 20 countries worldwide, and a team of R&D innovators that are experts in parenteral drug delivery.

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Andrei Yosef is Chief Executive Officer of Sorrel Medical, an Eitan Group company focused on the development and manufacture of wearable drug delivery solutions for easy and efficient self-administration. He is a leading expert in drug delivery device technology and high-end development processes, having served in several executive positions at Q Core Medical – a leading developer of smart infusion systems for hospital and ambulatory care settings. Dr Yosef holds a PhD in Biomedical Engineering and an MA in Mechanical Engineering, both from the Technion – Israel Institute of Technology.

SHL GROUP

DIGITAL HEALTH REFORMULATION: FROM HOPE TO HYPE TO HEALTH

In this article, Chelsea Williams, MPH, Healthcare Analyst; Ramin Rafiei, PhD, Director of Digital Healthcare; and Ralph Howald, MSc, MBA, Chief Technology Officer, all of SHL Medical, discuss the accelerating value of digital health to improve the patient experience, achieve improved health outcomes, and increase health system efficiency and value through the work at SHL.

It would be remiss to fail to acknowledge that over the past decade digital health has not led to mass disruption of how patient care is delivered. In an era where the smartphone will shortly turn 15 years old, and society has moved towards the expectation of on-demand delivery of services and access to all of humanity's knowledge in the palm of their hands, health technology adoption has, by and large, not moved along as fast as some would wish.[1]

We are in a transitory period where digital health is still being positioned within the healthcare landscape – and a myriad of road bumps are being encountered. There are well over 40,000 health and medical apps, yet there are no criteria for what constitutes "good" or "bad".[2,3] Telehealth has much potential to drive patient care but practitioners are slow to adopt and regulations are laborious. Sensors are being added to medical devices but we are still not seeing them applied well clinically.[4]

Finally, everyone gravitates towards artificial intelligence in healthcare, while the greater barrier – health information – still faces the difficulty of interoperability to gather and interpret. In many ways, the digital health story needs to change – and the time is upon us as the field meets maturity.[5]

"In many ways, the digital health story needs to change."

HOPE VERSUS HYPE

Looking back over the past decade's worth of keynotes, presentations and publications on digital health, it would be hard not to empathise with the hope of what digital health could have led to in patient care. The use of technology to lower barriers to access and improve health outcomes, all the while making care affordable, were all items championed for this digital revolution. Healthcare providers saw an opportunity to improve patient care, and the pharmaceutical industry saw novel opportunities to conduct clinical trials and expand clinical outcomes. Nonetheless, this hope arguably led to much hype that was misplaced by technology-focused newcomers to the health space with no experience or insight to succeed.

As an example, look at the story of Theranos, headed by a Stanford dropout. Once valued at US$10 billion (£7.9 billion), Theranos achieved national acclaim at the forefront of development for blood testing.[6] Its appeal – a highly usable product that could disrupt the blood-testing industry – was irresistable to many interested in the health space. But, in the end, the real utility of Theranos was non-existent, and it is probably one of the best examples of the hype of digital health technology that can grab global attention along with fast cash investments, yet fail to deliver.

Difficulties can be seen across the digital healthcare industry, where there is no shortage of companies over the past decade that pursued aggressive growth metrics then

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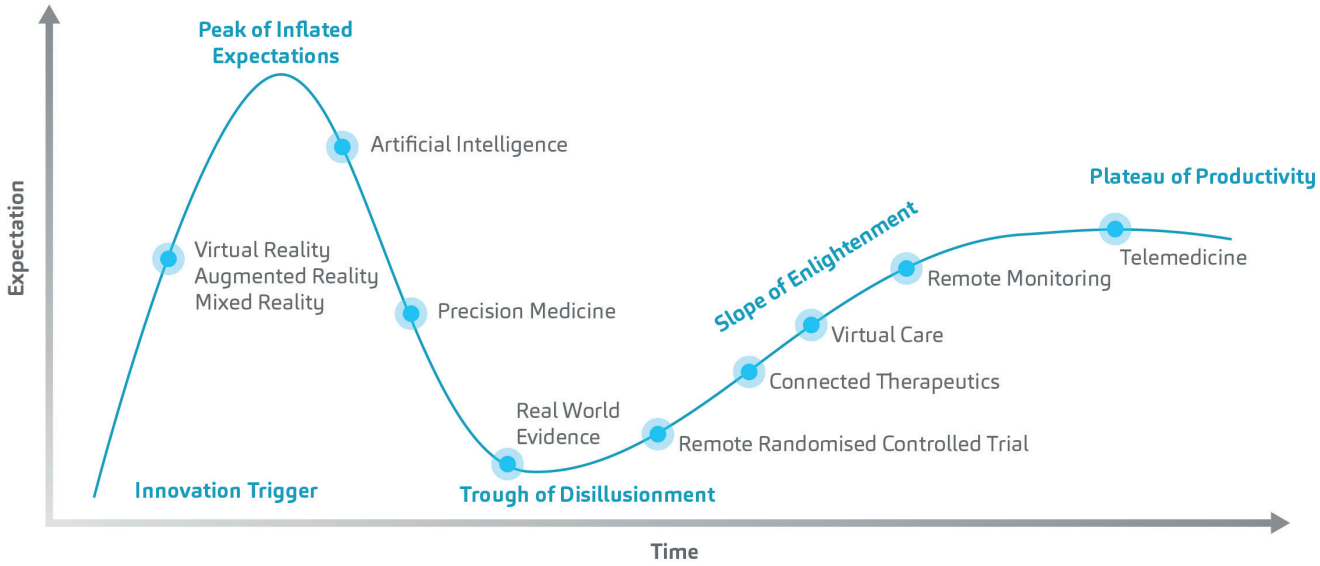

Figure 1: The digital health hype cycle, adopted from the Gartner Hype Cycle.

> "Merely creating a digital tool of yesterday's practice for tomorrow's care, and expecting uptake, is a fallacy."

collapsed, whether focused on a mobile app or novel sensor-based technology. The impact has been comparatively mute in the grand scheme of health, and it is still difficult to point to a mobile app and claim it meaningfully shifted how health is delivered.[7]

Undeniably, one of the most significant issues has been a focus on creating and providing a product that naïve founders expected patients and healthcare providers to flock towards. This "innovation without integration" is likely one of the most notable missteps in the digital health space, as many companies focused on disruption over integrating with current medical practice which, despite much hype, is more realistically a slower-paced environment of change.[8]

However, like other industries that have undergone digital transformation, health companies have matured with the realisation that digital health is here to stay but will need a thorough mindset and ideology to achieve it in practice.

TO DELIVER WITH DIGITAL HEALTH

A paradigm shift in how care is delivered does not occur overnight and, arguably, the practice of medicine is grounded in the realm of science, which expects the rigor of evidence-based decision making founded on well-constructed trials and data supporting best practice. Merely creating a digital tool of yesterday's practice for tomorrow's care, and expecting uptake, is a fallacy in thought. As such, a well-designed product needs to meet multiple criteria to escape the hype cycle of digital health (Figure 1) and yield actual health outcomes.

Digital health is transitioning the drug delivery industry towards connected therapeutics. Over the past three decades, SHL has set the foundation for the decentralisation of drug administration. Complex treatments have graduated from focusing solely on safety and efficacy to acknowledging the importance of patient convenience and adherence.

The parenteral drug delivery innovation curve (Figure 2), illustrates the evolution of drug delivery from a simple vial and syringe (A) to the convenience and safety of an autoinjector (B). The addition of sensors and connectivity now provides a digital representation of patient behaviours, by enabling dose-level data collection (C). Ultimately, innovation in drug delivery matures to connected therapeutics (D), which allows patients to self-manage their conditions as part of their integrated care plans – pairing health with technology.

This move from self-administration to self-management relies on patient activation, engagement and retention to ensure a successful transition towards a decentralised, continuous and proactive model of care delivery.

The ubiquity of connected drug delivery devices, as a precursor to connected therapeutics, will empower better behaviours and minimise care errors, as well as delivering timely clinical support. However, this will be an untenable goal without factoring in crucial concepts that have led to the hype cycle (Figure 1) which has plagued other companies competing in the digital health space. Instead, a focus on three pillars of thought – usability, usefulness and utility – is essential for the realisation of connected devices, and subsequently connected therapeutics.

HAVE USABILITY

A key aspect of product design is factoring in the usability of a product by the ultimate consumer. For instance, the initial rollout of the iPhone used skeuomorphism to help new users become accustomed to mobile apps as their go-to tools. Since this rollout, the growing convenience, responsiveness and hyper personalisation delivered by top technology brands and their integration into other industry sectors has created an expectation for digital health to deliver the same experience.

The inability to meet this expectation has rendered the majority of digital health programmes ineffective. Drugs don't work in patients who don't take them; similarly, digital health programmes don't work for patients who don't engage with them. Take, for example, the sheer number of wearables and mobile apps on the market, which sees a substantial dropout in use after just a few weeks of initiation. In one study looking at engagement with 93 popular mental health apps currently available, less than 10% of users were still retained after one month of downloading the app.[9] Finding the right design to get a patient engaged in digital tools is a science under development.

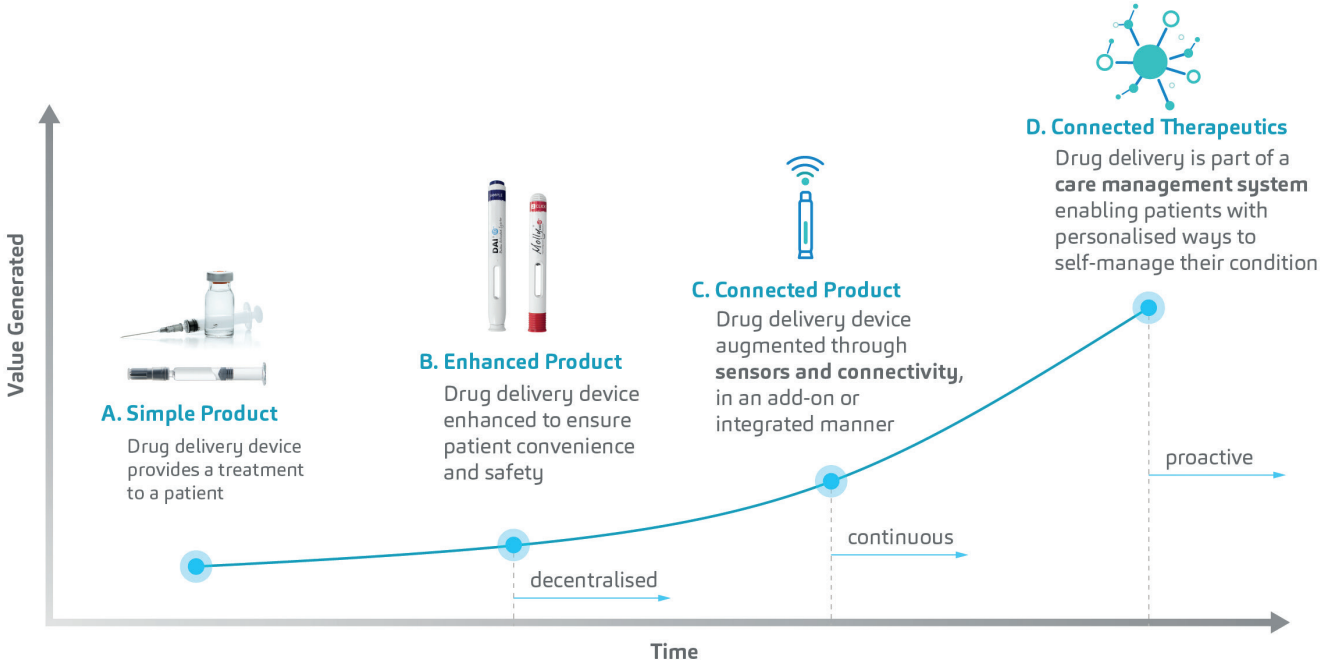

Figure 2: The parenteral drug delivery innovation curve.

The ubiquitous needle and syringe have been encapsulated by the autoinjector market as a viable means to be a more natural fit for medication administration. But the creation of such a product takes effort, patient-centric design studies, human factors design and continuous feedback. As the drug delivery industry transitions towards connected therapeutics, the same experience will be required to consider these aspects and design products that succeed. Simply adding Bluetooth-enabled sensors to a product will not yield a product of worth if users cannot put it to use.

Therefore, taking into consideration how a patient uses the product – such as setting it up, interpreting their own data (e.g., adherence, routes, timing) – will be tantamount to increasing user engagement in their own personal health. In many ways, the usability of a product can lead to a personalised level of care that can be leveraged by pharma and healthcare providers to drive the outcome change needed at this time. Lessons learned by a company to create safe, engaging, convenient and autonomous devices will be a knowledge base for digital health development.[10,11] Nonetheless, a usable product means nothing if it is not useful.

BE USEFUL

Deriving the usefulness of a product is perhaps one of the most notable weaknesses of early digital health products. We have seen multiple iterations where an Internet of Things (IoT) strategy was used to upgrade a conventional health device into a digital health product. These include wearable devices that are merely an updated pedometer or blood pressure cuff capable of collecting vital information in the patient's home – or even smart pill bottles that can subjectively track adherence and yet did not change patient outcomes.

Several trials that hypothesised the use of digital tools would yield significant patient outcomes such as reduced hospitalisations, meeting target goals and increasing patient safety, failed to demonstrate their clinical endpoints. The BEAT-HF study evaluated the impact of remote patient monitoring (RPM) in reducing rehospitalisation amongst patients recently discharged with an acute heart failure exacerbation.[12] More than 1,400 participants were evaluated for 180 days, using Bluetooth-enabled devices to track relevant patient data – yet rehospitalisation rates saw no statistical difference with the intervention compared with standard care.

Similar results can be found in other RPM studies looking at apps and devices to manage blood pressure in that they have also failed to meet their clinical outcomes.[13,14] Perhaps even more tragic is that, in an analysis of 280 diabetes apps for self-management, only 11 apps were found to have data supporting clinical value – and, of those, only five demonstrated a significant impact on HbA1c (glycated haemoglobin).[3]

Possible reasons may stem from a lack of judicious use of this novel technology as we continuously learn how best to enrol and have patients use the devices, and for health practitioners to then direct therapeutic care with real-time data acquisition. After all, this is a change in medical practice where digital health takes us from intermittent data collection towards real-time care. Patients are consumers; hence adaption does not occur overnight and the industry is bound to see multiple failures.

> "Companies that have invested significant resources into understanding clinical workflows, patient adherence characteristics and behavioural interventions to maximise their impact will have a higher likelihood of succeeding in this evolving market."

The nature of science, and the medical literature as a whole, benefits from these failures as it helps educate organisations about what to improve upon.[15] Companies that have invested significant resources into understanding clinical workflows, patient adherence characteristics and behavioural interventions to maximise their impact will have a higher likelihood of succeeding in this evolving market.

We are now seeing this maturation built upon, as different stakeholders – such as medical practitioners and pharma – are finally taking note. The American Medical Association, for example, has created a digital health group focused on helping physicians use novel tools to adopt clinical care for the next decade. This includes topics such as remote patient monitoring and telemedicine, which were increasingly needed as a result of the COVID-19 pandemic that has swept the world this year.

Indeed, the pandemic will perhaps go on to be one of the largest game changers in the digital health industry, as healthcare providers turn to remote patient monitoring and communication to treat patients, while pharma learns to adapt to an environment it never had to face.[16,17] For years, the topic of remote patient trials has seen much discussion, with few companies going beyond pilots or small feasibility trials.[18,19] The current limitations in logistics, with patients social distancing, will increase the need for digital health technologies in clinical trial design and will need to be stress tested.

Consequently, companies that offer novel solutions and technology may serve as apt partners for pharma to consider.[20] Companies will need to be prepared to pivot to this sudden need and cultural shift due to sweeping changes occurring across the world as patient care delivery changes.

FIND UTILITY

Utility is healthcare economics. Demonstrating the utility of a product and service will be the final pillar to see digital health completely gain acceptance in the market. Whether this includes a push for value-based care using digital health tools, whereby healthcare providers view such devices and software as a means to maximise patient outcomes, or payers see digital health as a data-driven resource to improve their covered populations, remains to be seen.[21]

Providers of healthcare services and payers do not always share the same perspective as patients. Accordingly, a digital health product that may be beneficial to a provider may not be something a patient finds useful (or even usable). Likewise, a digital health product that addresses a patient need may not find traction with a payer or provider, requiring the patient to pay out-of-pocket. Even if a product itself addresses usability and clinical evidence shows it is useful, if it doesn't find utility within the financial interests of all stakeholders, then adoption will be limited and even the most revolutionary technology will not realise its potential.

Digital health isn't going away any time soon. Using the Gartner Hype Cycle, as adapted to digital health (Figure 1),[22] we see that market demand for demonstration of utility squeezed out many early players – leaving only those companies with a longer-term vision and healthcare industry experience. We could view the past decade as the peak of inflated expectations, with the past few years as the trough of disillusionment and the 2020s as a period of enlightenment towards productivity.[23] This can be seen with market changes where over 60% of digital health companies pivot from business-to-consumer (B2C) to business-to-business (B2B) or B2B2C solutions, as they were developed in the vacuum of the tech sector, and applied a tech strategy which is not transferable to the idiosyncrasies of healthcare.[24]

Ultimately, companies and organisations are becoming aware of the need for evidence generation through randomised controlled trials (RCTs) and real-world evidence (RWE) to convince payers of the utility of their digital health products.[25,26] This calls for large resources and experience to accomplish what smaller organisations cannot accomplish alone.[27] Research and development spending for creation of new products,[28,29] and research to discover novel digital biomarkers, guide clinical care.[30,31]

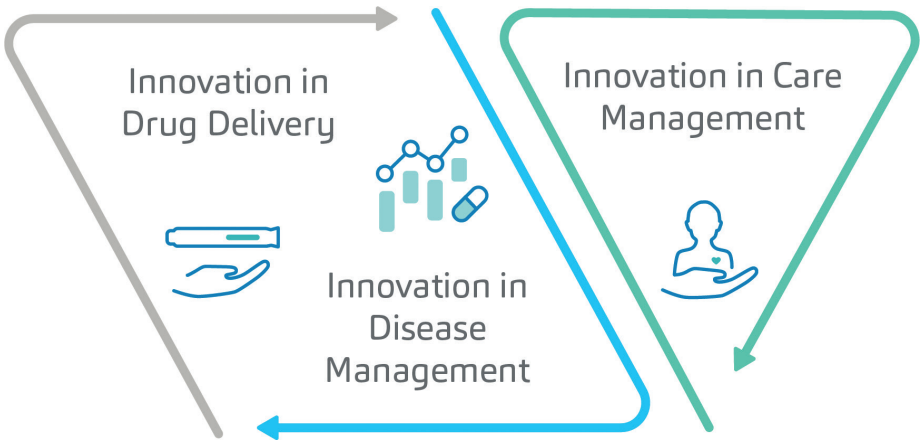

Figure 3: Digital health innovation at SHL encompasses drug delivery, disease management and care management.

However, commercialisation can only be achieved once these most basic hurdles are crossed and become data driven. Ultimately, this will incentivise healthcare providers and pharma to integrate such digital health products into their patient care management and disease treatment solutions in ways that we could never do in the past.[32-34] It may also spur novel developments in relationships between pharma and payers, such as performance-based, risk-sharing agreements based on collected data.[35] This is reinforced with a growing focus on developing digital health formularies for health systems and payers to adopt, with clinical evidence and usability data key for inclusion.[36]

REFORMULATING DIGITAL HEALTH

The term digital healthcare will become synonymous with healthcare in the future, and current terminology will be relegated as a marker to this transitory period of healthcare evolution.[37] Nonetheless, this will be an uphill battle that will play to first-mover advantage for those that take on the risk of innovation.[38] Pharma has yet to achieve its "beyond the pill" moment but the current *status quo* should not dissuade it from trying. Instead, key partnerships will be essential for bringing digital health to fruition.

At SHL Medical we are accelerating the evolution of drug delivery from a focus on patient self-administration towards a holistic patient-centered self-management paradigm across a spectrum of chronic diseases and conditions (Figure 3).

In transforming our patient-centric drug delivery devices to life-centric therapeutic solutions, we have shifted focus to the whole patient-journey by combining innovation in drug delivery with innovation in disease management. This will ensure we meet the disease management needs of our pharmaceutical partners, through new means to track and utilise the data that was previously not available in the injectables market. Innovation in disease management will lead to innovation in care management as patients become more informed, empowered and engaged with their treatment. Anticipating this demand, our care management solutions are currently undergoing validation within a randomised, controlled trial setting, focusing on the patient's individual needs, and creating personalised and tailored care pathways that can be delivered continuously and remotely.

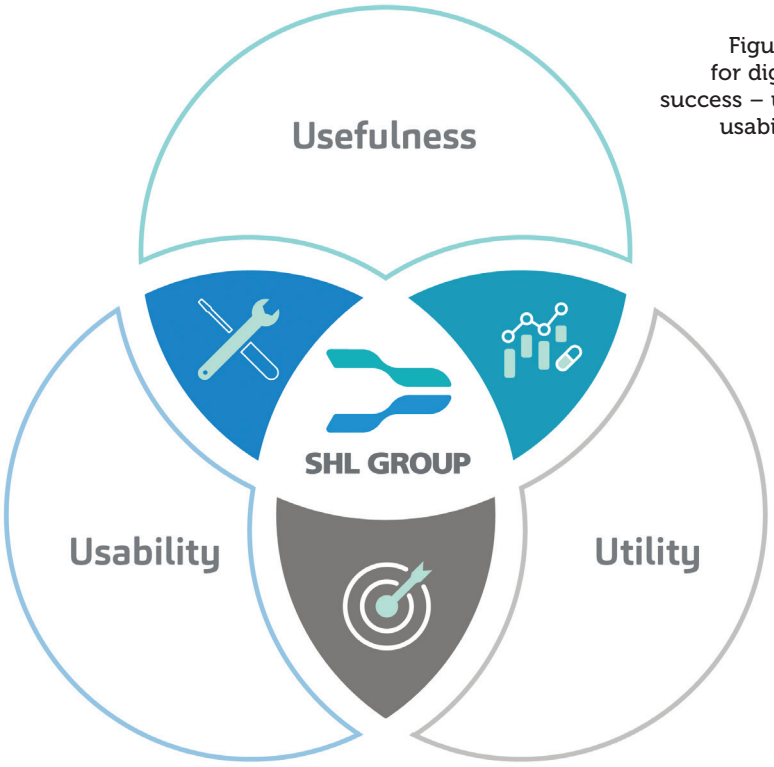

Figure 4: Goals for digital health success – usefulness, usability, utility.

Our passion and work in ensuring that our products are usable and useful – and can be utilised across the healthcare industry – is a formula for digital health success (Figure 4). As we scale our digital health investments this decade, and expand our partnerships, we will continue to capitalise on an innovation culture which has brought three decades of industry-shaping leadership. This next decade of digital healthcare innovation towards connected therapeutics is well and truly underway.

"Our passion and work in ensuring that our products are usable and useful – and can be utilised across the healthcare industry – is a formula for digital health success. As we scale our digital health investments this decade, and expand our partnerships, we will continue to capitalise on an innovation culture which has brought three decades of industry-shaping leadership."

ABOUT THE COMPANY

SHL Medical is a world-leading solution provider in the design, development, and manufacturing of advanced delivery devices such as autoinjectors, pen injectors, and advanced inhaler systems. With locations in Taiwan, Switzerland, Sweden, China, and the US, our experienced engineers and designers develop product enhancements as well as breakthrough drug delivery and patient care solutions for pharma and biotech clients globally. Significant investment in R&D has enhanced our broad pipeline of next-generation drug delivery systems that support ongoing innovations in drug development and digital healthcare. This includes advanced reusable and disposable injectors that can accommodate high volume and high viscosities and can be enhanced through digital implementations.

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Chelsea Williams, MPH, is a Healthcare Analyst at SHL Medical, focusing on digital healthcare innovation and healthcare service delivery. Her passion for promoting public health initiatives through interactive research, educational outreach and policy development helps guide the digital health strategy for SHL Medical. She brings nearly a decade of experience in healthcare technology services, from both health IT and government contracting industries. Ms Williams gained a Master's degree in global health program design, monitoring and evaluation from The George Washington University (US).

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Ralph Howald, MSc, MBA, is the Chief Technology Officer at SHL Medical, overseeing the global technical organisation across three continents, covering the entire product creation process within the company and leading the strategic product pipeline development. Mr Howald has more than 20 years' experience in the medical device industry, with a track record of leading technical and commercial organisations into new markets and segments. He holds a Master's degree in mechanical engineering from The Swiss Federal Institute of Technology (Zurich, Switzerland) and an Executive MBA from the University of St Gallen (Switzerland).

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EPIWATCH: A NOVEL LIFE-SAVING MICRO AUTOINJECTOR IN A SMART WATCH

Here, Amber Witteman, Managing Director, Thijs Roebers, Chief Executive Officer, and Dirk-Jan Opstelten, PhD, Chief Scientific Officer, all of EpiWatch, introduce the company's patented innovation, a wearable autoinjector customised to fit the wrist.

EPIWatch (Figure 1) is a small, wearable proprietary autoinjector that can make a big difference in the daily lives of patients with a life-threatening allergy. EPIWatch offers a novel way to self-inject and tackles some of the big problems of traditional autoinjection devices. The company's goal is to serve the market with this complementary product to provide comfort, allay fears and save lives.

WHY IS EPIWATCH NOVEL?

EPIWatch is the first wearable autoinjector customised to fit the wrist. EPIWatch can inject a drug intramuscularly, subcutaneously, or intradermally, while the device is in a wearable state.

The current focus is on the development of the EPIWatch for intramuscular injection applications. It is designed to be discreetly worn on the wrist. EPIWatch is in direct contact with the patient's skin 24/7 allowing future sensor technology to collect individual data from the patient's skin through healthcare apps. AI data analytics preventative warnings signals could possibly be generated to alert patients.

The patient does not need to release the watch from the wrist to inject the medication. This makes the injection position stable and safer to use, and it involves fewer user steps than many other devices. The time saving advantage is extremely important when every second counts, in the case of an acute allergic reaction.

EPIWatch injects in just one direction, warns the patient by a flickering red led light when the drug is expiring and when the patient needs to replace EPIWatch. EPIWatch also has an "assistance button" that, once activated, helps the patient through a stressful emergency situation by a voice guide so the patient can feel more secure about how to administer the drug.

HOW IS IT USED?

The patient places the EPIWatch, still in place as worn on their wrist, onto their upper thigh to inject. This position gives the patient a very steady grip, without having

> "By definition, an emergency is not expected, and that is the key – to have your life-saving drug always at hand. The one accessory you always have at hand, even while you sleep, is a bracelet or watch."

Figure 1: EPIWatch is a wearable autoinjector customised to fit the wrist, which can inject intramuscularly, subcutaneously, or intradermally, while the device is in a wearable state.

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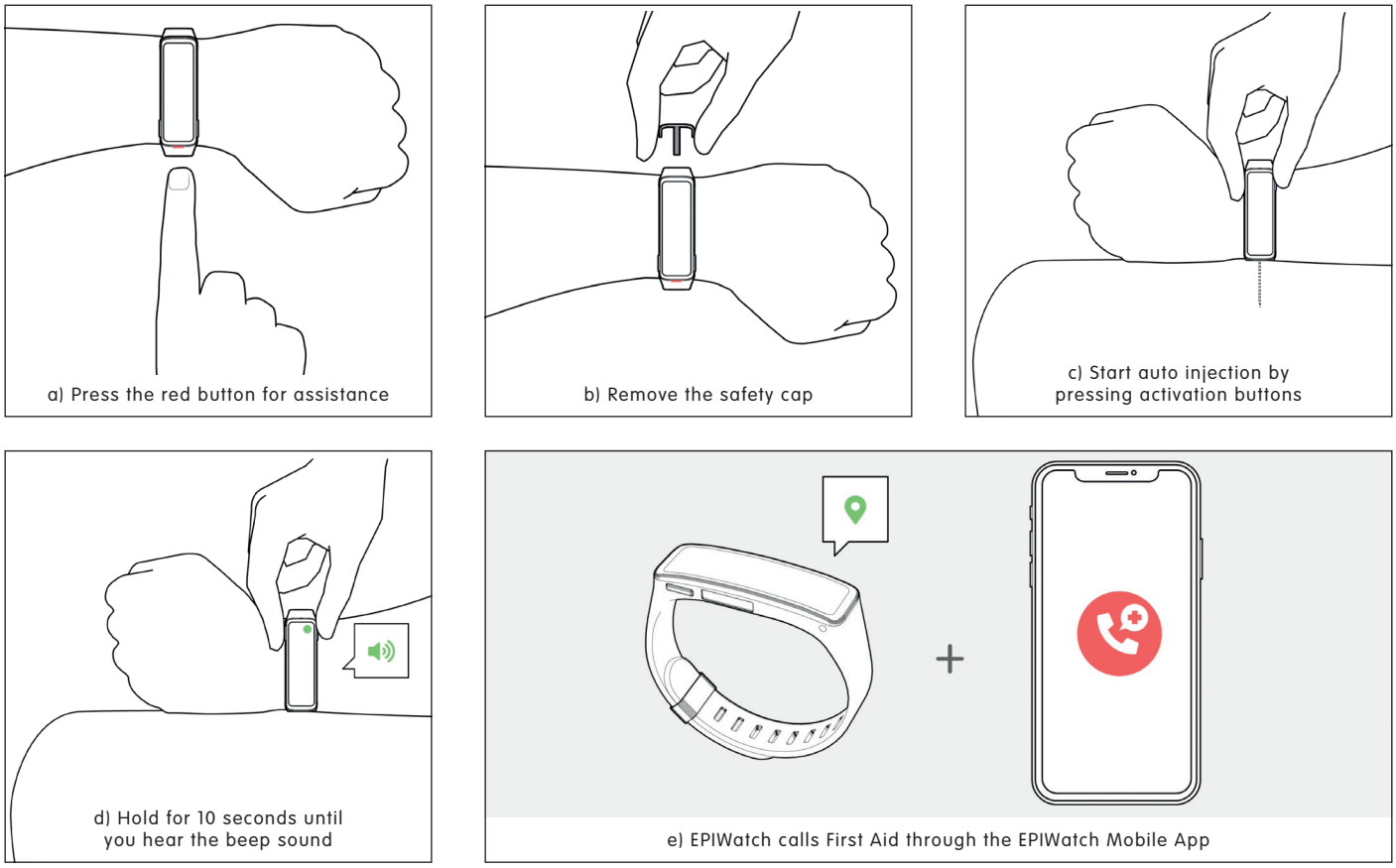

Figure 2: EPIWatch main use steps.

to see a needle. The patient is assisted throughout the process by the voice guide.

The uniqueness lies in the fact that EPIWatch is an injectable in a wearable state and thereby we reduced the user steps to the minimum, which is time saving when seconds and minutes count. The device cannot easily be forgotten, and the drug cannot expire unnoticed. User steps are summarised in Figure 2.

ABOUT THE AUTHORS

Amber Wittman, Managing Director, EPIWatch, is an entrepreneur and inventor of the EPIWatch autoinjector. Ms Wittman is also responsible for the intellectual property landscape, device component developments and is continuously working on project prosperity.

Thijs Roebers, Chief Executive Officer, EPIWatch, is an experienced entrepreneur supporting start-ups that translate innovative technology into viable commercial products. He has gained extensive knowhow in setting up two medical device startups, as Chief Executive Officer and Chief Operating Officer. At EPIWatch he is responsible for writing the business plan, financials, technical development and leading the subsequent market introduction.

Dirk-Jan Opstelten, PhD, Chief Scientific Officer, EPIWatch, is an independent life science consultant whose goal is to support the development and medical application of EPIWatch. With >20 years of experience in the pharmaceutical/biotech industry, he has developed leadership skills to manage complex R&D projects. His professional background, experience and achievements include: R&D management at HAL Allergy (Leiden, the Netherlands) as Chief Scientific Officer, and project management at J&J subsidiary Crucell (Leiden, the Netherlands) as Project Director, Biologicals. Under his leadership two new pharmaceutical allergy products were granted regulatory approval in 2018, and a new immunotherapeutic drug for peanut allergy was brought from research into clinical development under a US FDA-approved IND application. Dr Opstelten holds a PhD from Utrecht University (the Netherlands).

WHO IS EPIWATCH FOR?

EPIWatch is designed to be safely used by patients who might need an emergency or daily dose of a drug potentially to save their lives, or to alleviate symptoms, such as those associated with a severe allergic reaction.

These patients need to have their drugs at hand when an emergency situation arises. By definition, an emergency is not expected, and that is the key – to have a life-saving drug always at hand. The one accessory always at hand, even while sleep, is a bracelet or watch.

EPIWatch is thrilled to be turning this concept into a valid, working, intuitive device to meet the requirements to get it to market and meet patients' needs. The company is investigating CDMO opportunities and is excited that it will shortly announce its CDMO.

Watch a video introducing the EPIWatch here: https://youtu.be/0nwMqMB4rkE

ABOUT THE COMPANY

EPIWatch is a start-up company based in the Netherlands dedicated to creating viable solutions for patients who need immediate access to self-injected emergency medications.

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