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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.

EDITORIAL CALENDAR

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BIOCORP'S MALLYA – CHRONICLING A SUCCESS STORY

In this article, Arnaud Guillet, Vice-President Business Development at Biocorp, and colleagues from across the industry, discuss Bicorp's Mallya add-on device for disposable insulin pens, providing details on the main country launches and key software integrations, as well as presenting initial feedback from healthcare professionals and patients.

Diabetes is the most common chronic disease in the world, affecting over 460 million people. If left untreated, diabetes can lead to serious complications, which is why self-monitoring and regular disease management are so important.

In recent years, growing interest and research in the field of connected health have led to major advances in diabetes management. Innovations have taken place in the field of glucose monitoring, with the first connected blood glucose monitors (BGMs) and continuous glucose monitors (CGMs) reaching the market. At the same time, dozens of diabetes management software applications have appeared on the market, aiming to ease the daily life of patients.

There has also been innovation in the field of treatment management. The combination of CGMs, AI and connected insulin pumps has led to fully automated diabetes management systems. However, these "closed-loop systems" are only available to a limited number of users due to their high cost and many patients being reluctant to use such invasive solutions. Pen injectors are likely to remain the primary mode of insulin delivery for the foreseeable future, for most Type 1 (T1) diabetes and a huge majority of Type 2 (T2) diabetes.

With this in mind, major players in the diabetes space are looking into smart pen options to close the loop and complete their service offering. For instance, Medtronic (Dublin, Ireland), a leader in the insulin pump market, recently acquired Companion Medical (San Diego, CA, US) and its InPen™, a Bluetooth Low Energy (BLE) enabled reusable insulin injector, to expand their addressable market. Other smart reusable pen options, such as NovoNordisk's (Bagsværd, Denmark) NovoPen 6® and NovoPen Echo® Plus, have been launched this year in Europe.

However, most people with diabetes use disposable insulin pens rather than reusable ones. This is due to a variety of factors, including convenience, physician/patient awareness and preference. With the goal of simplifying life and improving the well-being of people with diabetes using disposable insulin pens, Biocorp saw an opportunity to answer an unmet need by developing and marketing Mallya (Figure 1).

Mallya automatically captures, reports and displays the insulin injection data, including the number of insulin units (IU) delivered, date and time, in a mobile application acting as a digital logbook. The device is accurate and compatible with major disposable insulin pens – Solostar

Figure 1: Mallya is a connected add-on device for disposable pen injectors.

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from Sanofi, KiwkPen from Eli Lilly and FlexPen from Novo Nordisk – and began commercialisation in November 2020. After a major partnership was signed with Sanofi for the global distribution of Mallya, Biocorp unveiled an additional distribution agreement in 2020 with Roche Diabetes Care for the French market. Mallya is already available in France, Romania, South Africa and Taiwan, and additional launches are planned for 2021, including Europe, Asia, the Middle East, Latin America and ultimately the United States.

Since Mallya has now reached the market and become a concrete experience for thousands of patients the world over, the authors would like to present the main initiatives engaged in more detail, and provide some initial feedback from end users. This review will begin with a specific focus on two of the main country launches in France and Taiwan through Biocorp's key partners, Roche Diabetes Care and Sanofi, then moving on to integration with software as a medical devices (SaMD) players that are adding valuable features to Mallya, such as basal insulin titration or a bolus calculator, and finally highlighting Mallya's benefits to end users through a patient testimonial and the feedback from a clinical study using Mallya devices.

MALLYA LAUNCH IN FRANCE WITH ROCHE DIABETES CARE

With Valérie Armani, Head of Marketing, Healthcare Development and Innovation at Roche Diabetes Care, France.

For more than 40 years, Roche Diabetes Care has been developing solutions to meet both the needs of patients with diabetes and healthcare professionals, with the goal of helping patients think less about the daily management of their disease. To this end, Roche Diabetes Care France has created an open ecosystem connecting devices, such as the company's Accu-Chek® glucometers, to digital solutions for patients and healthcare professionals. With the connection of Mallya to the Gluci-Chek companion app (Figure 2), patients have one more option to lighten the cognitive burden of their disease. Downloaded by more than 60,000 people, Gluci-Chek combines three major functionalities:

- A carbohydrate calculation tool
- A blood glucose self-monitoring diary
- A graphic visualisation of glycaemic results.

Once Mallya and Gluci-Chek are connected, patients no longer need to report their insulin doses manually; their blood glucose logbook collects and displays accurate data for them to rely on. Furthermore, when shared with them through the dedicated Roche Diabetes Care Platform, insulin data allow healthcare professionals to monitor the progress of their patients' disease, refine their interpretation and help adjust treatment decisions.

Figure 2: Biocorp's Mallya links with Roche Diabetes Care's Gluci-Chek app.

MALLYA LAUNCH IN TAIWAN WITH SANOFI AND HEALTH2SYNC

With Francois Barbé, Head of Integrated Care for the diabetes franchise at Sanofi, and Ed Deng, Co-Founder and CEO of Health2Sync.

The prevalence of diabetes in Taiwan has grown in line with the global trend; the most recently published data states that, in 2014, around 2.2 million people in a population of 23.4 million live with diabetes mellitus. While several treatment options have entered the Taiwanese market in the last decade, there is still a significant unmet need, with only 42% of these people having well-controlled blood sugar levels. Additionally, survey data published in 2019 states that, in 2014, the rate of insulin use in Taiwan was low (13%), with people with T2 diabetes starting injectable therapies on average between 10 and 12 years after their initial diagnosis.

> "Patients using the connected ecosystem can seamlessly track, synchronise and plan reminders for their insulin injections thanks to Mallya and the Health2Sync platform, which empowers them to manage their diabetes."

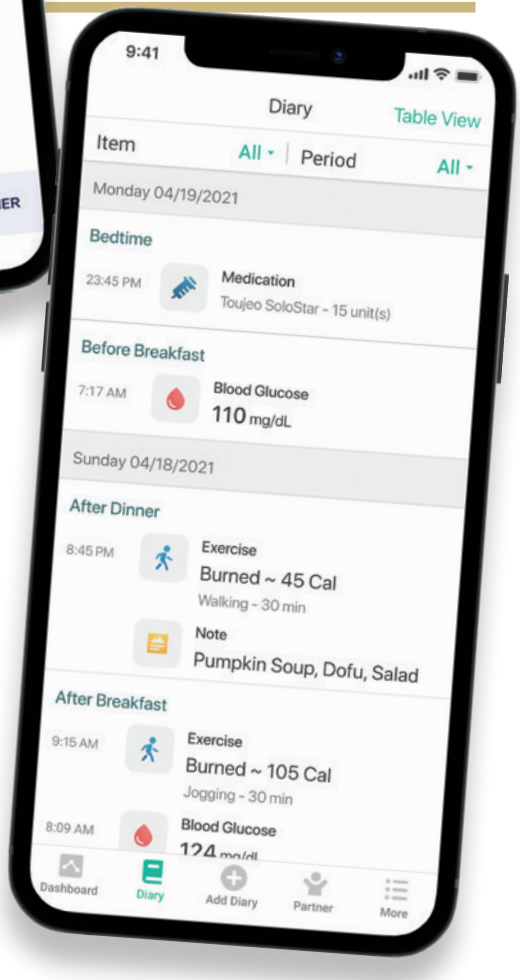

Figure 3: Combined, Sanofi's distribution network, Health2Sync's digital platform and Bicorp's Mallya device are able to provide a digital logbook for diabetes care.

Since 2007, the Taiwanese diabetes healthcare system has evolved towards promoting higher quality care. Healthcare organisations are now increasingly leveraging digital solutions to improve the quality of diabetes care, and the healthcare technology ecosystem is growing to further support both healthcare professionals and patients.

In this context, Sanofi, Health2Sync and Biocorp are realising their shared ambition to improve chronic disease management through a fully connected ecosystem for diabetes management in Taiwan. This connected ecosystem comprises Sanofi's insulin-based treatment options and strong distribution network, Health2Sync's digital healthcare platform that enables connectivity with various sources of patient data, and Biocorp's Mallya connected insulin pen cap, which is provided to patients to track their insulin injections (Figure 3).

Patients using the connected ecosystem can seamlessly track, synchronise and plan reminders for their insulin injections thanks to Mallya and the Health2Sync platform, which empowers them to manage their diabetes. Healthcare providers are given access to real-time insulin injection data alongside other patient-tracked behavioural data through the patient management platform, providing a new layer of information on adherence to insulin treatment and helping to optimise the clinical decision-making process.

Prior to launch of the connected ecosystem for diabetes in Taiwan, Sanofi and Health2Sync worked hand-in-hand to accelerate digital adoption and transformation in clinics and hospitals. Since late 2020, more than 150 Taiwanese clinics have joined the programme, with over 20,000 patients recruited on the Health2Sync platform. Sanofi initiated distribution of Mallya across Taiwanese clinics and hospitals in May 2021.

Other integrations or technology partnerships signed with SocialDiabetes, Amalgam Rx and Diabeloop have opened a new high potential international market and enabled rapid adoption of Mallya.

INTEGRATION WITH AMALGAM RX'S ISAGE PLATFORM

With Ryan Sysko, CEO of Amalgam Rx.

Amalgam Rx is a leader in bringing providers, life sciences and digital solutions together. For more than 15 years, the company's team has been reimagining care delivery and creating lasting change across the chronic care ecosystem. Working in partnership with many of the world's leading life sciences companies and healthcare systems, Amalgam Rx has built an innovative platform for rapidly developing and scaling digital solutions. iSage, Amalgam Rx's flagship product, was the first US FDA-approved insulin titration application that supports all basal insulins. iSage will soon have additional regulatory clearance and be deployed on four continents. Amalgam Rx shared findings from its first clinical trial of iSage during the poster presentations at the American Diabetes Association's (Arlington, VA, US) 79th Scientific Sessions. The results of the study showed that patients can benefit from the use of automated insulin optimisation support. The outcomes included the following:

- On average, patients in the treatment arm reduced their A1C by 1.04% (p=0.002) from baseline by study termination.
- Patients with a beginning A1C of greater than 8% reduced their A1C by 1.88% (p=0.005) from baseline by study termination.
- The average starting and app-directed final doses of insulin increased by 39% (p=0.047), with less than 2% of the fasting glucose readings recorded in iSage below 70 mg/dL.

Pairing iSage and Mallya simplifies insulin dose capture for patients with diabetes. The combined solution creates an easy and accurate way for patients to record their basal insulin intake while receiving automated guidance on how to adjust their dose over time. This simplifies the often complex and confusing journey for T2 diabetics starting on basal insulin and, to date, offers the most powerful environment for diabetes digitalisation and patient support.

INTEGRATION WITH SOCIALDIABETES

With María Jesús Salido, Co-Founder and CEO of SocialDiabetes.

SocialDiabetes is a complete digital health platform with a mobile app and a medical dashboard that connects physicians with patients, in real time, to optimise outcomes through smart connectivity and data insight. In detail, the platform developed by SocialDiabetes (CE marked and FDA 510(k) cleared) allows self-monitoring of insulin doses and offers personalised recommendations to patients. The collected data feeds a telemedicine platform using augmented intelligence for physicians and specialised call centres.

"The association between the SocialDiabetes bolus advisor, which provides insulin recommendations to patients before each meal, and Mallya is particularly powerful for patients whose therapy requires multiple daily insulin injections."

Patients using the combined solution are able to automatically synchronise the data recorded by Mallya, thus benefiting from the complete monitoring offered by combining glycaemic data analysis and insulin dose feedback. The association between the SocialDiabetes bolus advisor, which provides insulin recommendations to patients before each meal, and Mallya is particularly powerful for patients whose therapy requires multiple daily insulin injections. The information collected is transmitted to healthcare providers to give them a complete overview of their patients' status and compliance with their treatment plans. This improves the quality of dialogue between the healthcare provider and their patients, enabling adjustments of treatment plans and personalised recommendations.

SocialDiabetes is a leader in digital management of diabetes in Spanish-speaking markets. The company, headquartered in Barcelona and with offices in London and Ciudad de Mexico, serves 300,000 patients and more than 20,000 physicians. The company's alliance with Biocorp represents a new integrated care ecosystem for delivering an effective, consistent and meaningful response to the global diabetes challenge.

END USERS AS THE ULTIMATE JUDGES

All these efforts to build the relevant service offering and ecosystems are in pursuit of the same goal: delivering a solution that simplifies diabetes management for patients and brings greater comfort and serenity, and helps doctors better monitor their patients and adjust their recommendations based on objective data. Therefore, it is important to conclude this article by presenting some feedback from healthcare professionals and patients (Box 1) who have used Mallya for the past few months.

BOX 1: MALLYA USER TESTIMONIAL – "MALLYA ALLOWS ME TO BE SERENE"

"I have been a Type 1 diabetes patient for several years now. I was contacted by Biocorp last year to preview Mallya. The simple and elegant design immediately appealed to me. I appreciated the technology added to my insulin pen. Keeping a track of every injection is a real plus. It offers me a lot more peace of mind concerning my injections and allows me to keep better track of my insulin doses, especially when I am not thinking straight.

"On top of that, this device is easy to use, useful and very fun. The application to which Mallya is linked is clear and intuitive. You do not need to be computer literate to use it. From the first time I used it, I was completely convinced by Mallya and, today, I trust it to monitor my treatment. This smart device allows me to be serene and to better live with my diabetes."

Clinical Study Using Mallya at Croydon University Hospital

With Edward Holloway, MD, Clinical Lead for the paediatric diabetes service at Croydon University Hospital, UK.

The paediatric diabetes services at Croydon University Hospital, UK, has a cohort of 150 patients. The demographics include a high percentage of non-white ethnic groups (55%) and patients from the lowest quintile of the index of social deprivation (23%). The percentage of patients with very high A1C (>80 mmol/mol) is also very high (24% in 2020).

This group of patients are at the highest risk of experiencing serious complications from their diabetes and requiring emergency hospital admission. Therefore, they need greatest attention from clinicians working in the field. Over recent years, technological improvements in diabetes care, such as pump therapy and CGMs tend to see greatest uptake by those with the best diabetes control and are shunned by the cohort of patients with very high A1C who stand to gain the most.

The reasons for persistent high A1C are complex and multifactorial. However, missed doses, underdosing and overdosing with insulin are much more common in this demographic, and it can be very hard for clinical teams to have a productive discussion about these issues with patients, as monitoring focuses on glucose control with very little in the way of options for data collection on insulin administration with non-pump users.

The hospital ran a pilot study using Mallya devices from December 2019, however it was cut short by the covid-19 pandemic. Few patients with very poor diabetes control (including those with A1C levels as high as 130 mmol/mol) confirmed an important role for Mallya devices in informing the clinical team about the true insulin usage and allowing for a more open

discussion to explore the themes behind missed/inappropriate dosing of insulin. As such, Mallya offers an exciting insight into the real-world use of insulin in adolescents with very high A1C, and has been incorporated into the hospital's "high A1C pathway" as a novel tool to help guide these patients towards improved diabetes care.

CONCLUSION

This large-scale launch is an exciting moment for Biocorp. Initial feedback from the daily use of Mallya by patients all over the world is very promising and strongly reinforces the company's confidence in the usefulness and reliability of the platform.

In parallel to this intense activity in the field of insulin, Mallya has already expanded into other therapeutic areas involving drug delivery through pen injectors, such as growth hormone deficiency and fertility. Although form factor, device requirements and treatment objectives slightly vary from one area to another, the core promise of the technology remains intact; to record the dialled dose with the highest level of accuracy, while minimising the usability impact for patients and implementation constraints for the healthcare industry.

Beyond simply monitoring injection, Mallya presents a means to offer reassurance and peace of mind to patients, providing them with evidence that they have properly injected their medication and giving them confidence that they are on the right track to achieve their treatment objectives, whether it's improving their quality of life, reaching optimal growth or becoming a parent.

Aiming to further improve patients' compliance and follow up, Biocorp continues to work on its medical device platforms, confirming its ambition to be a world leader in the market.

ABOUT THE COMPANY

Recognised for its expertise in the development and manufacture of medical devices and delivery systems, Biocorp has acquired a leading 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 diabetics. Available for sale from 2020, Mallya spearheads Biocorp's product portfolio of innovative connected solutions.

ABOUT THE AUTHORS

Arnaud Guillet is Vice-President, Business Development 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 he has additional past experience in the pharmaceutical industry with Sanofi and the insurance industry with AXA (Paris, France). He graduated from HEC Paris (France), a major European business school.

Ed Deng is the Co-Founder and Chief Executive Officer of Health2Sync. He helped found the company after witnessing many in his family battle diabetes and learning what works in managing diabetes. Mr Deng is also a partner of Verge Capital Management, the world's first seed-stage healthtech fund investing globally in solutions relevant to emerging health economies.

Ryan Sysko is the Chief Executive Officer of Amalgam Rx, and is a pioneer in the digital health industry. Mr Sysko is the founder of two successful digital health companies, Amalgam Rx and WellDoc. He has over 15 years' experience in digital therapeutics, with domain expertise from product development through commercialisation.

Valérie Armani is Head of Marketing, Healthcare Development and Innovation at Roche Diabetes Care, France. She oversees digital strategy, the development of new solutions and services for patients and healthcare professionals, as well as product and company promotion.

María Jesús Salido is the Co-Founder and Chief Executive Officer of SocialDiabetes. She has a wealth of experience in managing complex IT projects at large health organisations and providing consultancy services related to knowledge management, innovation processes and collaborative dynamics.

Francois Barbé is Head of Integrated Care for the diabetes franchise at Sanofi HK/TW MCO. He is responsible for the strategy and execution of integrated care programmes, notably the collaboration with Biocorp and Health2Sync in Taiwan.

Edward Holloway, MD, is Clinical Lead for the paediatric diabetes service at Croydon University Hospital, UK. He also co-chairs the paediatric diabetes network for London and the south-east coast, a regional network of over 20 hospitals working with young people with diabetes in the UK.

ON drugDELIVERY

2021/22 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
July 2021	Novel Oral Delivery Systems	DEADLINE PASSED
August	Industrialising Drug Delivery	Jul 15, 2021
September	Wearable Injectors	Aug 5, 2021
September/October	Drug Delivery & Environmental Sustainability	Aug 19, 2021
October	Prefilled Syringes & Injection Devices	Sep 9, 2021
November	Pulmonary & Nasal Drug Delivery	Oct 7, 2021
December	Connecting Drug Delivery	Nov 4, 2021
January 2022	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 9, 2021
February	Prefilled Syringes & Injection Devices	Jan 6, 2022
March	Ophthalmic Drug Delivery	Feb 3, 2022
April	Pulmonary & Nasal Drug Delivery	Mar 3, 2022
April/May	Drug Delivery & Environmental Sustainability	Mar 17, 2022
May	Delivering Injectables: Devices & Formulations	Apr 7, 2022
June	Connecting Drug Delivery	May 5, 2022

CYBERSECURITY AND CONNECTED DRUG DELIVERY – AN INTEGRATED RISK-BASED APPROACH

In this article, John Whitehouse, Senior Software Engineer, Rob Veasey, Senior Sector Manager, Medical and Scientific, and Shane Day, Electronics and Software Skills Leader, of DCA Design, discuss the value of integrating cybersecurity into a holistic, multidisciplinary approach to risk management for connected medical devices.

We are all becoming increasingly aware of concerns about the security of digital information impacting our lives. Most people routinely communicate online and, in the wake of covid-19, many of us now also extensively work, shop, bank and socialise in the digital space. This inexorable trend is revolutionising the way we live and is impacting the medical industry as both healthcare providers and device companies embrace digital technology as a means to improve patient outcomes and streamline service efficiency.

> "Reports by cybersecurity researchers have demonstrated the potential vulnerability of safety-critical devices, such as wireless-connected insulin pumps and pacemakers, to hacking, raising the genuinely sinister prospect of targeted, remote, life-endangering attacks on individuals."

Of course, electronically programmable medical devices have been around for decades; what is different now is the widespread integration of these devices with a patient's own electronic products and systems, such as mobile phones and home networks. This integration significantly increases the vulnerability of personal medical data to cyber-snooping and raises the very serious prospect that malicious attacks could be made that disrupt safe and effective operation of devices that are critical to the health and well-being of patients.

In 2017, the WannaCry ransomware attack affected hundreds of thousands of computers around the world. Whilst this attack was not specifically targeted at medical systems, it exposed the vulnerability of large, interconnected healthcare providers, such as the UK's NHS. The attack resulted in the cancellation of thousands of appointments and operations within the NHS. It was also reported that some staff had to revert to pen and paper and the use of private mobile phones, as centralised IT systems had become completely disrupted. Perhaps even more alarmingly, reports by cybersecurity researchers have demonstrated the potential vulnerability of safety-critical devices, such as wireless-connected insulin pumps and pacemakers, to hacking,[1]

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> "The device developer should aim to generate a comprehensive list of cybersecurity risks that require consideration and mitigation during the development of the detailed design for the device."

raising the genuinely sinister prospect of targeted, remote, life-endangering attacks on individuals.

Whether inadvertently or deliberately, it is clear that cyber-attacks have the potential to inflict serious harm on patients. In response, regulators expect that cybersecurity vulnerabilities are adequately identified and addressed by developers and manufacturers of all electronically programmable medical devices.

WHAT NEEDS TO BE PROTECTED?

When determining how to protect the cybersecurity of a medical device, the first step is to understand the data assets that the device manages. Data records, especially sensitive patient data, need protection from snooping and manipulation for both privacy and safety reasons. Additionally, the software running on the device may be a key intellectual property asset that needs to be protected from theft or tampering.

As a second step, one needs to consider the environment in which the device will be used. For example:

- Will the device be connected to the internet?
- Does sensitive data need to be transferred to, as well as from, the device?
- Does the device need to be operating at all times?
- Will the device be used in public or private spaces?

The answers to these questions will help to inform decisions on the most appropriate type of communications technology for the device, such as Bluetooth, near-field communication (NFC) or cellular, which in turn enables the developer to explore potential system risks and vulnerabilities.

Consider a hypothetical scenario, wherein a new drug delivery device is being designed with connectivity features to support a patient in tracking their medication and to enable live monitoring by clinicians (Figure 1). In this scenario, a patient interacts with their device using an app on their smartphone via a short-range, personal area network (e.g. Bluetooth Low Energy), which allows the patient to read a log of their dose history. Additionally, the device has an internet connection that allows data to be uploaded to a cloud-hosted database server. The patient's clinician can access the data from the database for remote patient monitoring. The device also includes a wired access port for device maintenance and diagnostics by the manufacturer.

An initial cybersecurity assessment identifies that there are a number of possible points of interest for a potential attacker. Data records, including the details of a patient's medication history and any sensitive personal data, could be of interest to an attacker looking to profile or track

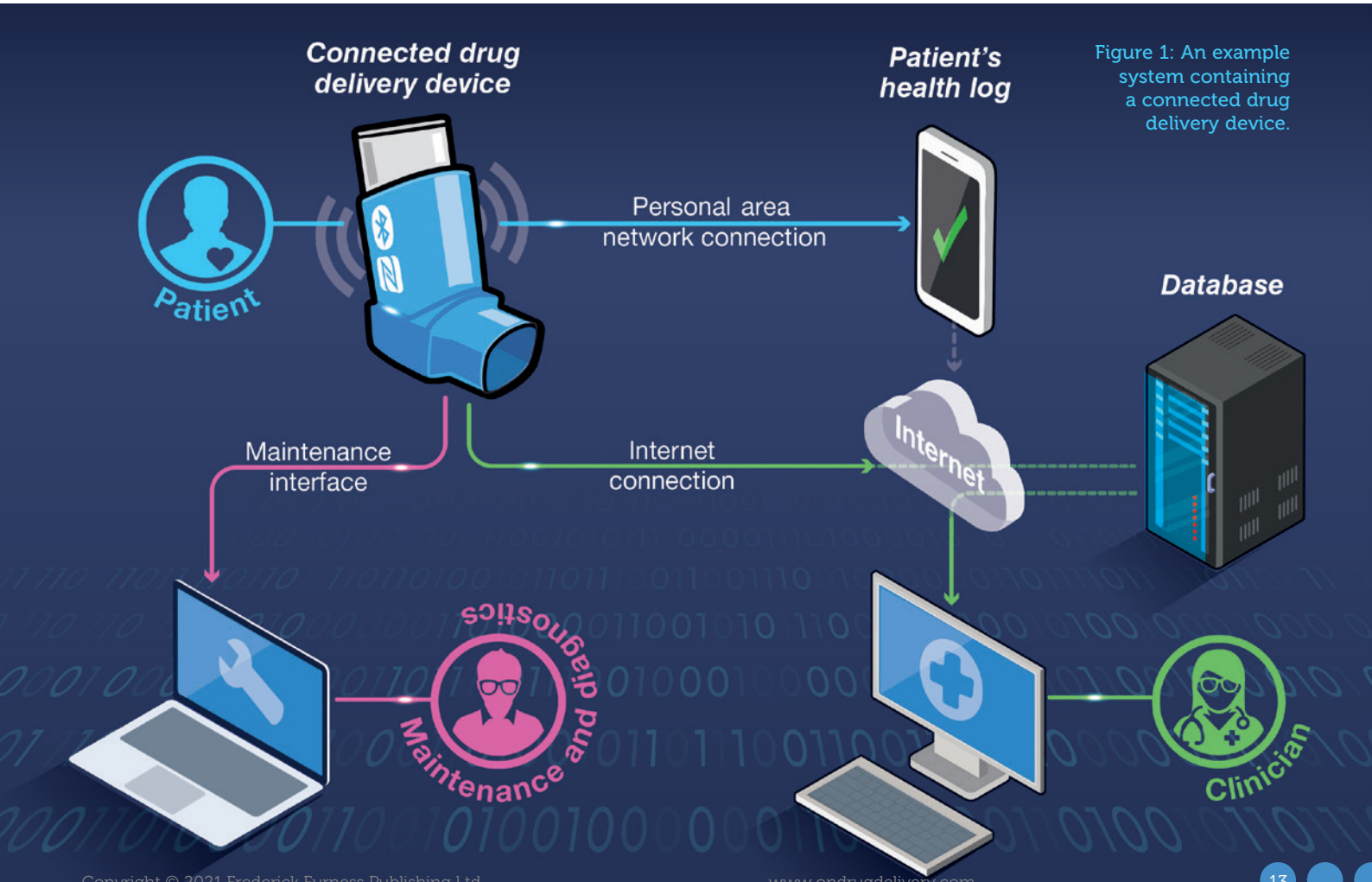

Figure 1: An example system containing a connected drug delivery device.

an individual. Access to the software and configuration settings that control the device's behaviour, either via the wired access port or wirelessly, could provide an avenue for malicious attacks, as well as theft of intellectual property. The presence of an internet connection could also make the device vulnerable to a variety of attacks, such as "denial-of-service", where the device is flooded with superfluous requests in an attempt to make it unavailable to its intended users.

IDENTIFYING VULNERABILITIES

Once the device and its system architecture are defined, threat modelling should be applied methodically to identify potential vulnerabilities that need to be addressed. By examining the potential for cyber-attacks, such as spoofing (disguising a communication from an unknown source as being from a known and trusted source), tampering, data repudiation (hidden manipulation or invalidation of data), information leaks, unauthorised use or denial-of-service, the potential impacts on device behaviour can be explored. The device developer should aim to generate a comprehensive list of cybersecurity risks that require consideration and mitigation during the development of the detailed design for the device.

> "After identifying potential cybersecurity risks, DCA's approach is to manage and review the identified vulnerabilities as part of the overall risk management process for the device. This approach helps to ensure that all aspects of performance are considered and appropriately balanced."

When evaluating the potential severity of cybersecurity risks and assessing possible risk controls, a common approach is to consider confidentiality, integrity and availability (CIA) for each scenario. The US National Institute of Standards and Technology (NIST) defines these terms as follows:[2]

- **Confidentiality**: Preserving authorised restrictions on information access and disclosure, including means for protecting personal privacy and proprietary information.
- **Integrity**: Guarding against improper information modification or destruction, including ensuring information non-repudiation and authenticity.
- **Availability**: Ensuring timely and reliable access to and use of information.

	Risk	Confidentiality	Integrity	Availability
1	Dose data transmitted via the wireless link is intercepted, manipulated or corrupted in transit.	Data sent via the internet connection is likely to transit untrusted networks, so could be monitored by a third party. Data sent via the personal area network could likewise potentially be visible outside of the target app on the patient's smartphone. **SEVERITY: HIGH**	Data sent via the internet connection could be manipulated on an untrusted network. Data sent via the personal area network could be manipulated before reaching the target app on the smartphone. **SEVERITY: HIGH**	Attempts at manipulation or corruption of data might stop it reaching the patient or clinician at all. **SEVERITY: MEDIUM**
2	Dose data stored on the device is accessed or manipulated via a wired or wireless link.	Unauthorised data access results in a leak of sensitive dose data. **SEVERITY: HIGH**	Access to dose data could result in it being manipulated without the patient's knowledge. **SEVERITY: HIGH**	Dose data is irrecoverably corrupted or deleted. **SEVERITY: HIGH**
3	Software on the device has a bug, resulting in a cybersecurity vulnerability.	If the vulnerability can be exploited, unauthorised data access may result in a leak of sensitive dose data. **SEVERITY: HIGH**	If the vulnerability can be exploited, dose data could be manipulated without the patient's consent or knowledge. **SEVERITY: HIGH**	If the vulnerability can be exploited, device behaviour could be modified, resulting in loss of connectivity. **SEVERITY: HIGH**
4	Spoofing (mimicking) of the device means that the patient or clinician unknowingly receives invalid data.	An unauthorised user discloses false dose data information to the patient and clinician. **SEVERITY: HIGH**	False dose data sent to patient / clinician. **SEVERITY: HIGH**	Spoofing by another device could deny genuine device access to a patient's smartphone or clinician's database. **SEVERITY: MEDIUM**
5	Denial-of-service attack prevents the patient or clinician receiving dose data.	Depending on the nature of the attack, dose data may not be directly exposed, so there may be no significant confidentiality risk. **SEVERITY: LOW**	Unauthorised user able to interfere with device behaviour. **SEVERITY: MEDIUM**	Dose data may not be retrievable from the device. Risk that timing of safety-critical device functions could be impacted. **SEVERITY: HIGH**

Table 1: Example cybersecurity risks identified using the CIA framework.

The relative importance of each criterion will depend on the intended use of a medical device. For a connected drug delivery device, integrity of data, such as records of drug delivery activity, may often be considered more important than confidentiality or availability. However, availability of data might be more important in scenarios where the drug delivery device needs to provide real-time updates, such as alerting a clinician to an occurring problem.

Taking our hypothetical drug delivery device example, we have identified a few example cybersecurity risks and evaluated their potential impact using the CIA framework in Table 1. Having identified cybersecurity risks in this way, they can then be resolved within the overarching connected device risk analysis.

When developing electronically programmable medical devices at DCA, the company also performs detailed research into known issues and published vulnerabilities for the hardware and software used in a medical device to support further risk identification. This includes examining supporting software documentation and assessing published information in open-source databases, such as the Common Vulnerabilities and Exposures (CVE) database. DCA also consults any appropriate guidance on the secure use of data communication protocols, such as Bluetooth Low Energy, that has been published by authorities like NIST.[3]

CYBERSECURITY AS A PART OF MULTIDISCIPLINARY RISK MANAGEMENT

After identifying potential cybersecurity risks, DCA's approach is to manage and review the identified vulnerabilities as part of the overall risk management process for the device. This approach helps to ensure that all aspects of performance are considered and appropriately balanced. It is important to remember that a secure device is not necessarily a safe one, as shown in Figure 2, adapted from the Association for the Advancement of Medical Instrumentation's (AAMI's) technical report on the principles of medical device cybersecurity.[4] The application of a cybersecurity-focused risk control measure in isolation from safety-related risk management could compromise essential performance of the device, for example by negatively impacting usability. One possible situation where this might arise is if extra authentication steps are added to improve the security of the data shared from the device.

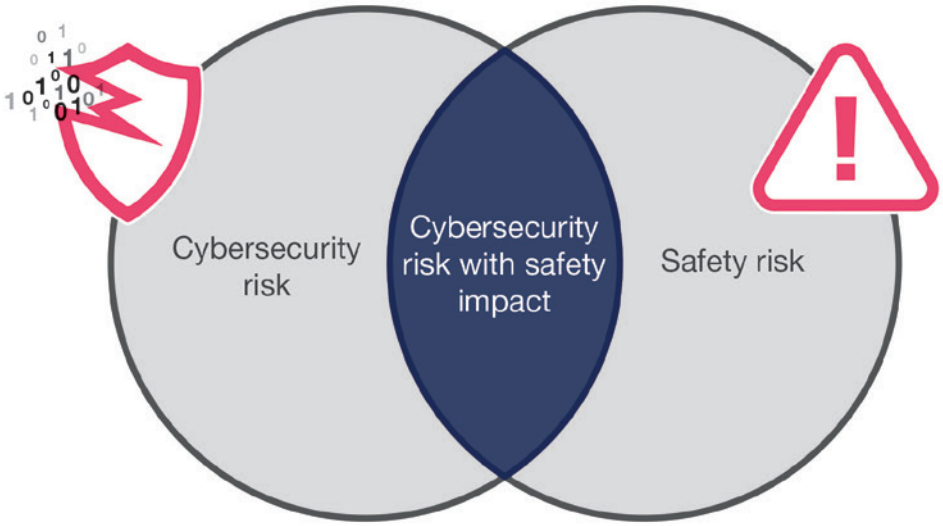

Figure 2: The relationship between cybersecurity and safety risks.

Returning to our hypothetical example device, let us consider some potential mitigations to the cybersecurity risks highlighted in Table 1 and the wider design impacts that their adoption could involve.

Risk 1 – Dose Data Transmitted Via the Wireless Link is Intercepted, Manipulated or Corrupted in Transit

In the case of dose data interception, manipulation or corruption in transit, one mitigation could be to specify and implement end-to-end encryption when dose data is transferred from the device to a smartphone or database. This could be supported by some form of pre-shared encryption key, though a better approach would probably be to use a secure key agreement protocol, such as Diffie-Hellman, for generating a shared encryption key across an insecure communications channel.

In reviewing this proposed mitigation, a relevant safety consideration would be whether the use of a computationally intensive encryption algorithm could impact on the timing of safety-critical functions, such as generating new dose activity records. This may require new design constraints to be specified to ensure that other device functions which impact patient safety are not compromised, such as the segregation of data transfer functionality from dose delivery or monitoring activities.

Risk 2 – Dose Data Stored on the Device is Accessed or Manipulated Via a Wired or Wireless Link

When considering this risk, minimising the opportunities for data to be changed from outside of the device after manufacture would provide a useful mitigation. This could include restricting access to dose data via the wireless and wired links, such as making it read-only. Adding integrity checks, such as error detection codes, could provide an additional detection mechanism in case of inadvertent data manipulation due to a device fault. In these cases, cybersecurity and safety mitigations are likely to be complementary, though the impact on essential performance should always be considered.

Implementing a user authentication scheme could provide a further mitigation for this risk, as well as for risks involving spoofing of a device. Authentication could, for example, involve the patient using their smartphone to scan a unique identifier printed on the device. Data from this identifier would subsequently be used to cryptographically confirm that the data is coming from the expected device. When reviewing this potential mitigation, however, there is a usability trade-off that needs careful consideration. The developer must assess whether the addition of this type of authentication means that the device remains usable and accessible for all target patients. Requiring additional authentication steps via a smartphone app may well be beyond the capabilities of some elderly or cognitively impaired users.

Risk 3 – Software on the Device Has a Bug, Resulting in a Cybersecurity Vulnerability

Where a software bug is published that may result in cybersecurity vulnerability, a couple of mitigation strategies can be employed. To improve monitoring and detection of such risks, a cybersecurity bill of materials

(CBoM) can be prepared, which holds a list of software and hardware components that are, or could become, susceptible to cybersecurity vulnerabilities. The CBoM can be used to support risk management through the device's lifecycle. This includes assessment of purchasing controls and supply chains during manufacture and monitoring exposure to new vulnerabilities when the device is on the market.

Additionally, a device could be designed such that it supports remote software updates to patch software bugs associated with cybersecurity vulnerabilities. However, design of such a capability needs to be carefully considered to prevent the introduction of new cybersecurity risks. Such an update feature may provide a "back door" into the device for data manipulation, allowing pathways for unauthorised software changes or reloading of an old version of the software that has exploitable vulnerabilities. The remote software update protocol also needs to be sufficiently secure to avoid inadvertent loss of intellectual property. Microprocessor manufacturers are improving their capabilities for supporting secure remote software updates, but these should be carefully reviewed and evaluated as part of device risk management, as well as in design verification and validation planning.

Risk 4 – Spoofing of the Device Means That the Patient or Clinician Unknowingly Receive Invalid Data

Considering the risk of device spoofing, a potential cybersecurity mitigation could be to authenticate a patient's device before accepting data from it. As with Risk 2, this could take the form of the patient using their smartphone to scan a unique identifier printed on the device, to confirm that the data is coming from the expected source.

Risk 5 – Denial-Of-Service Attack Prevents the Patient or Clinician Receiving Data

Denial-of-service attacks can be mitigated by implementing a firewall to filter out opportunistic attacks on the wired or wireless interfaces. Consideration of the intended use and careful design is then required to ensure that the risk is appropriately mitigated. Essential performance could still be impacted if most of the on-board computing resource on the device is required to service the firewall. A failsafe function could be considered in this situation too, which temporarily disables data communications to ensure essential performance is not compromised. However, this may not be appropriate where high availability is required; in this situation, a means of prioritising communications, such as alerts, might be required if the device needs to communicate whilst under a denial-of-service attack.

CONCLUSION

This overview only scratches the surface, as there are many technical solutions available to combat potential cybersecurity threats. When developing a connected drug delivery device, these solutions must be carefully considered in the context of the intended use, so that potential impacts on safety and usability are also appropriately balanced.

DCA believes that a detailed multidisciplinary approach to identifying and countering cybersecurity risks should be deployed throughout the development and lifecycle management of connected drug delivery devices, seeking to identify potential problems early, untangle conflicts and thereby achieve optimised design solutions. An effective development process is one that couples risk identification with informed design decision making to deliver safe, usable and cyber-secure connected devices.

ABOUT THE COMPANY

Founded in 1960, DCA is a leading product design and development consultancy. Its multidisciplinary service offering includes systems engineering, mechanical engineering, industrial design, insight and strategy, UX/UI, human factors, electronics, software and prototyping.

With a range of global pharmaceutical, biotech and device companies amongst its long-standing clients, DCA has deep experience in the field of drug delivery devices. Work undertaken in this area includes design, development, analysis and industrialisation support for injection devices, inhalers, wearables and intranasal devices and applicators, including smart and connected devices. DCA has won multiple major industry awards and contributed to over 1,000 granted patents in the last 10 years. The company's development service is certified to ISO 9001 and ISO 13485 standards.

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Rob Veasey is Senior Sector Manager, Medical and Scientific, leading drug delivery device development projects within DCA's medical device sector. He has 30 years' experience in engineering, design and management roles for leading manufacturing and consultancy businesses and has worked exclusively on development of drug delivery devices for 20 years. Mr Veasey's experience encompasses mechanical and electromechanical drug delivery devices, including work in the fields of injection, body-worn devices, metered dose inhalers, dry powder inhalers, intranasal sprays and topical applicators for global pharmaceutical and medical device companies.

Shane Day is the Electronics and Software Skills Leader at DCA, with a background in systems engineering and over 30 years of medical device development experience. Mr Day has in-depth knowledge of the software development lifecycle and the associated standards and regulations. He believes that, by adopting a pragmatic, risk-based approach to software and system development, we can develop better, safer connected devices.

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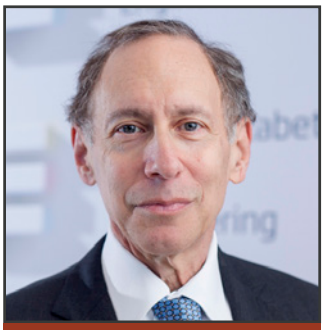

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MEANING-CENTRED PRODUCT DEVELOPMENT: THE KEY TO SUCCESSFUL CONNECTED DISEASE MANAGEMENT

In this article, Christina Philpott, Senior Strategist, Miles Hawley, Founder and Chief Executive Officer, and Natasha French, Client Services Lead, all of Recipe Design, discuss the future of connected disease management and the potential benefits for asthma treatment.

Asthma affects over 300 million people worldwide.[1] As a lifelong condition with no cure, implementing an effective management strategy that combines patient education and prescribed medication is currently recommended as the most successful way to treat asthma in adults by charities such as Asthma UK.[2]

Whilst paper-based tools and regular GP and asthma nurse appointments are established aspects of monitoring and controlling asthma, advances in technology have provided a much greater opportunity to obtain insights into patients' device usage, compliance and lived experience of asthma. These insights can be used to enable better treatment outcomes, whether informing patient-facing interfaces, providing additional information to healthcare professionals (HCPs) or feeding back to medical device developers and component manufacturers – shaping and improving future product pipelines and new condition management approaches.

Outside of medicine, the growth and omnipresence of Internet of Things (IoT)- and AI-enabled technologies are driving targeted and personalised solutions in analogous categories – directly influencing what patients are coming to expect from their healthcare solutions.

Connected fitness wearables such as FitBit and Garmin watches have brought biometric monitoring into everyday life. Menstruation-tracking apps have made symptom prediction tangible and personalised. The covid-19 pandemic has accelerated people's fluency with virtual interaction and their acceptance of self-testing, making telemedicine and remote healthcare more achievable and accessible than ever.

The developments in these analogous categories are shaping not just how patients

> "Developing connected respiratory disease treatments is far from simple, requiring collaboration between complex networks of parties with differing expertise and interests, with years – sometimes decades – of development before launch."

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expect their medical devices to look, feel and perform but how they expect information to be communicated and what they define as successful condition management for themselves as individuals. For instance, an arbitrary assessment of "improved symptoms" will no longer be satisfactory when patients are accustomed to consumer offerings that measure biomarkers to the percentile improvement.

Developing connected respiratory disease treatments is far from simple, requiring collaboration between complex networks of parties with differing expertise and interests,[3] with years – sometimes decades – of development before launch. The technologies that can enable advanced, connected asthma solutions already exist. However, the variety of specialist expertise and technical capability required to successfully apply these technologies to the treatment of pulmonary disease is currently held by many disparate parties. Experts in all aspects of pulmonary disease management and connected data technologies must work together collaboratively to drive continuous improvement towards the common goal of safer and more effective treatments.[4]

It is therefore essential that connected health platforms are developed with foresight as a priority – an ability to understand how emerging technological developments and legislation changes can translate into successful product offerings by the time of launch. Critical to ensuring this is establishing direct ties with patients[3] and identifying the strategic opportunities that provide commercial differentiation alongside meaningful patient benefits.

THE MEANING CENTRED DESIGN APPROACH

Meaning Centred Design is a research-led approach to brand and product development pioneered by Recipe Design, a strategic design consultancy based in London. The team at Recipe has spent over a decade practising Meaning Centred Design to help clients achieve growth through product and service innovation across the healthcare and home sectors.

Meaning Centred Design uses a range of techniques such as semiotic and discursive analysis, expert and stakeholder interviews, iterative co-design sessions with patients and HCPs, and technology forecasting. Insights drive strategic responses that can be used to inform product pipelines that factor in social, economic and technological developments. Understanding how meanings are likely to shift is a powerful way of identifying design opportunities that intersect, blend and define changing attributes to develop offerings that resonate deeply with people.

EVOLVING THE MEANING OF ASTHMA MANAGEMENT

When examining the potential for connected asthma management platforms, there are many evolving meanings running in parallel, with the opportunity to intersect in new and differentiated ways. To articulate these shifts in meaning, Recipe Design has developed ADD•FLO, a conceptual study that explores a holistic, future-facing platform approach to asthma management, grounded in insights obtained from over 15 years of user research and product development with partners in the respiratory health and metered dose inhaler (MDI) industries.

ADD•FLO uses a unique combination of digital and physical tools (Figure 1) that enable asthma patients to better understand and manage their condition at home. Informed by the shifts in meanings spanning multiple categories of products, ADD•FLO proposes a new dynamic

> "ADD•FLO proposes a new dynamic for asthma management that bridges prescription medication with evolving attitudes in healthcare, wellness and connected devices."

Figure 1: ADD•FLO combines a smart hub, an MDI actuator and a connected app.

for asthma management that bridges prescription medication with evolving attitudes in healthcare, wellness and connected devices.

ANTICIPATING EVOLVING PATIENT EXPECTATIONS AND NEEDS

Many patients rarely, or reluctantly, describe themselves as "sufferers" – or, indeed, "patients" – in an effort not to self-identify as sick or vulnerable. They choose to manage their condition as discreetly as possible, rejecting overly medicalised inhalers and shunning any connotations of ill-health.

There are also anecdotes of patients who have requested a more stylised inhaler, citing the MDI used by Le Chiffre in the film Casino Royale as something desirable and aspirational. Similarly, Recipe's award-winning work on the Mundipharma (Cambridge, UK) K-Haler not only provided improved device compliance and competitor differentiation but led to the youngest and least compliant patients describing the inhaler as "cool" – a product they were happy to be seen with, resulting in increased engagement with condition management.

In response to these shifts, the ADD•FLO study explores a design language that combines the trusted reassurance of medical devices with premium forms, materials and finishes. A smart hub base (Figure 2) creates a designated place for asthma care in the home, displays notifications generated in the ADD•FLO app and provides UV LED sterilisation for the MDI actuator and spirometry mouthpiece to ensure it stays clean and hygienic between uses.

Figure 2: The ADD•FLO smart hub displays notifications and provides UV sterilisation.

Patients are also encouraged to perform breathing exercises through the actuator before administering their daily preventer medication. There is increasing evidence that practising breathing exercises can improve inhalation technique[5] and reduce reliance on rescue medication,[6,7] with the potential for further positive implications on both mental health and general health, such as lowering blood pressure.[8]

These factors combine to create a system of products that sit comfortably and proudly in the evolving smart home environment, accommodating increased awareness of hygiene in a post-covid-19 world and responding to evolving patient attitudes about blended mental and physical health interventions.

> "With an increased understanding of the analogous factors that can cause, affect and exacerbate asthma... connected healthcare platforms can help to explore the impact of behavioural changes and alternative treatments that are reported to alleviate asthma symptoms."

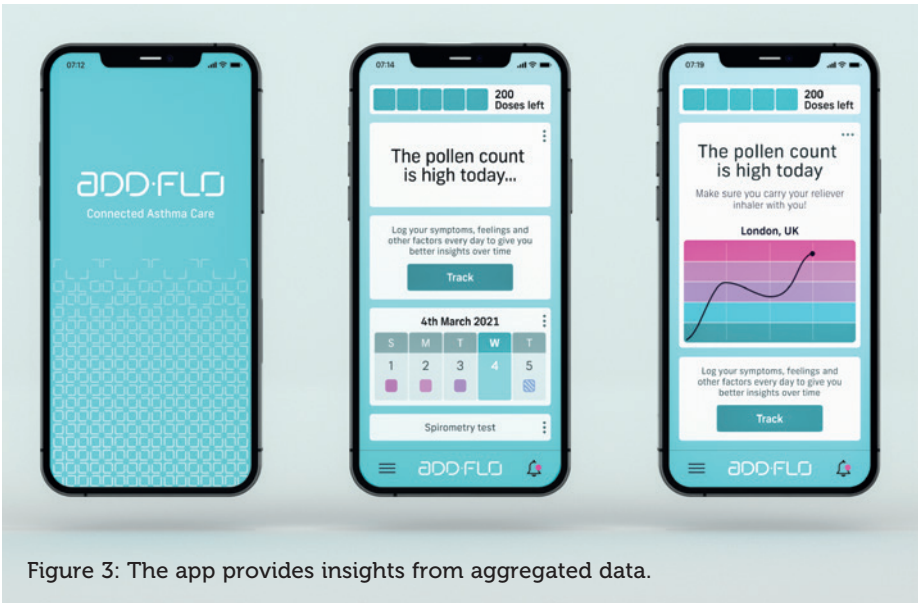

Figure 3: The app provides insights from aggregated data.

USING STRATEGIC COMBINATIONS OF EXISTING TECHNOLOGIES

With an increased understanding of the analogous factors that can cause, affect and exacerbate asthma[1] – such as indoor and outdoor air quality, airway microbiome and dietary factors – connected healthcare platforms can help to explore the impact of behavioural changes and alternative treatments that are reported to alleviate asthma symptoms, such as practising breathing exercises and consuming certain vitamins.[9] The ADD•FLO app looks to further this understanding – on both an individual patient level and from a global health perspective – with the potential to contribute data to clinical studies or directly inform and improve new product development.

Patients can manually track their symptoms alongside data imported from third-party apps, such as biometric data from wearables, diet, location and weather information (Figure 3). Over time, machine-

> "By prioritising the patient's experience of the platform – ensuring ease of use, providing meaningful insights and reminders, establishing habitual behaviours and supporting compliance – patients can access marked improvements and benefits that help them to feel more informed and more in control."

learning capabilities can provide rich insights about the factors that may be exacerbating the patient's symptoms, finding correlations it would otherwise be difficult to observe and prompting the patient to intervene to avoid preventable suffering.

Additionally, the ADD•FLO smart hub automatically logs each actuator use to inform an activity log and dose-counting function on the app, estimating how much medication is left and reminding patients to renew prescriptions, as required. In theory, this could prevent the need for add-on mechanical or electronic dose counters by using digital platforms and predictive analytics to estimate the contents remaining in a drug cannister.

Figure 4: An additional mouthpiece enables patients to perform spirometry tests at home.

By prioritising the patient's experience of the platform – ensuring ease of use, providing meaningful insights and reminders, establishing habitual behaviours and supporting compliance – patients can access marked improvements and benefits that help them to feel more informed and more in control.

ESTABLISHING AGILE SYSTEMS THAT RESPOND TO FUTURE DEVELOPMENTS

In line with evolving sustainability legislation, the ADD•FLO actuator houses an MDI cannister of liquid medication, which can be replaced when depleted by unscrewing the top section of the actuator. The actuator can then be reused, kept sterile by the smart hub, reducing both the need for disposable actuators and the overall packaging necessary to fulfil renewed prescriptions. This modular, sustainable approach to actuator design can be applied to future MDI solutions, especially as new propellants and canisters are introduced in line with changing sustainability legislation.

The ADD•FLO system also incorporates an additional mouthpiece (Figure 4) which enables a spirometry test to be performed by the patient at home. Test results can then be shared with their HCP remotely via the app, overlaid with the data obtained from tracked symptoms, to provide insight into the effectiveness of their current prescribed treatment and guide the HCP on the necessity for medical interventions.

Remote clinical assessments conducted by the patient, in their own home, have the potential to reduce the need for in-person appointments, as well as reducing footfall in clinical settings – a trend that may continue to be advantageous beyond the covid-19 pandemic. This approach empowers the HCP-patient relationship, driving appointment efficiency, whilst offering patients more autonomy and control.

Laying considered foundations for developments in legislation and anticipating the disruption of global shifts, such as those brought about by the covid-19 pandemic, can enable device developers and manufacturers to remain agile and responsive to change, rather than reactive.

THE EVOLVING FUTURE OF CONNECTED ASTHMA MANAGEMENT

To ensure new connected healthcare platforms are successful, multiple factors must be considered in parallel. As well as the patient and HCP experience, other stakeholders must be considered, taking into account emerging drug delivery technologies, manufacturing methods, sustainability targets and data privacy legislation that will continue to shape and govern the connected healthcare category.

ADD•FLO articulates a potential future of connected condition management. It explores how asthma treatment could evolve, drawing on insights from parallel and analogous categories such as wellness products and smart home technology. It proposes a solution that sits at the point where the meanings of these categories will intersect in the near future, with considerations to the manufacturing and regulatory constraints surrounding the category as they emerge and evolve simultaneously.

ADD•FLO demonstrates the effectiveness of a Meaning Centred Design approach; the concept offers a holistic and future-facing

perspective for connected health that unifies the many ideas circulating in the category, whilst addressing many long-standing issues.

ABOUT THE COMPANY

Recipe Design is a strategic design consultancy, dedicated to helping clients achieve growth through product and service innovation across the healthcare and home sectors. The team has spent over a decade pioneering the use of Meaning Centred Design – a unique process that helps clients understand their customers or end users and how they perceive their brand and proposition. Insights from Meaning Centred Design can be translated into new strategies and design solutions that are more relevant and meaningful, creating sustainable business value and minimising risk.

The team at Recipe has delivered award-winning work for market-leading brands including Sanofi, Kohler, Braun, Galderma and Bang & Olufsen.

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ABOUT THE AUTHORS

Christina Philpott is Senior Strategist at Recipe Design. She graduated from Central Saint Martins in London (UK) as a product designer before joining the Strategic Insight team. With a unique perspective and ability to see pattern and potential in complex sets of data, Miss Philpott discovers the insights that resonate with people and translates them into design activities that deliver great business outcomes. Her recent work includes diagnosis and disease management platforms for chronic diseases, such as asthma, diabetes and migraine, as well as brand strategy and implementation for companies spanning pharma, personal care and biotech markets.

Miles Hawley has a 30-year industry track record with senior positions held at several of the UK's most prestigious design consultancies. His creative background, coupled with leadership experience and strategic business thinking, has enabled his transition through various high-profile design roles, Creative Director positions and, more recently, Chief Design Officer of Precipice Design, to his current role as Founder and Chief Executive Officer of Recipe Design. Mr Hawley has experience across multiple sectors, majoring in healthcare and home markets. From award-winning medical devices and consumer durables to innovative structural packaging and global rebrands, a few of his noteworthy clients have included Ford, Bang & Olufsen, Braun and Sanofi. Mr Hawley has been responsible for delivering global innovation programmes for some of the world's biggest healthcare businesses including Novartis, Mundipharma, Novo Nordisk, Circassia and Roche.

Natasha French, Client Services Lead at Recipe Design, is a seasoned business development professional with over 13 years' experience in selling creative services and technical solutions. During her career to date, she has developed relationships with R&D teams within global brands and innovation centres defining the leading edge of psychology, neuroscience and clinical research. Ms French uses her unique blend of creative thinking, empathy and data to pinpoint opportunities that have meaning, generate business value and are often quite unexpected.

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We create product, packaging and brand pipelines from concept definition to commercialisation.

Recipe is a strategic design consultancy, dedicated to helping clients achieve growth through product and service innovation across the healthcare and home sectors.

The team at Recipe has spent over a decade pioneering the use of Meaning Centred Design™ to deliver award-winning work for market leading brands including Circassia, Mundipharma, Sanofi and Roche.

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IMPROVING PATIENT OUTCOMES WITH ADVANCED DIGITAL BIOMARKERS

In this article, Matthew Sarkar, Vice-President Medical, and Imantha Samaranayake, Electronics, Software and Systems Consultant, both of Sagentia Innovation, consider the contribution digital biomarker devices make towards healthcare and the challenges faced by the evolution of such devices.

Digital biomarker devices could bring about a new age of intelligent, personalised treatments and care plans that significantly improve healthcare effectiveness and cost-efficiency. However, to make a meaningful difference to patient experiences and outcomes, they need to do more than simply monitor an individual's condition. They also need to analyse and leverage biomarker data to generate actionable insights that can inform decisions as patients progress along treatment plans.

As the technology that underpins digital biomarker devices becomes more advanced, exciting new capabilities are within reach. However, the development of digitally enabled medical devices is rarely straightforward. To gain regulatory approval, they need to satisfy stringent safety and security measures that go beyond the safety of treatment itself. This introduces an additional layer of complexity to the product development journey. Many practical and technical factors can impact effectiveness and uptake as well.

Innovation teams developing solutions using digital biomarkers need to consider the role they will play in wider digital therapeutics as well as technical and regulatory matters. Making time for this at the earliest possible stage in product development is crucial. When decisions are shaped by an awareness of the bigger picture, it makes for a smoother and faster product development journey.

WHAT ARE DIGITAL BIOMARKERS?

Digital biomarkers are quantifiable, measurable health indicators that can be collected and analysed in the cloud or, as capability improves, at the network edge. Comparing data gathered at the individual level with big data from wider cohorts or populations can help explain, influence or predict health-related outcomes. Devices incorporating digital biomarker technology can be implemented in different formats, such as wearable, implantable, or even ingestible.[1]

> "In a world reshaped by covid-19, perhaps one of the most noteworthy opportunities related to digital biomarkers is the ability to monitor, and thereby manage, disease outbreaks. For instance, digital biomarkers might be used to track indicators such as oxygen saturation, temperature, respiratory rate and voice characteristics."

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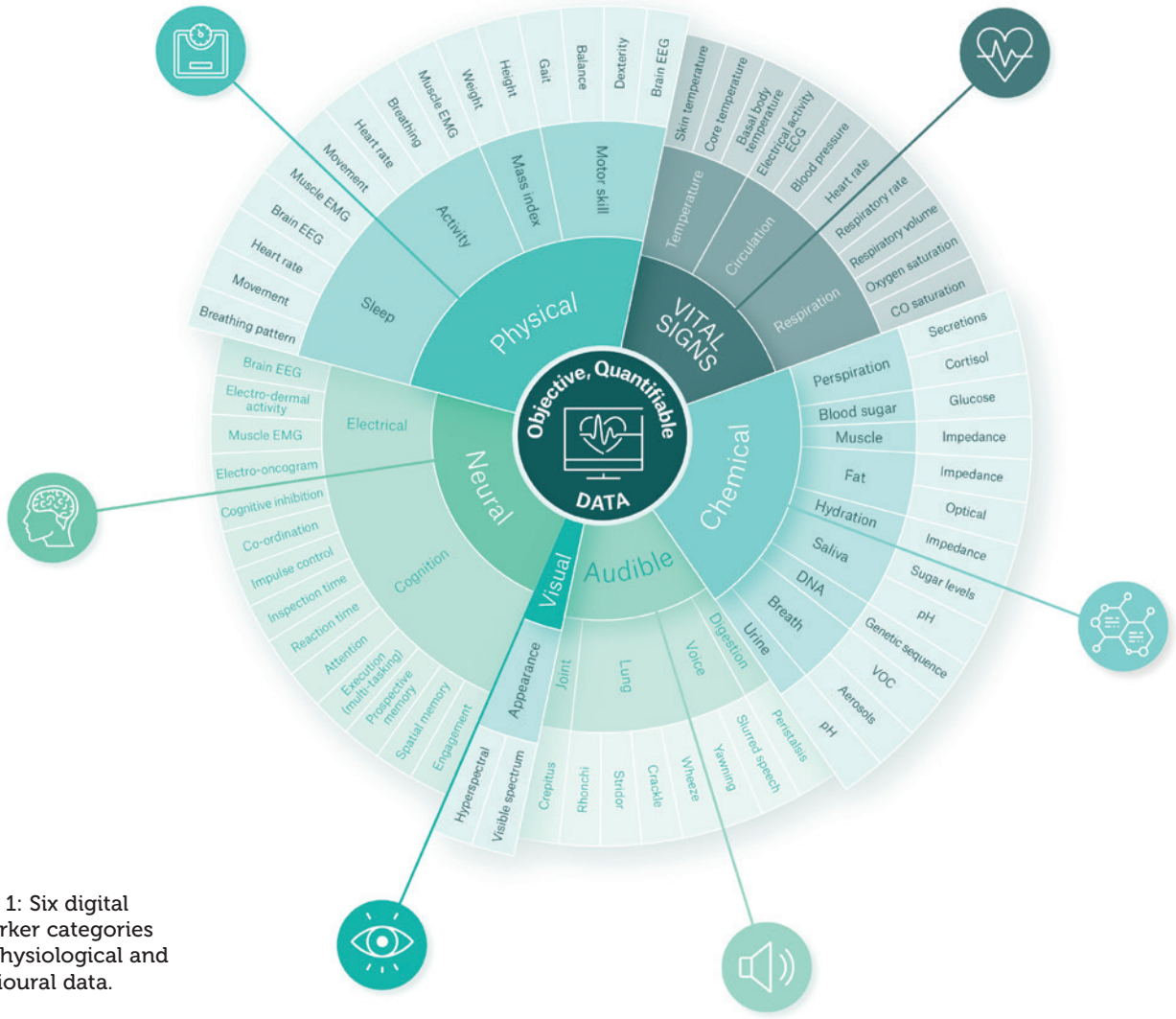

Figure 1: Six digital biomarker categories with physiological and behavioural data.

Figure 1 shows various digital biomarker types across six categories (vital signs, physical, chemical, neural, visual and audible). For more detail on each category, such as application areas and biomarker formats, there is an extended, interactive version of the diagram available on Sagentia's website. This online resource also demonstrates the value of using multiple digital biomarkers in the detection and management of certain conditions.

OPPORTUNITIES IN THE DIGITAL BIOMARKER SPACE

Disease Management

In a world reshaped by covid-19, perhaps one of the most noteworthy opportunities related to digital biomarkers is the ability to monitor, and thereby manage, disease outbreaks. For instance, digital biomarkers might be used to track indicators such as oxygen saturation, temperature, respiratory rate and voice characteristics. This could happen in discrete hospital settings, the care home network or even within the larger population of patients with the illness, or people at high risk.

Such developments could drive benefits at a global, national, local or individual level. They might provide early warning of infection, triggering self-isolation, or be used to enable rapid identification of illness clusters by predicting areas where hospital resources are likely to come under pressure. At a larger scale, data could be used to generate insights on the disease symptom trajectory. This could inform trials for treatments and vaccines or enable national and global surveillance.

> "With the creation of biomarker "profiles", there could be a step-change in general diagnostics for many, if not all, illnesses and conditions."

Risk Stratification

Monitoring digital biomarkers throughout disease progression unlocks exciting opportunities. It is possible to gain a deeper understanding of illnesses and conditions and then stratify potential outcomes for different patients, offering new ways to personalise treatment. Detailed studies on the rates of change for certain biomarkers over time could offer valuable insights too.

Take increased body temperature – in general terms, this signifies a viral infection. But does the shape of a certain temperature profile over a matter of hours or days signify a particular infection or condition? It may be possible to establish longitudinal profiles for seasonal flu viruses or SARS-CoV-2, for instance.

When looking beyond an individual episode of care, the potential is even greater. With the creation of biomarker "profiles", there could be a step-change in general diagnostics for

many, if not all, illnesses and conditions. Does the way a particular biomarker changes over time suggest a particular illness? It could certainly narrow down the range of likely illnesses, providing early indication on a much broader scale than current capabilities allow, and facilitating a more targeted and precise diagnosis. Combining longitudinal profiling with the ability to cross-compare and blend a multitude of biomarkers would drive significant progress.

Long-Term Care

The treatment of chronic conditions, especially in the context of ageing populations, can be greatly enhanced with the use of digital biomarker devices. Continuous monitoring provides opportunities for earlier intervention, an objective overview of disease management effectiveness or early warning signs if a condition deteriorates. This potentially goes beyond current goals of rapid intervention at the onset of exacerbation, to true early intervention avoiding the exacerbation altogether.

Advantages for both patient health and health system economics are enormous. For example, if a COPD patient is alerted early, takes preventative action and avoids a hospital stay. Conducting this by remote patient management is potentially cheaper, avoids the risk of infection in healthcare environments and is more convenient for people experiencing pain or mobility issues. More than 15 million people are living with chronic conditions and require long-term disease management in the UK alone. And many countries are facing the challenge of caring for ageing populations. In this context, digital biomarker devices could play a significant and valuable role in improving patients' quality of life while reducing the burden on healthcare systems.

Mental Health Conditions

The increased incidence, and awareness of, mental health issues presents another avenue where digital biomarker devices could vastly improve patient outcomes and quality of life. Such devices can act as a constant companion, monitoring conditions in real-time and then triggering interventions at critical moments prior to the onset of a significant event. They can promote activities to help counter or prevent negative or destructive thoughts, and provide access to supportive communities.

> "Devices need to operate within existing regulatory parameters while being future-proofed for potential changes. Monitoring current developments beyond the medical sector can help inform decisions related to this."

Personalised Preventative Care

Early intervention to prevent or delay the onset of chronic conditions is a prime area for the next generation of digital biomarker devices. For instance, tracking an individual's weight and glucose levels could aid the prediction and prevention of Type 2 diabetes. This concept of personalised, preventative healthcare linked to digital biomarker devices is gaining a lot of attention. For instance, in the US it has the potential to drive more sophisticated approaches to healthcare provision, such as personalised insurance premiums and value-based treatment.

The Digital Health Act (DVG), which took effect in Germany in 2020, looks set to drive increased use of digital biomarkers. Under the DVG, doctors or psychotherapists will be able to prescribe low-risk digital health apps where efficacy has been proven to the Federal Institute for Drugs and Medical Devices (BfArM). This is part of a range of measures geared towards expanding the digitalisation of Germany's health services. Regulatory requirements for DVG apps include privacy law compliance and a high level of data security. Nevertheless, patient advocacy groups have raised concerns surrounding the inability to opt-out of anonymised data sharing for research purposes. This situation underlines the complexities facing digital biomarker device development.

CHALLENGES IN DIGITAL BIOMARKER DEVICE DEVELOPMENT

Many of the barriers to digital biomarker device approval, effectiveness and uptake, relate to the use and management of patient data. Much of the time, there is a lag between standards or regulations and emerging technical capabilities. So, devices need to operate within existing regulatory parameters while being future-proofed for potential changes. Monitoring current developments beyond the medical sector can help inform decisions related to this.

Another challenging area that can hinder device approval is the need for continuous modification of the algorithms related to digital biomarkers. Again, careful consideration at an early stage in device development is the best solution. In this way, it is possible to maintain substantial equivalence from the point that the device is approved.

Finally, since digital biomarkers are generally proxy measurements for disease conditions, rigorous validation of what they indicate is essential. However, intellectual property concerns and the nature of compiled code can lead to a lack of transparency, which makes independent scrutiny a challenge. Machine-learned algorithms further obscure underlying mechanisms as they learn and adapt according to the data provided.

Data Privacy, Quality, Management and Analysis

For digital biomarkers to drive effective medical treatments and practices, they need to draw on large datasets. Yet, there are many factors that hinder this in practice. Challenges range from data privacy laws – and disparities in those laws between different countries – to the storage, analysis and standardisation of patient information. In addition, electronic medical records are currently not designed to store large amounts of continuous data or to conduct real-time analytics. Data quality is an issue as well. Variations between devices, and in the ways people use or wear them, can lead to significant differences in data collected. This can skew analysis and anomalies may not be easy to distinguish.

Lack of standardisation between healthcare settings and countries can also impede the value of digital biomarker data. As data is collected and controlled by separate entities, silos inevitably arise. This limits data liquidity preventing its flow through the wider healthcare system.

The Need for Standardisation

All the above factors impact the collection, analysis and value of digital biomarker data. So, there is a pressing need to achieve better standardisation of data storage, labelling and tagging.

This is partly about improving the ease with which information can be processed and exchanged. But more importantly, it is about providing context for each datapoint to drive deeper levels of insight that enhance understanding at the macro-level while driving better patient experiences at the individual level.

New frameworks are emerging to address some of the challenges surrounding security, ethics and informed consent in digital phenotyping. For instance, the US FDA's proposed Cybersecurity Bill of Materials for the premarket submission of medical software would aim to identify issues related to security vulnerabilities, transparency and accuracy.

Digital biomarkers are inherently changeable, and the understanding of the way they signpost conditions evolves over time as more data are gathered. However, patient consent tends to relate to specific, predefined scenarios. So, the ability to update consent easily and conveniently on a regular basis can be a critical success factor in the regulatory approval of devices.

Room for Improvement

While many of the technologies that underpin digital biomarker devices are maturing, there are some serious issues that need to be addressed. For instance, when users from different ethnic backgrounds interact with devices the results must be consistently reliable. However, this is not always the case. Facial recognition software tends to deliver higher levels of accuracy for light-skinned users than for darker-skinned users. Issues like this need to be anticipated and resolved at an early stage in product development. It is sobering to recognise that an "unbiased" algorithm will machine learn the unconscious bias of a coder who provides it with a skewed data set. Without scrutiny at a fundamental dataset level, this ghost in the machine could proliferate at an alarming rate, obscured by machine-learned code and scaled through digital deployment.

> "As digital biomarker devices evolve to offer more robust, actionable, predictive insight, they are set to play a fundamental role in the wider digital therapeutics space."

THE WAY FORWARD

In recent times, we have seen a convergence of technical capabilities, healthcare industry needs and wider acceptance of remote, digitally enabled medical treatment. Together, these factors indicate that the market is calling out for innovative medical devices rooted in digital biomarkers. Additionally, as digital biomarker devices evolve to offer more robust, actionable, predictive insights, they are set to play a fundamental role in the wider digital therapeutics space.

Challenges do exist, and they are complex. But they are not insurmountable. At Sagentia Innovation, scientists and technology specialists with extensive experience in the medical sector work collaboratively to solve problems of this nature. When potential barriers to approval or adoption are properly accounted for early in the design phase, the underlying software can be adapted to accommodate or mitigate them.

Digital biomarkers are transforming our understanding of diseases and chronic health conditions. As the devices measuring them progress to offer predictive analytics, which enables early intervention, we will see a revolution in treatment protocols. Over time, this will drive better patient experiences and outcomes while making healthcare provision more efficient, effective and individualised. Medical device manufacturers that act now will be in a strong position to play a lead role in this new age of healthcare.

ABOUT THE AUTHORS

Matthew Sarkar, Vice-President Medical at Sagentia Innovation, has more than 20 years' experience in the healthcare sector. He has been involved with the development of medical devices and digital therapeutics derived from innovative technologies, such as wearable patient monitoring technology, which helps surgeons and hospitals consistently track patients throughout the continuum of care. Mr Sarkar's work drives emphasis from descriptive to predictive analytical technologies to reduce and even prevent illnesses, shifting services from "sick-care" towards the provision of true healthcare.

Imantha Samaranayake is an Electronics, Software and Systems Consultant at Sagentia Innovation. He is registered as a Chartered Engineer with the Institution of Engineering and Technology and is a graduate of the University of Cambridge where he completed a master's degree in electrical and electronic engineering. Mr Samaranayake's work in the digital health space includes building a framework to define current, successful real-world applications of digital technology throughout the care pathway and identify potential growth areas.

ABOUT THE COMPANY

Sagentia Innovation works with industry leaders and innovative start-up companies in the healthcare industry that have a shared vision to drive better patient outcomes through increased market understanding and technological innovation. The business provides independent advisory and leading-edge product development services focused on science and technology initiatives.

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PUTTING THEIR HEALTH IN THEIR HANDS: ENHANCING RESPIRATORY PATIENT OUTCOMES THROUGH DIGITAL THERAPEUTICS

Here, Adam Shain, Director, Business Development, Global Digital Healthcare Systems, Aptar Pharma, discusses the role digital therapeutics play in respiratory patient outcomes and looks at the potential for expansion into other therapy areas.

For patients suffering from chronic respiratory diseases, the opportunity for greater control over their condition not only benefits their physical health but can also significantly enhance their overall quality of life.

Recent advances in drug and device development have enabled increasing numbers of patients to manage their health by controlling symptoms and responding to acute situations, thereby reducing the level of intervention required by healthcare professionals (HCPs) in the process, and avoiding acute exacerbations and visits to A&E.

> "Recent advances in drug and device development have enabled increasing numbers of patients to manage their health by controlling symptoms and responding to acute situations, thereby reducing the level of intervention required by HCPs in the process, and avoiding acute exacerbations and visits to A&E."

As such, self-management is welcomed by most patients. Analysis of published reviews and syntheses of qualitative research related to 14 long-term conditions, including asthma and COPD, concluded that patients have a clear appetite for a better understanding about their illnesses, and desire stronger, more collaborative relationships with their HCPs.

While the patient is arguably the greatest benefactor in the self-care model, they can also be the greatest flaw. Due to the critical part they play in the process, patients can be a major barrier to success in therapy management if their behaviour does not correlate with the actions prescribed by HCPs.[1]

MANAGING PATIENT BEHAVIOUR

Poor levels of adherence can be attributed to several factors, from poor engagement to low levels of motivation and lack of informational awareness. Confidence can also be an issue; patients suffering from long-term conditions have been found to be less self-assured in managing their health compared with the population at large. Furthermore, this confidence issue is most prevalent in older age groups, which represent the vast majority of people living with chronic conditions.[2]

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Figure 1. BreatheSmart® Connect digital health platform – a care co-ordination and HIPAA-compliant SaaS cloud service that captures and securely stores data from Cohero Health's devices and BreatheSmart® software for remote monitoring and patient communications to help manage patient therapy.

For HCPs, there is currently very little that can be done to monitor and address these gaps in patients' self-management regimes. Medical appointments provide important points of interaction, but they can be infrequent and relatively transient. These appointments therefore provide only limited opportunities to identify poor adherence, address the root causes and create individualised plans for behavioural change in the patient. The net result of this lack of touchpoints is evidenced through high levels of medicine wastage and missed opportunities for patients to optimise their self-management and improve their healthcare on an ongoing basis.

In recent years, we have witnessed the introduction of several digital healthcare solutions designed to address some of these challenges. Cohero Health®, an Aptar Pharma company, was founded in 2013 with a vision of transforming the traditional approach to respiratory disease management through smart mobile technologies. This vision resulted in the development of BreatheSmart®, a comprehensive digital therapeutics platform that enables patients and HCPs to better screen, track and manage asthma and COPD at a personalised level (Figure 1).

The BreatheSmart® app is designed for patient habit creation and behaviour change, driving appropriate medication use. The app provides real-time tracking of medication adherence and lung function, along with reminders, educational materials and symptom/trigger recording (Figure 2).

PATIENT-CENTRIC DESIGN

The system incorporates all the hardware and software required to form an interactive digital environment between the patient and their HCP. This includes mSpirometer™, which details up to six

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Figure 2. BreatheSmart® app – designed for patient habit creation and behaviour change, driving appropriate medication use.

Figure 3. mSpirometer™ and cSpirometer™ lung function diagnostic sensors – enables comprehensive pulmonary lung function testing in a handheld wireless device.

different measurements, including FEV_1, FVC and peak-flow volumes (Figure 3). The Bluetooth-enabled HeroTracker® is fitted to both control and rescue inhalers to record time and date of dose (Figure 4).

The main patient interface is a mobile app, available in iOS and Android versions, for real-time tracking of medication adherence and lung function, as well as the recording of symptoms and triggers, and the delivery of dosing reminders and educational materials. Due to the app's pivotal role in trying to secure patient engagement and facilitate ongoing use of the system, great care was taken in the development of the interface to ensure it provided an intuitive experience for patients.

This was achieved by incorporating behavioural modelling alongside user interface and user experience design methodologies. Colour, for example, is used to provide a visual representation of peak-flow data, with the universally recognised RAG (red, amber or green) colour coding used in screen backgrounds to provide a clear indication of lung performance.

Ultimately, modelling such as this creates a platform that is accessible and helpful, as well as rewarding and enjoyable for patients.

Design was just one aspect of an extensive development and test process for BreatheSmart®, which also incorporated clinical input from pulmonologists, care guidance from regulatory bodies and feedback from extensive user and focus groups. Looking ahead, Aptar Pharma is committed to the continued development of the platform with a view to further exploiting the benefits for patients and HCPs.

DRIVEN BY DATA

When in use, all patient data captured on the BreatheSmart® platform is stored on a secure cloud-based server designed to be HIPAA- and GDPR-compliant, accessible to patients and clinicians via the BreatheSmart® Connect interface. This provides a dashboard view of a patient's medical information. The BreatheSmart® platform supports API-based integration with electronic health records to support a contextual view of patient information.

Because data is recorded in real time at the point of use, the platform can paint an accurate in-depth picture of an individual patient's engagement with their medicine regime. This provides invaluable information for the HCP to understand and optimise therapy management.

While a great deal of the developments in digital healthcare to date have been aspirational and theoretical in nature, a commercial-stage product, such as BreatheSmart®, has been validated through actual use, in pharmaceutical research applications and clinical trials.

Analysis of real-world user data shows how BreatheSmart® has been overwhelmingly welcomed by patients, with a pleasing 92% user-satisfaction rate.[3] Crucially, it has also been shown to improve adherence to medicine regimes by a factor of 3:1 and a user-retention rate of 72% after a year of use. This data demonstrates the platform's ability to deliver long-term engagement as well as support a 95% reduction in the use of rescue medication, and a 50% reduction in A&E visits among users.

CONTROLLING LONG-TERM RISK

With higher levels of adherence comes better levels of self-care, leading to improved overall health and quality of life. From the perspective of a medical professional, better adherence also equates to greater control over a patient's long-term risk.

As the severity of COPD increases over time, patient suffering increases exponentially as a direct result of their condition. They are also more likely to need to manage a range of associated health issues and complications. Examples include loss of mobility and weight gain, which almost inevitably lead to poor mental health, including anxiety and depression. Ever more complex medical needs correlate with an increase in the overall cost of care. This is just one more reason why connected digital platforms, such as BreatheSmart®, are critical to delivering cost savings alongside the proven health benefits.

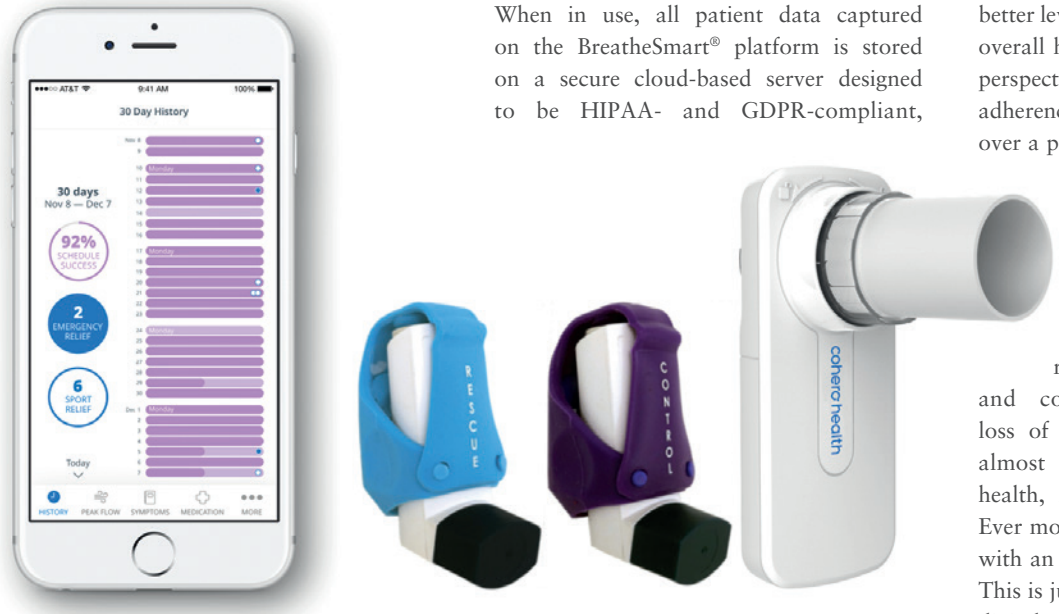

Figure 4. HeroTracker® sensors – Bluetooth-enabled medication smart inhaler sensors designed for both control and rescue medications. They attach to respiratory medications to automatically record time and date of doses taken.

Putting your health in your hands

Accelerate the journey towards a patient-focused, digital healthcare solution for improved patient health in asthma and COPD, from clinical trials to disease management and beyond.

Start BreatheSmart® with Cohero Health®, an Aptar Pharma company **www.aptar.com/pharmaceutical** or **www.coherohealth.com**

Delivering solutions, shaping the future.

Aptar pharma

LBL-MKT-454 April 2021

Good communication is a crucial element on the journey to improving patient outcomes through digital healthcare services. BreatheSmart® supports effective communication by showing targeted educational information in text and video form. The chat function connects patients directly with designated HCP contacts, enabling patients or their caregivers to ask questions that relate to their situation at a given point in time. This provides HCPs with an invaluable window into the patient's world, when otherwise they would have to rely on information reported after the event. The soon-to-be-added videoconferencing functionality will pave the way to further enhance remote care and introduces the potential for virtual clinics.

CHANGING THE PATIENT-CLINICIAN DYNAMIC

Having pioneered the technology for pulmonary conditions, there is huge potential for expansion into other therapy areas. This technology forms part of the growing area of digital therapeutics (DTx), where the combination of technology and drug treatments delivers evidence-based behavioural change and improved patient outcomes, enabling individuals or their caregivers to take greater control in preventing, managing and treating illness.

The optimism around DTx in recent years has been founded largely on its potential for changing the dynamic between HCPs and patients, particularly those with chronic conditions. This potential is now increasingly realised in commercial situations due to the alignment of a complex network of elements, including the drug and the device, hardware and software, data transfer and network connectivity, patient and HCP, and pharmaceutical companies and development partners.

> "Good communication is a crucial element on the journey to improving patient outcomes through digital healthcare services. BreatheSmart® supports effective communication by showing targeted educational information in text and video form."

As well as the continued introduction of innovative DTx products, these platforms are also being employed in applications such as clinical trials to return valuable data direct from the patients involved. In addition, the data on patient outcomes and clinical effectiveness held in DTx systems are used as the basis for value-based care contracts between HCPs and payers.

All these developments have been accelerated by the covid-19 pandemic, which has raised questions around the requirement for face-to-face interactions in more traditional healthcare settings, while also ushering in far greater acceptance of remote interactions via digital channels. Indeed, throughout 2020, the Digital Therapeutics Alliance, a non-profit association, petitioned international government bodies in Australia, Europe, the Middle East and North America to promote access to clinically validated digital therapeutic products during and after the pandemic.[4]

Even before covid-19, continued investment in DTx was expected to drive market value to a projected US$9 billion (£6.4 billion) by 2025.[5] Perhaps more significantly, DTx has the potential to trigger a paradigm shift in the treatment of chronic conditions, driven by a robust, data-led evidence base.

ABOUT THE COMPANY

Aptar Pharma provides drug delivery systems, components and services globally. Products include: nasal spray pumps, MDI valves, dose indicators and counters, DPIs, electronic/connected devices, eye-droppers, elastomeric components (for injectable delivery devices) and a two-step autoinjector.

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SPECIALTY LCP COMPOUNDS FOR ELECTRONICS INTEGRATION IN CONNECTED MEDICAL DEVICES

In this article, Young Kim, PhD, Senior Principal Engineer/Chemist, Don DeMello, Principal Engineer Field Development, and Philip Wilson, PhD, Marketing Director Medical, all of Celanese, discuss the benefits of recent advances in liquid crystal polymer for connected medical devices.

Remote monitoring of patient health, closed-loop control of therapeutic devices and the use of artificial intelligence for improving diagnoses through the analysis of continuously captured biometrics are all revolutionary ideas that show promise for improving patient outcomes and reducing the overall cost of healthcare. Full implementation of each of these industry initiatives requires the connection of medical devices to other nearby devices and to the Internet of Things (IoT).

Empowerment of patients to monitor their own health indicators and make decisions through familiar user interfaces, such as smartwatches or mobile phone apps, is leading to a convergence of medical devices with common consumer electronics. As consumer electronics have evolved in the 21st century to become faster, more powerful, more compact and more affordable, speciality materials have met the challenges of that industry.

While Celanese has more than two decades of clinical history for the use of Vectra® MT liquid crystal polymer (LCP) in medical devices, Zenite® LCP compounds have been developed to serve the electronics market. In this article, the authors envision the benefits of recent advances in LCP compounds optimised for dimensionally stable precision microstructures, for dielectric properties enabling wireless communications and for patterning of circuits on structural device components for part integration and total device miniaturisation.

In the December 2020 issue of ONdrugDelivery, Michael Kiely *et al* highlighted design considerations for high-volume manufacturing and tolerances in the electromechanical interface as critical components of a design strategy for connected devices.[1] The authors further note the need for cross-functional expertise for optimising device reliability. In this article, the authors highlight the role that Vectra and Zenite LCP compounds are able to play in this industry-wide effort.

DESIGN BENEFITS FROM THE USE OF LCP

Medical product designers are seeking to increase the number of electronic and electromechanical components in tighter and

> "Vectra MT LCP polymers are a natural fit for pushing the envelope on thin-wall designs to free up more internal space without sacrificing product strength, stiffness or dimensional control."

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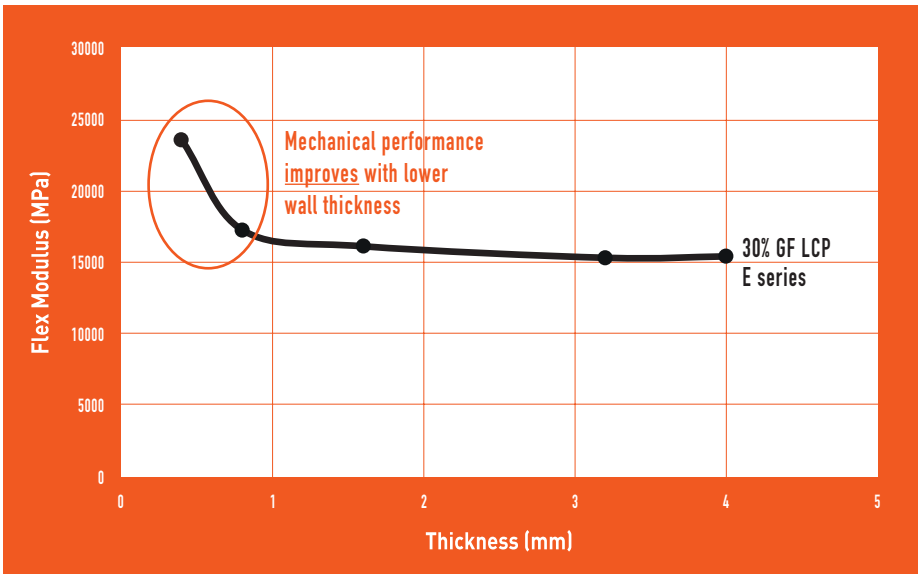

Figure 1: Paradigm shift in polymer thinking – design thinness determines LCP stiffness properties.

lighter spaces for patient utility, comfort and concealment. Vectra MT LCP compounds have proven valuable for wearable, portable injector designs, diagnostic devices, injector pen internals, surgical staple cartridges, surgical instruments and microneedle arrays.

Liquid crystalline polymers are a natural fit for pushing the envelope on thin-wall designs to free up more internal space without sacrificing product strength, stiffness or dimensional control. LCP resins increase in strength and stiffness with thin-wall designs due to their unique rod like molecular orientation, with optimum mechanical properties below 1 mm, as shown in Figure 1.

For specific application needs, Vectra and Zenite LCP resins can be tailored through comonomer chemistries and additive compounding to produce optimal mechanical, dimensional, thermal and tribological properties. Due to the extreme shear-thinning behaviour of LCP, complex thin-wall designs that can't be filled with other resins can be filled with LCP and a high microreplication of mould surface achieved – one reason why LCP is useful for micromoulded parts and microneedle arrays.

"For specific application needs, Vectra and Zenite LCP resins can be tailored through comonomer chemistries and additive compounding to produce optimal mechanical, dimensional, thermal and tribological properties."

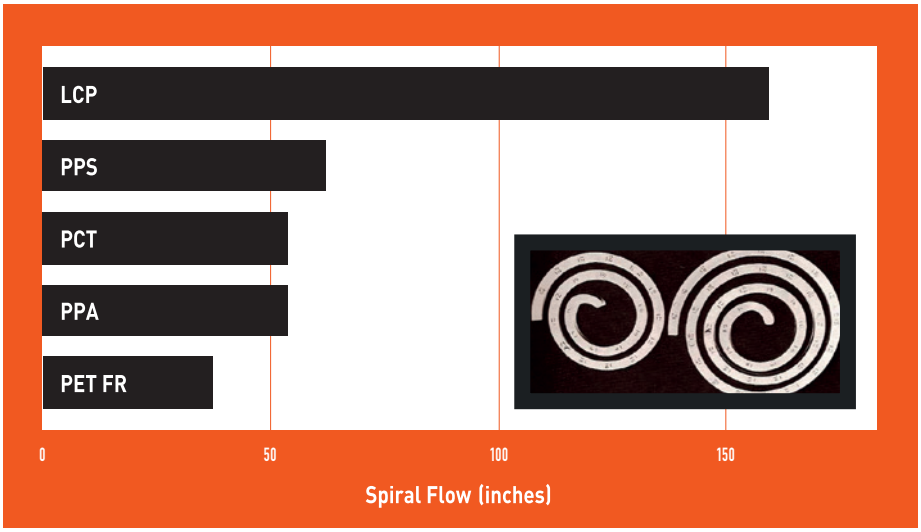

Figure 2: LCP offers superior flow and fill for thin wall structure and micromoulding details.

"High flow combined with high stiffness and strength allows designers to make thinner structures without sacrificing structural performance, enabling smaller parts and liberating more internal space for pharma or other components."

POLYMER AND PROCESSING CHARACTERISTICS OF LIQUID CRYSTAL POLYMERS

LCP compounds are unique in the world of engineering resins. LCP is a high-heat thermoplastic but its value for most medical devices is its exceptional flow in thin-wall designs. The morphology of LCP resin's nematic rod-like crystalline structure is very different from amorphous and semi-crystalline resins. Even unfilled LCP is extremely strong and stiff, behaving like a self-reinforcing polymer, with similar or greater mechanical properties than 20–30% glass fibre (GF) composites.

As described in a Celanese white paper on high-volume manufacture of thin-wall medical device components (https://explore.celanese.com/Thinwallmedicaldevices_LP-Registration.html) with Vectra MT LCP,[2] the material's high flow combined with high stiffness and strength allows designers to make thinner structures without sacrificing structural performance, enabling smaller parts and liberating more internal space for pharma or other components.

As shown in Figure 2, spiral flow characterisation of 30% GF LCP versus other 30–40% GF resins at 3.2 mm (0.125 inches) demonstrates the remarkable ability for LCP to fill long, thin channels compared with other engineering resins.

As illustrated in Figure 3, LCP has a low heat of fusion from its ordered molecular structure, which changes very little between its molten and solid phase – allowing a rapid

cycle from melt injection to part ejection.

Rapid cycling means higher moulding productivity, which leads to lower capital cost as fewer moulds are needed for high-volume production without the high mould temperatures commonly necessary with polyphenylene sulfide (PPS) or polyetheretherketone (PEEK). LCP can be processed at mould temperatures less than 100 °C, similar to many engineering resins and requiring only lower-cost, water-based temperature control units.

Other characteristics of LCP include:

- Excellent dimensional stability with low moisture absorption (0.03%) and low mould shrinkage (0.1–0.4%)
- Inherently flame retardant (FR) without FR additives
- Very clean, low extractables and ionics, food contact compliant
- Can be biocompatible with MT grades being US FDA master file listed
- Service temperature from -190 °C up to 240 °C, short term up to 340 °C
- High tensile strength (up to 185 MPa) and high tensile modulus (up to 30,000 MPa)
- Excellent barrier property to oxygen and moisture
- Sterilisable by steam, ethylene oxide, gamma radiation or H_2O_2 plasma
- Excellent chemical resistance
- Natural colour is opaque, off-white ivory with options for colouration.

TRANSLATING CONSUMER ELECTRONICS TECHNOLOGY TO MEDICAL DEVICES

In addition to medical devices, the benefits of LCP outlined above, combined with its thermal stability at temperatures used in common soldering processes and consistent humidity-stable dielectric properties at high frequencies, have enabled the reliable manufacture of high-speed electronic connectors of ever-decreasing size for electronic devices – beginning with personal computers and evolving into mobile phones and other connected consumer electronic and telecommunication devices from Bluetooth to 5G. As a broadly accepted, indispensable material for consumer electronics, Zenite LCP is a natural choice for the development of speciality compounds to meet adjacent needs for antenna substrates, micro-optical assemblies and circuits integrated into the framework or housing of these devices.

> "A higher D_k substrate allows the design of smaller antennas at the target signal frequency."

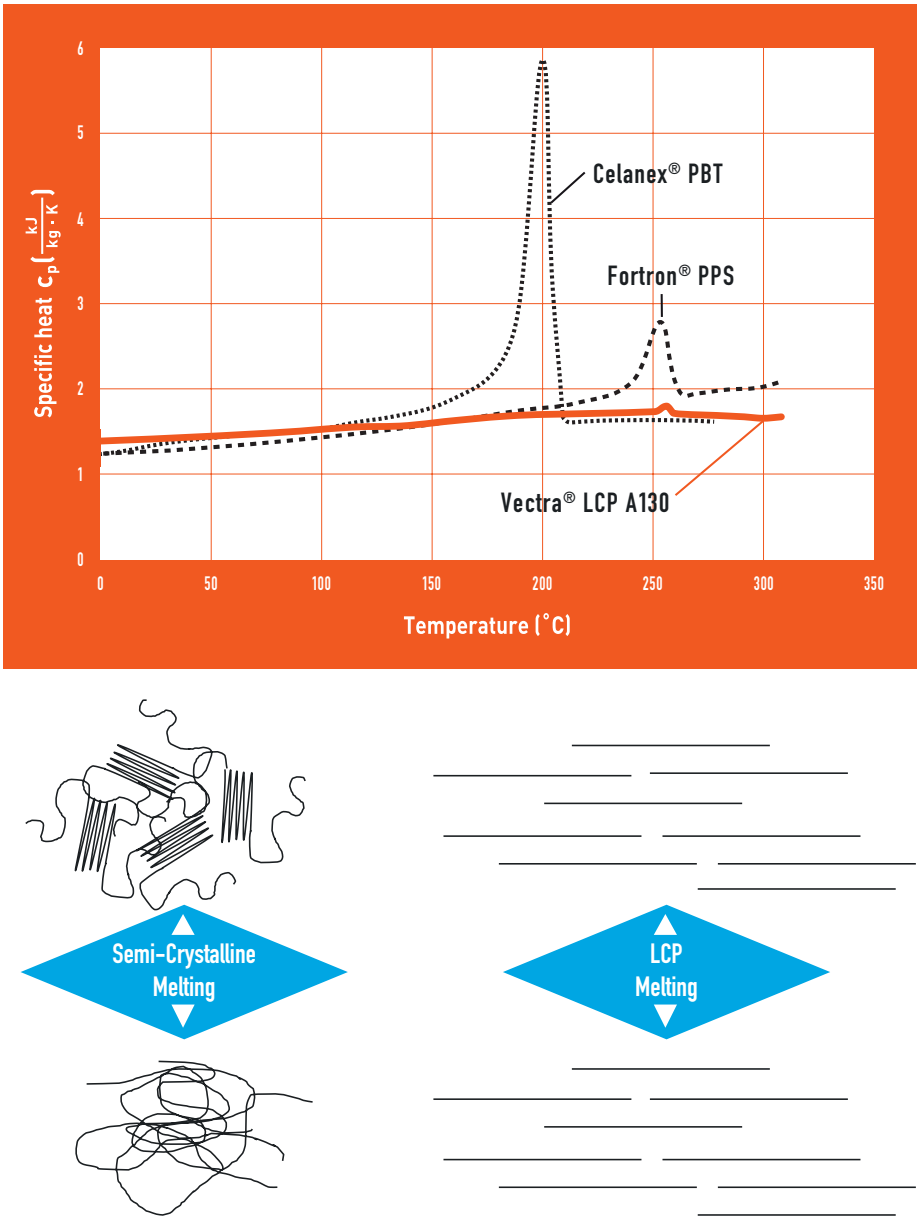

Figure 3: The unique morphology of LCP leads to rapid solidification and short moulding cycles.

Antenna Substrates

Medical devices may potentially be connected using any of several communications standards, depending on the desired connection, be it to a patient's personal device via Bluetooth or home WiFi network, to a 5G network for external monitoring via the IoT or to the Wireless Medical Telemetry Service (WMTS) for hospital use. Each of these require engineered antennas fabricated on low-dielectric loss substrates and can benefit from the ability to optimise the dielectric constant to the circuit or antenna array design.

For patch antenna arrays, each microstrip array element will be resonant with the operating frequency, f, at a patch length, L, equal to approximately one-half wavelength in the antenna substrate which is dependent on the dielectric constant D_k...

$$L \approx \frac{c}{f\sqrt{D_k}}$$

...where c is the speed of light. A higher D_k substrate allows the design of smaller antennas at the target signal frequency. In other design cases, low D_k improves signal integrity by reducing coupling between neighbouring antenna array

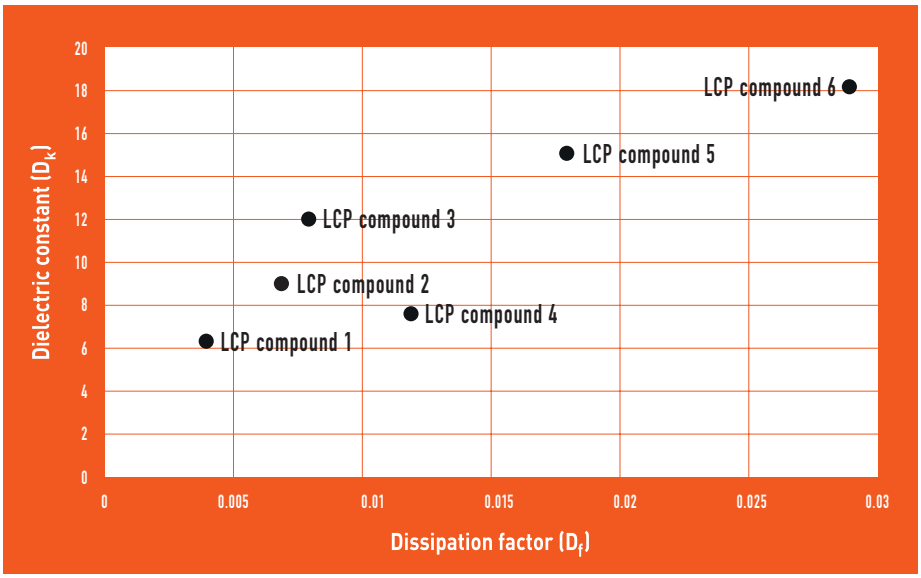

Figure 4: D_k/D_f values for high D_k Zenite LCPs, measured via International Electrotechnical Commission (IEC) 61189-2-721 method at 2 GHz.

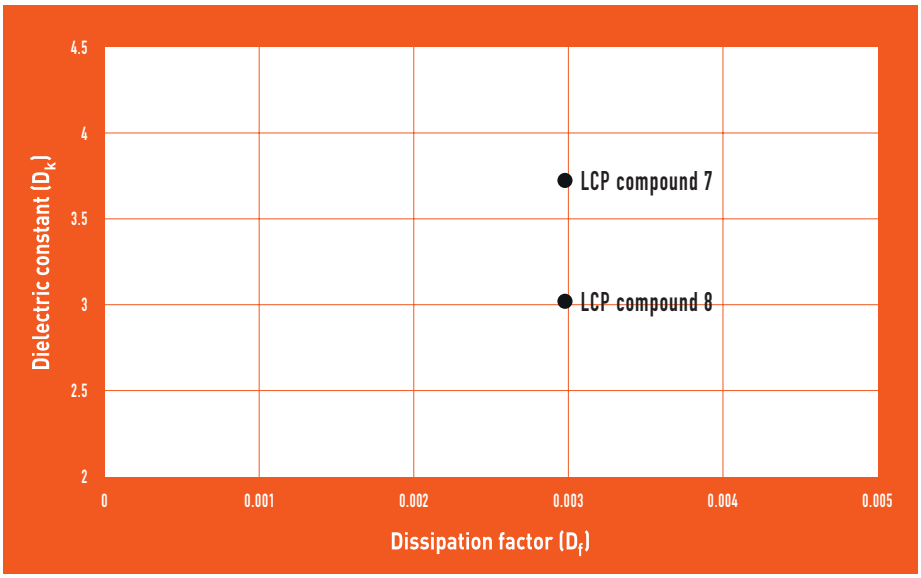

Figure 5: D_k/D_f values for low D_k Zenite LCPs, measured via IEC 61189-2-721 method at 2 GHz.

elements. LCPs have a D_k for typical filled compounds of >3.5, depending on polymer composition and filler type. The dielectric loss, D_f, can be less than 0.005. As shown in Figure 4, D_k can be increased through additives up to >20 while retaining the inherently excellent mouldability of LCP. The D_f increases with increasing D_k but still remains very low. As most fillers will have a higher D_k than polymers, lowering the D_k is more difficult than increasing it. Yet novel compound formulations have been identified, as shown in Figure 5, that can reduce the D_k to 3.0.

Patterned Circuits

Antennas that are conformally integrated into devices may use flexible films or moulded articles as substrates. These substrates must be suitable for the robust processes required to pattern conductive traces on them to form the elements of the antenna or antenna array. Typical methods for patterning circuits on LCP may be screen printing or ink-jet printing of conductive inks followed by electroplating.[3]

Laser direct structuring (LDS) is an alternative to the printing of conductive inks. LDS uses a photoactivated additive to create conductive traces in the host LCP polymer which can then be selectively patterned through electroless plating to complete the circuit fabrication process. Figure 6 (next page) shows an example of a test part demonstrating the steps of this process, starting with a moulded part (A), then a laser-marked photoactivated surface (B) and electroplated interconnects (C).

Micro-optical Assemblies

For the ubiquitous mobile phone, the incorporation of cameras requires precision

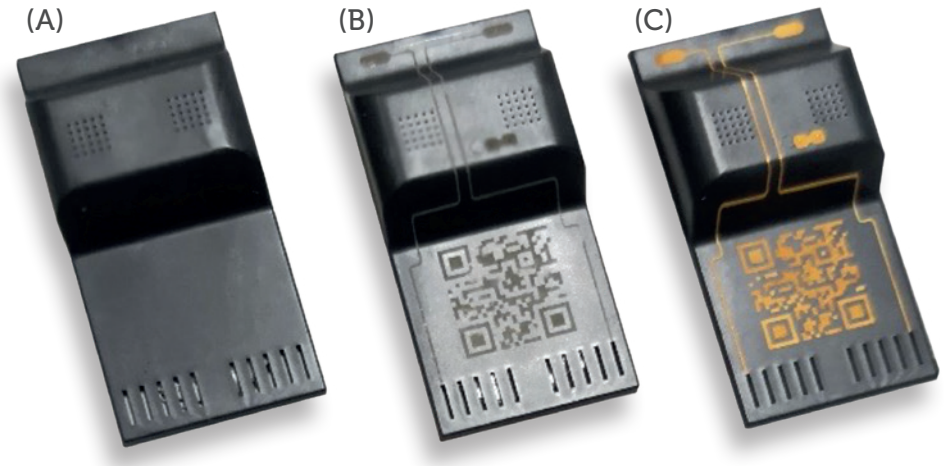

Figure 6: Example of laser direct structuring of circuit interconnects.

manufacture of highly durable micro-optical assemblies to properly align lenses to the imaging array (Figure 7). These assemblies must be dimensionally precise and stable, durable against torturous use by consumers and capable of reliable production of hundreds of millions of assemblies per year. Zenite® LCP SEA30N is the leading material for the manufacture of compact camera modules for mobile phones.

Many current smartwatches and fitness trackers and emerging wearable medical devices also rely on integrated optical systems for the photoplethysmographic (PPG) detection of volumetric variations of blood circulation.[4] Continuous monitoring of heart-rate variability can be used to detect a plethora of cardiovascular disorders. Sophisticated machine learning algorithms can provide further insights into major medical risks for atrial fibrillation, stroke and cardiomyopathy.[5]

This powerful technology can be integrated into the wrist, torso, forehead or earlobe – with the potential to combine this function with other existing wearable medical devices, such as hearing aids and glucose monitors, or consumer products, such as earphones and smartwatches. This combination of functions into a single device is likely to benefit from further reduction of the size of the optical assemblies and, subsequently, from the translation of the well-established technologies for the manufacture of mobile phone cameras – including the use of specialty LCP compounds.

SUMMARY

Connected medical devices promise to improve the effectiveness and reduce the cost of healthcare. Fortunately, the adjacent industry in consumer electronics can inform these solutions. Suppliers with a presence in both industries can provide unique insights and support to device designers in their product development endeavours. The Vectra and Zenite LCP lines of engineered compounds offer a translatable solution set, yet products alone are not a complete solution. The necessary innovations in how devices are designed, manufactured, regulated and secured[6] call for a creative and collaborative problem-solving approach that relies on a new type of expansive thinking, less constrained by the solutions of the past and more open to creating the solutions of the future.

NOTE: Vectra MT LCP is the medical grade of Vectra/Zenite LCP developed and manufactured with the medical and pharmaceutical regulatory landscape in consideration.

ABOUT THE COMPANY

Celanese Corporation is a global leader in the production of differentiated chemistry solutions and speciality materials used in most major industries and consumer applications. The company's businesses use the full breadth of Celanese's global chemistry, technology and commercial expertise to create value for customers, employees, shareholders and the corporation. As Celanese partners with its customers to solve their most critical business needs, the company strives to make a positive impact on its communities and the world through The Celanese Foundation. Based in Dallas (US), Celanese employs approximately 7,700 employees worldwide and had 2020 net sales of US$5.7 billion (£4.1 billion).

Celanese supports key applications and the demanding requirements of the medical market, with 40 years' experience and one of the broadest ranges of high-performance polymers and thermoplastics in the world. Its medical technology portfolio includes solutions for applications in the

Figure 7: (A) Exploded view of compact camera (module frame identified by arrow). (B) Photograph of a compact camera module frame. Image courtesy adventtr / iStock / Getty Images Plus.

space of drug delivery, medical devices, orthopaedics, advanced surgical instruments and connected devices. From feasibility to development to commercialisation, Celanese scientists and engineers provide a range of development services, GMP material supply and regulatory support.

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ABOUT THE AUTHORS

Young Kim, received a PhD in Materials Science and Engineering from the University of Delaware (US). He joined Celanese in 2008 and currently works as a Senior Principal Engineer. He has commercialised more than 15 new products in the electronics and automotive industries and filed more than 40 patents in engineering plastics and conductive plastics over the last 10 years.

Don DeMello is a Principal Field Development Engineer with the medical polymers business of Celanese Engineered Materials. Mr DeMello has a BSME from Worcester Polytechnic Institute (US) and, since university, has worked in the engineering resins industry for over 30 years in a variety of application and market development roles across a wide range of markets. He enjoys working with customers on the forefront of new and improved product developments where resin specification decisions are made based on design and performance needs.

Philip Wilson, PhD, is a Marketing Director with the medical polymers business of Celanese Engineered Materials. He has a PhD in Physics from the University of Texas at Austin (US) and has worked for 20 years in a wide range of roles in the materials and chemical industry. He enjoys learning about new areas of technology to identify new opportunities for innovation.

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NEW DIRECTIONS
Technology Consulting

PATENTS ARE IMPORTANT FOR SMART HEALTHCARE PRODUCTS

Here, Napoleon Monroe, Managing Director of New Directions Technology Consulting, discusses the value of internet-connected smart devices in present-day healthcare, and introduces the mMed patent portfolio, of which Mr Monroe is the sole inventor, and which contains five US patents for key connected health technologies.

A BRIEF HISTORY OF SMART MEDICAL DEVICES

Once upon a time, in the days before 2006, the healthcare forest was smaller and inhabited by fewer animals of the healthcare family. No commercially available wireless communications devices, such as smartphones, for monitoring pharmaceuticals and medical devices in near real time existed in the real world. There was no Internet of Things (IoT) and certainly no Internet of Healthcare Things (IoHT). There were few tools available to assist patients with the use of their pharmaceuticals and little information on patients' health outcomes as related to compliance with therapeutic protocols.

But, even in 2006, there was some recognition that patient compliance with drug regimens was poor. That year, an article was published discussing possibilities for a smart pill case with its own internal memory.[1]

As time passed, more and more products started to be used in the home by patients, rather than by practitioners in professional healthcare and clinical settings. Animals in the forest saw that technology could help patients with their medications. New Directions Technology Consulting began filing the mMed portfolio patent applications in 2006.

By the early 2000s, an industry of combination product contract development and manufacturing organisations (CDMOs) began to take shape. Some device design companies were vertically integrated internally and, through mergers and acquisitions, became full-blown pharma contract manufacturers. CDMOs filled the gaps in pharma's knowledge of medical devices and helped to avoid problems which can lead to device-related complaints, recalls and warning letters (Figure 1). The first smart autoinjector combination product – Bayer's Beta Connect for multiple sclerosis -- was approved by the US FDA in September 2015.

By 2021, the healthcare forest population had grown very large; new genera and species in the healthcare family had been identified and studied. There were many new treatments available that were unknown in 2006. Biologic products had come to prominence. There were hundreds of companies developing or making smart IoHT products and systems, including

Figure 1: CDMOs have filled gaps in pharma companies' device design knowledge, helping them to avoid device-related complaints, warnings and recalls.

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Figure 2: Between 2006, when the mMed patent portfolio was filed, and now in 2021, the number of animals in the healthcare forest has grown immensely; they will all need to adapt to the coming storm of telemedicine, or be blown away by it.

smartphone-connected portable drug delivery and other medical products. Mergers and acquisitions activity was brisk.

However, there were also new challenges to face. The ageing patient demographic and shortages of healthcare practitioners had been known of for years. And while opportunities for improving patient outcomes and stakeholder benefits from telemedicine and product internet-connectivity had been touted for years, the technology was yet to see a major breakthrough into mainstream healthcare.

In 2020, the covid-19 pandemic dramatically accelerated the need for and acceptance of telemedicine. Serious efforts to validate telemedicine systems and demonstrate outcome improvements followed this suddenly increased need. The time for serious adoption had finally arrived… thanks to a global pandemic.

A modern Aesop might compare telemedicine now to a persistent severe storm in the forest. Some animals will adapt and thrive in the storm, while others will perish. Old trees which had been home to some species will be felled, and those animals that made their homes there will need to move on or be lost to history (Figure 2).

PATENTS IN THE FOREST

To help make sense of the current state of connectivity patents filed in the healthcare forest, New Directions recently commissioned a patent research service to review applications and patents owned by a handful of known smart combination product stakeholders and other firms believed to be interested in smart drug delivery, including some prominent CDMOs. New Directions specified some companies and also suggested keyword searches, including Bluetooth, smartphone, drug, pharmaceutical, biologic, autoinjector or pill.

The initial review of the patent research service report and other research supports the following statements about the commercial relevance of smart healthcare:

- **Acting on patent opportunities and risks related to smart combination product and drug-delivery product patents was neglected by many stakeholders.** Their focus was elsewhere. Such neglect has had no immediate effect. However, within a few years, there may be unwelcome consequences. Some stakeholders may regret not filing patents earlier.
- **Regulatory (US and international) authorisation holders (AHs) concentrated their patent filings on their pharmaceuticals and biologics rather than drug delivery.** Pharma companies and venture capitalists are the typical AHs looked at here. This approach followed the classic first-to-market imperative. Only later did designs for smart patient support become a norm. Smart medical and consumer health device companies tended to concentrate filings on diagnostics, digital therapeutics and information systems other than medication management.
- **Until after 2010, most, but not all, smart drug delivery organisations and CDMOs concentrated primarily on the means that made their non-connected devices function.** Those who chose to focus on connectivity earlier will have better odds for long-term success.
- **The mMed patent application filings predate most of the filings made by others on smart drug delivery products.** This makes patents in the portfolio valuable defensively and offers possibly lucrative offensive opportunities.
- **A wave of digital start-up patent application filings began in the early 2000s.** Some have been abandoned. Post covid-19 filings may be, as yet, unpublished. All filings are subject to review for patentability over prior art.
- **Disruptors of legacy healthcare assumptions and institutions are expanding in telemedicine, including MD consultations, prescription fulfilment and home drug delivery assistance.**
- **Competition in the connectivity space is becoming intense.** There is a huge market looming. Companies who figure out how to secure traction first and maintain their momentum will reap huge rewards. When companies in these categories concentrate on medication management, the fighting will be fierce within and between the category silos.

TRENDS AND CDMOS

More and more often, pharmaceutical payers, such as insurance companies, now require real-world evidence of outcomes before they provide reimbursement. Regulators are demanding product lifecycle

> "Demands for improving homecare during the covid-19 pandemic have driven acceptance and expansion of telemedicine. This expansion has gone into fields including psychiatry, dentistry and veterinary medicine, all of which prescribe Rx medications."

Figure 3: New Directions has published multiple articles in ONdrugDelivery on the subject of telehealth and smart medical devices.

management and that more attention be given to corrective and preventive actions. Internet connectivity for pharma/biotech-related delivery products is integral to gaining value from telemedicine and homecare services. The mMed portfolio enables internet-connected combination products and other medical devices to become smart products.

Demands for improving homecare during the covid-19 pandemic have driven acceptance and expansion of telemedicine. This expansion has gone into fields including psychiatry, dentistry and veterinary medicine, all of which prescribe Rx medications. Recognition of health disparities is another rather new factor driving change. Smart combination and diagnostic products are critical to homecare outcomes for pharma treatment.

The literature over the last decade is replete with discussions of the many reasons that patients do not benefit from pharma products, including medication cost, lack of patient training, understanding and support, and the siloed US healthcare system. In 2021, the recognition of the lost health and economic opportunities related to medication use is becoming widely understood. To date, New Directions has published and presented on multiple smart pharma and related products (Figure 3).[2-5]

Pharma companies frequently use CDMOs to develop and/or manufacture drug delivery devices for their products. Each pharma customer has market estimates for its own specific products. CDMOs can aggregate the information from working with their customers to gain a clearer understanding of the market size and probable growth. Therefore, CDMOs know quite well the market for smart drug delivery devices. Such devices are a primary focus of the mMed patent portfolio.

Many smart device CDMOs are sound, profitable companies, and even CDMOs and AHs based abroad wish to supply products to the US market. Smart device CDMOs have grown based upon the pharma industry's desire to design and plan manufacturing for an eventual introduction of smart drug delivery systems. The exact terms of the CDMO/pharma contracts are known to the principals; however, ownership of related intellectual property (IP) has sometimes been contentious. CDMOs have the proprietary knowledge to monetise the mMed patent portfolio across their customer and competitor bases. By sub-licensing, they can co-operate and profit where appropriate.

"The literature over the last decade is replete with discussions of the many reasons that patients do not benefit from pharma products, including medication cost, lack of patient training, understanding and support, and the siloed US healthcare system."

The covid-19 pandemic has focused national attention on health at both the personal and the population-wide level. This focus, among other factors, has accelerated investment in internet-connected drug delivery and connected diagnostics. The covid-19 pandemic has also catalysed investments in smart healthcare products. Investment in the sector remains exceptionally strong as the US and other countries worldwide continue to focus on ways to promote a healthier society. The benefits of connected home-based delivery of healthcare, combined with practitioner care, is fuelling demand.

Connectivity is becoming the "new normal" for self-administered products; one pharma company has even announced its intention to introduce connectivity for all its self-administered combination products. Delivery devices are now "digital by design", not digital as an afterthought. It is evident that smart medication management is essential to improving health.

THE MMED PATENT PORTFOLIO

The mMed patent portfolio is particularly strong in claims related to smart combination and related products. It also covers some internet-connected consumer products and packaging related to drug delivery products and some medical devices. It is believed that many healthcare manufacturers making smart products may already be practising the mMed patents.

New Directions Technology Consulting, a single member LLC, is the assignee of the mMed portfolio of medication and telemanagement patents. As the sole inventor of the mMed portfolio, I have published and presented on the portfolio for some years. The mMed portfolio contains five granted US patents which have 16 independent and 179 dependent claims (Figure 4). Granted Israeli and Australian patents are also included in the portfolio. None of the patents in the portfolio have been challenged.

"Connectivity is becoming the 'new normal' for self-administered products; one pharma company has even announced their intent to introduce connectivity for all its self-administered combination products."

Figure 4: The mMed patent portfolio contains five granted US patents, all lasting until 2026 at the earliest.[6-10]

Patents granted to others have cited patents in the mMed portfolio. Currently, there are no licensees or encumbrances on any of the patents. The licence for a smart device to monitor epinephrine autoinjectors for treatment of anaphylaxis has expired. This simple ownership and clear, unencumbered title simplifies any transaction.

Other offers for purchase and licensing have expired or have been declined as inadequate. Terms of all previous licences and offers to purchase are confidential. My belief that the value of the portfolio will now become apparent to practising entities has been validated by research on patents held by others.

History Related to the mMed Patent Portfolio

We began filing the mMed patent portfolio in 2006. The iPhone was introduced in 2007. Standards for medical device and pharmaceutical identification came in 2013. Because of United States Patent and Trademark Office (USPTO) prosecution delays, the '085 patent product information management systems extend to Autumn 2028. This patent claims a "product tag", which may be a barcode.[6]

Pharma manufacturers are now required to serialise Rx pharmaceuticals with a product tag. Medical device manufacturers are required to place an informative product tag on many products. When we filed the application for the '085 patent, there was no such requirement. A phrase used in a call with the patent examiner on the '085 patent was "in the wild," referring to the use of barcodes and other automated identity and data capture (AIDC) methods outside institutions. At the time of filing and at the time of the publication there was, to the best of our knowledge, no discussion at the FDA on the subject at all, as there is now with today's focus on "real-world data" generating "real-world evidence" for pharma or medical devices. At that time, regulators were essentially relying on randomised clinical trials for new product approval decisions. The unique device identifier (UDI) and Drug Supply Chain Security Act (DSCSA) became regulations and laws separately in 2013.

Regulatory bodies in the US and elsewhere now often demand ongoing real-world evidence across a broad population for a product to remain on the market. Payers are demanding proof of improved patient outcomes. Manufacturers, distributors and others use these tags for supply chain management. As ever more

products incorporate or communicate with software, it becomes essential that software versions be tracked through the supply chain to the patients. Near real-time knowledge allows greater responsiveness to patient experience.

Portfolio Specifics

Some smart portable product containers are, for example, product containers intended for use with communications devices, such as smartphones, which have both long- and short-range communications capabilities, as claimed in the portfolio's '658 patent.[7] Because smartphones, with their expansive range of capabilities, have become rather ubiquitous, this type of product container is most frequently developed and promoted as a smart drug delivery system.

Injection devices with reporting capabilities are claimed in the portfolio's '393 patent.[8] Some companies have elected to build communications into their injection devices. Some other smart drug delivery products and systems are, for example, injection devices and cases with reporting ability, which are covered by the '778 patent.[9] Product containers or attachments covering all or part of the drug delivery device are claimed in the '658 patent. The portfolio also contains a US patent on central facilities that communicate with a portable container via a mobile device.[10]

The '085 patent extends to 2028, while the other four US patents and foreign patents in the mMed portfolio extend variously into 2026 or 2027. While the portfolio was filed early, please note that "35 US Code § 286 – Time limitation on damages" allows filing of infringement complaints for six years after patent expiration in some cases.

Smart drug delivery devices, such as smart autoinjectors, have only started becoming profitable for pharma companies in the last couple of years. Pharma's accounting is likely to be complex. However, some smart drug delivery CDMOs have been profitable for years. Government infringement could be the basis for a claim.

Given that the earliest expiration of any US patent in the mMed portfolio is 2026, a purchaser's or licensee's damages claim period remains long. This improves the commercial relevance of the portfolio.

New Directions Technology Consulting currently owns the mMed Patent Portfolio and welcomes inquires.

ONCOMING DISRUPTION IN THE HEALTHCARE SPACE

Telemedicine is also opening the door to healthcare innovator disruptors. One of these disruptors has:

- A greater capacity for collecting and analysing data than many existing healthcare stakeholders combined
- Massive capital reserves
- A deep and through understanding of the US consumer market
- Know-how on gaining value through customer centricity
- The ability to synthesise a range of information to serve its customers both profitably and conveniently
- An extensive knowledge of US law
- Experience with a wide variety of vendor relationships
- An appetite for growth in the healthcare industry
- Independence.

This disruptor is Amazon, the pioneer of "retailing without walls" – tele-retailing. New Directions will be digging into this subject and the potential of Amazon in the healthcare space in ONdrugDelivery's August 2021 issue on Industrialising Drug Delivery.

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.

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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.

The Value of Intellectual Property (IP) for Connected Drug Delivery Now

COVID-19 Drives Telemedicine and Connectivity:

Healthcare stakeholders are investing heavily in telemedicine and connectivity.

Pharma's and other stakeholders' growth, profitability, shareholder value and reputation are threatened. Competitive, legislative, regulatory and administrative pressures to prove the value of treatments and reduce costs are rapidly increasing. This is especially true for Pharma's expensive new treatments.

Connectivity can help address stakeholders' issues by increasing the value of treatments and improving patient outcomes through enhanced patient communication and the digitization of patient interactions.

The enablers for Pharma connectivity are in place. Researchers and suppliers have developed systems and devices for connectivity. The Informa MedDeviceTracker and BioMedTracker connectivity flags now allow patent owners and others to research opportunities for cooperation as well as competitive and infringing products.

Reasons To Focus on U.S. IP

The U.S. healthcare market is the largest unified Pharma market in the world and offered the greatest flexibility to recognize and reimburse the value of Pharma treatments.

The U.S. led in the development and marketing of many innovative, often expensive, healthcare products. U.S. regulatory systems for connectivity are better defined than those elsewhere. Consumer advertising is legal in the U.S. The emphasis on telemedicine has further enabled product connectivity.

The U.S. market provides world-leading access to venture capital and technology transfer in the largest specialty Pharma market. These entrepreneurial interests have sustained a robust U.S. healthcare innovation system. U.S. allows direct-to-consumer advertising for Rx products.

Advantages of Owning Patents Covering Technology for Pharma and Medical Devices Connectivity

Among the many advantages are:

- Freedom to make, use and sell using connectivity.
- Low investment to secure early-mover advantage and great potential returns in connectivity.
- Added profits from new sales of and loyalty to existing and future Pharma products and services based on connectivity, as well as sublicensing.
- Ability to stop infringement, including importation of infringing products, and to collect damages.
- Ability to implement systems to gather real world data, including information on patient preferences, patterns and experiences; to demonstrate product value to patients, prescribers and payers (offensive and defensive).
- Exclusivity in certain competition, or even in the use of connectivity with some products, including use in clinical trials.
- Avoidance of risks, including access to patents and use by competitors and trolls.
- Broader opportunities for scalability and regulatory compliance across a range of use cases, as compared to investments in any specific treatment or technology.
- Opportunities to encourage cooperation and synergies with other stakeholders, including affiliated and external businesses.
- Demonstrating vision and leadership in providing better patient outcomes, and in enhancing shareholder value and corporate reputation.
- Understanding related IP allows internal resources to understand, assess and advise on risks and opportunities.
- Ability to better address the unknown unknowns of product development and use.
- Potential tax-saving opportunities.

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HOW DIGITAL MEDICAL DEVICES ARE MEETING THE CHALLENGES OF CLINICAL TRIALS

In this article, Josh Hopkins, Program Manager at Noble, discusses the challenges that have been present in conducting clinical trials at a central brick-and-mortar location since their inception, and how modern digitisation presents an opportunity to improve clinical trial methodology by liberating it from the need for an in-person central study site via the use of digital medical devices and technologies.

The Internet of Things (IoT) – defined simply as a system of internet-connected devices that collect and transfer data over a wireless network – has transformed healthcare, from electronic health records and patient portals to telemedicine. The introduction of next-generation 5G wireless technology in 2019 is serving to further advance the vast potential of digital health technology.

UNDERSTANDING DIGITAL HEALTH

The broad scope of digital health includes categories such as mobile health, health information technology, wearable devices, telehealth and telemedicine. Using computing platforms, connectivity, software and sensors, digital health technology creates opportunities for healthcare providers (HCPs) and other stakeholders to improve medical outcomes for patients and enhance the efficacy of treatments.

These technologies span a wide range of uses, from applications in general wellness to applications in the medical device sector. They include technologies intended for use as a medical product, in a medical product, as companion diagnostics or as an adjunct to other medical products (devices, drugs and biologics). They may also be used to develop or study medical products.[1]

Digital Medical Devices

Connected devices, such as smart insulin pens, connected inhalers and asthma monitors, empower patients to better manage their own health and access help quickly if something goes wrong. These devices also allow HCPs to monitor ongoing conditions and gather data remotely, allowing for observation and treatment that was previously only possible in an institutional setting.[2]

Consider respiratory conditions, such as asthma, where a lack of adherence to

> "Clinical trials are a complex process, from site selection and patient enrolment to study monitoring and data management. Digital health technology, with its connected ecosystem of applications and devices, presents a clear opportunity to improve data management in the clinical trial process."

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prescribed medication and insufficient disease monitoring can lead to uncontrolled or exacerbated health problems. Connected inhalers can track medication use, provide audio and visual alerts to remind patients to take a dose, and offer guidance to improve their inhaler technique and adherence to a medication plan, all leading to better management of the patient's condition.

Aptar Pharma is a major player in this space and offers a broad range of digital healthcare solutions for the prevention, diagnosis and treatment of diseases, as well as patient monitoring and health management. Its wide range of connected devices, including in injectable and nasal drug delivery, is patient friendly, intuitive to use and supported by training devices from Noble, an Aptar Pharma company, that are developed and designed to replicate the real device experience.

DIGITAL HEALTH TECHNOLOGY AND CLINICAL TRIALS

Clinical trials are essential for evaluating the safety and efficacy of new drugs, medical devices and other health system interventions. Clinical trials are a complex process, from site selection and patient enrolment to study monitoring and data management. Digital health technology, with its connected ecosystem of applications and devices, presents a clear opportunity to improve data management in the clinical trial process.

The Challenges of Current Clinical Trial Methods

In 1943, the first modern clinical trial for treatment of the common cold was conducted in the UK. Over 1,000 patients participated in the double-blind trial, whereby neither patients nor doctors knew what treatments were being given to which patients until the clinical trial was complete. Each patient travelled an average of two to three hours to reach a single, centralised trial location. The observations by clinical investigators were written by hand, and it took 18 months to synthesise the results and generate a report.[3]

Nearly eight decades later, traditional clinical trials remain cumbersome and labour intensive. Biotechnology companies must still recruit large numbers of patients to get the correct, statistically significant sample size, and most trial participants still have to go to brick-and-mortar research centres to receive treatment, often recording their symptoms and side effects on paper forms.

"Sponsors, such as Sanofi and Pfizer, are aligning their business development strategies and designing new apps and wearables that not only enhance the collection of data, but also improve direct communication with patients, making it possible to adjust their studies on a timely basis."

These operational inefficiencies inflate costs, increase participant burden and extend already lengthy clinical trial timelines. In addition, for patients who do not live close to a research site or who have mobility or scheduling constraints, participation can be expensive, or even impossible, thus increasing disparities in access to research and limiting the diversity of participants in a trial.[4]

Compounding these problems, the covid-19 pandemic has caused more than 1,000 clinical trials to be put on hold due to the risk of the virus spreading among trial participants, other nearby patients and healthcare workers.[5] Nonetheless, more than half (54%) of surveyed device and diagnostics industry professionals anticipate a full recovery of clinical study activity before the end of 2021.[6]

One way to address these challenges lies in transforming the traditional clinical trial approach via the adoption of innovative new digital technologies to improve recruitment, patient retention, data collection and analytics.

The Future of Clinical Trials in the Digital Age

As the world progresses toward a more digitised future, sponsors involved in clinical trials reference four main benefits of adopting digital technology:[7]

1. Cost reduction by 50% per participant compared with current onsite clinical trial methods
2. Increased recruitment rate and diversification by making trial participation more convenient
3. Increased data collection from participants, since longer time spans can be monitored
4. Increased data quality based on participants' natural environment instead of data collected by survey at the trial site.

Sponsors, such as Sanofi and Pfizer, are aligning their business development strategies and designing new apps and wearables that not only enhance the collection of data, but also improve direct communication with patients, making it possible to adjust their studies on a timely basis.

Another emerging innovative strategy is patient centricity. This approach puts the focus of clinical trials on the patient, in order to better respond to their needs and ensure their commitment throughout the clinical process.[7]

The Role of Connected Medical Devices

Connected medical devices and other digital technologies are playing a growing role in clinical research, with important implications for stakeholders across the entire research ecosystem. In both 2017 and 2018, over 1,100 unique trials included use of a connected digital product – a tenfold increase since the early 2000s.[8]

For pharmaceutical manufacturers and contract research organisations (CROs), the emergence of connected digital products into the clinical research space presents an opportunity to include novel trial endpoints that use real-world evidence. For patients, connected digital products can reduce the burden of trial participation and increase inclusivity by fostering remote monitoring and encouraging the enrolment of individuals who might not otherwise be able to participate due to socioeconomic circumstances or travel limitations.[8]

NOBLE SOLUTIONS SUPPORT THE ADOPTION OF DIGITAL MEDICAL DEVICES IN CLINICAL TRIALS

The medical device industry shares common regulations and guidance with the pharmaceutical industry. However, differences can exist relative to the design and management of clinical studies. Having the right partners is important for the adoption of digital medical devices in clinical trials.

Noble is one such partner. An industry leader in providing drug delivery training device programmes for pharmaceutical companies and original equipment

Figure 1: The AdhereIT® 360 Base — one of two AdhereIT® devices. The device flashes green to illustrate a complete and proper injection.

Figure 2: A patient practising with a training autoinjector and the AdhereIT® 360 Base.

Figure 3: The AdhereIT® 360 Clip — one of two AdhereIT® devices. The device is shown here with a training autoinjector.

manufacturers, Noble manufactures training devices for autoinjectors, injectable prefilled syringes, on-body systems and respiratory devices for patients who self-administer their prescribed drug therapies.

According to the European clinical research organisation ZAK-Pharma, as many as 85% of clinical trials fail to recruit and retain enough patients to meet their enrolment timeline.[9] Alongside Aptar Pharma, Noble is developing connected training solutions that provide a more patient-centric experience and can support the digital transformation of clinical trials.

"Over the last year, we have seen an acceleration in pharma companies choosing to perform remote clinical trials," states Adam Shain, Director, Digital Healthcare at Aptar Pharma. "Having a real-time mechanism with both devices and apps to ensure patients are utilising their medication correctly is critical for the success of any self-administered clinical trial. Partnered with Aptar's digital ecosystem, Noble and Aptar Pharma's AdhereIT® – a connected device that uses Bluetooth technology to pair autoinjectors with a software application to provide real-time feedback, both through the device and through the paired app, about whether a patient's injection was performed correctly – plays a critical role in overcoming these challenges."

Tracking, Monitoring and Guiding Patients to Improved Adherence

As mentioned, one such example of a connected device used to monitor patient self-injection adherence is Noble and Aptar Pharma's connected device, AdhereIT® (Figures 1–3). In addition to adherence monitoring, both the device itself and the app give patients feedback about whether a proper injection was performed. AdhereIT®'s training platform also includes a dashboard for HCPs to monitor patients' therapeutic performance and provides biopharmaceutical companies with valuable non-patient-specific adherence behaviour information.

"Connected medical devices represent the future of healthcare for patients, pharmaceutical 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," said Tim McLeroy, Noble's executive director of marketing and patient services. "The connectivity of digital technology solutions like AdhereIT® also creates market differentiation and enables value-based contracting for biopharmaceutical companies and medical device manufacturers to survive in a competitive and challenging marketplace."

> "Another way Noble is contributing to streamlining and digitising clinical trials is with "Human Factors +", an expanded service that combines human factors engineering with Noble's robust training solutions."

Empirical and Analytical Evidence with Human Factors Engineering

Another way Noble is contributing to streamlining and digitising clinical trials is with "Human Factors +" (HF+), an expanded service that combines human factors engineering with Noble's robust training solutions. By doing so, Noble helps advance the development and testing of new self-administered medical products that optimise efficacy and safety while minimising use errors and the risk of adverse events.

"Human factors engineering provides empirical and analytical evidence that a device and its labelling can be used safely and effectively by the intended patient," said Kevin Cluff, PhD, Noble's acting

director of human factors. "The process involves testing the numerous touchpoints where patients interface with a drug product, including packaging, instructions for use (IFUs), prescribing information, quick reference guides and device indicators and controls."

Noble's HF+ capabilities complement the company's expertise in the areas of conceptualisation, design and development, mechanical/electrical/software engineering, project management, quality management, manufacturing, commercialisation and logistics services.

Meeting the Challenges of Clinical Trials

Noble's connected medical device solutions and other services offer the following benefits to meet the challenges of clinical trials:

- Reduction of timelines due to increased speed-to-market
- Reduction of false positives
- Reduction of dropouts due to non-compliance
- Remote patient monitoring
- Assurance that a complete dose has been given
- Identification of medication errors
- Capture of date and time of injection
- Easy and quick capture and aggregation of data
- Minimisation of the need for live visits and travel
- Decentralisation of study
- Patients are active stakeholders rather than passive participants.

CONCLUSION

Harnessing the digital convergence of people, information, technology and connectivity offers real opportunities to improve clinical trials. Digital medical devices can help meet the challenges of today's arduous clinical trials, providing a better patient experience and more holistic view of a patient's health, thus enabling remote patient monitoring and enhancing the quality, quantity and frequency of data collection during clinical trials and with connected devices in the real world.

ABOUT THE COMPANY

Noble develops robust training devices and onboarding solutions for the world's top pharma and biotech companies and is focused on fostering healthy patient outcomes for those who self-administer drug therapies. Noble manufactures and commercialises training devices that mimic the exact feel, force and function of drug delivery devices, including autoinjectors, prefilled syringes, on-body injectors, nasal sprays and pulmonary inhalers, in order to increase patient adherence and confidence and decrease usage errors. Noble was founded in 1994 and is based in Orlando, Florida.

Noble is an Aptar Pharma company, which is part of AptarGroup, Inc, a global leader in the design and manufacturing of a broad range of innovative drug delivery, consumer product dispensing and active material solutions that serve a variety of end markets, including pharmaceutical, beauty, personal care, home, food and beverage.

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Josh Hopkins is Program Manager at Noble and has successfully developed and championed the growth of regulated product pipelines at various organisations throughout his career. His experience includes leading development and strategy for innovative, flagship products while managing cross-functional teams for initiatives with leading pharmaceutical and medical device manufacturers. Mr Hopkins holds a bachelor's degree in Biological Engineering and a master's degree in Biomedical Engineering.

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THE POWER OF ONBOARDING: BUILDING PERSUASIVE USER EXPERIENCES FOR COMPANION APPS

In this article, Ben Cox, PhD, Head of Digital Design at Team Consulting, discusses the value of onboarding in drug delivery device companion apps, and how it is a key component of converting a one-time user to a repeat user, unlocking the true value of companion apps as a tool for combating poor adherence to medications and gathering high-quality data.

In recent years there has been a growing interest in using apps for improving adherence to medication. Smartphone ownership amongst adults in the US and parts of Europe is now approaching 90%[1] and, with increased access to this technology, the number of available health apps has grown to an astonishing 370,000.[2] While the covid-19 pandemic has led to a 25% surge in the number of health app downloads, up from four to five million downloads every day,[3] many patients are still not using these solutions as much as they might, especially for managing chronic conditions.[4]

With smartphone ownership set to increase further in the coming years, the pharmaceutical industry has been actively engaged in developing digital solutions. These include drug delivery companion apps to tackle the challenge of poor adherence to prescribed medications and to explore the huge potential of the new and better data apps can collect to improve outcomes. Some randomised controlled trials have reported promising data on adherence and clinical outcomes from app usage, however it is still difficult to draw firm conclusions regarding their impact and efficacy.[5]

> "There are a number of known challenges when it comes to health apps and apps in general. One of these is app abandonment, where around 25% of apps are used only once and then abandoned for a whole range of different reasons."

For drug delivery companion apps to realise their full potential, and for them to begin to tackle complex issues like intentional non-adherence, it is vital that users are informed, motivated and engaged. Effective onboarding is an important step in achieving this.

THE CHALLENGES FACING HEALTH APPS

There are a number of known challenges when it comes to health apps and apps in general. One of these is app abandonment, where around 25% of apps are used only once and then abandoned for a whole range of different reasons. Health apps are also hugely variable in terms of quality, with respect to both design and content, with failings including poor information, lack of security updates and insufficient awareness of regulatory requirements.

Companion apps will be viewed on the same platforms as non-regulated consumer-facing apps, fitness trackers and social media products. Widely used apps such as these have undergone significant development over many years, using the latest user experience (UX) and user interface (UI) design trends and behavioural insights. Therefore, user expectations will be set high – a companion app with a poor UX will likely increase the chance of abandonment.

Today's users are also likely to have other products, whether physical or digital, to manage their healthcare and to use in their day-to-day lives. However, in many cases they will have no prior experience using a digital health solution, so companion apps must work hard to demonstrate a real, tangible benefit, and encourage users to onboard and potentially opt in to sharing their data.

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WHY ARE COMPANION APPS NEEDED?

A key potential for medical companion apps is the ability to replicate interactions between a clinician and patient. When introducing patients to a new treatment, good communication between the clinician and the patient is key. Typically, a clinician makes a diagnosis, talks the patient through their condition and starts them off with a simple first step. Check-in appointments may be arranged where the clinician can adapt the treatment and give extra tasks to the patient. This method is normally quite effective, albeit time-consuming for everyone involved.

In other circumstances, in the interests of saving time and costs, a clinician may "front-load" a lot of information onto the patient, possibly in a group setting with other patients. In this situation a patient may be overwhelmed and not understand the purpose of a particular therapy or the implications of failing to adhere to a treatment regime.

Using a companion app to manage a patient's condition can offer an alternative, less time-consuming means of communicating key information about their treatment to them. Following a consultation with a clinician, a patient may be given some initial guidance before using the app for the first time. The app will then typically take them through a set of introductory steps to guide them into the treatment, called an "onboarding flow". These initial steps can be a crucial cut-off point for users, therefore it's important to get them right.

Figure 1: Packaging is the first point of contact of a product with a user, and so is an important aspect of the onboarding process.

"Good digital onboarding often starts with an onboarding flow; a specific set of screens or UI elements that are not part of the regular app interface."

THE POWER OF ONBOARDING

So, what is onboarding and why is it important? Aside from management jargon, it is a term widely used in digital UX design and represents one of the most important parts of a user journey for any digital product. It provides a crucial opportunity to inform and motivate users to adopt a new product or platform.

Imagine someone boarding a cruise ship for the first time. This experience can be very similar to onboarding with an app. Passengers are often a little disoriented when they board the ship; maybe they've never been on a cruise ship before, they're unaware of where to go, how to get settled in and how they're supposed to interact with other passengers. The ship's crew welcome passengers and get them settled in a way that makes them both comfortable and instantly knowledgeable about key aspects of the ship. The same applies to onboarding in a companion app. Users need to feel confident and assured in taking their first steps with a new treatment, with ready access to the essential information they need to get started in the way they want, but without being overwhelmed.

So how do you build an optimal onboarding experience for companion apps?

Delivery Device Packaging

Packaging and print make up some of the first steps in the user journey when starting out with a new drug delivery device (Figure 1). It is important to consider the whole UX and UI of the system in terms of opportunities to influence behaviour, with packaging and print serving to provide key information and education, reduce anxiety and guide users towards a successful digital onboarding experience.

One of the obvious initial barriers to adopting a companion app is access – a user needs to be introduced to your app before they can reap the benefits. The drug delivery device's packaging provides a good opportunity to help users understand that a companion app is available to them, how to access and download the app, and how it can help in their treatment. If the device needs to be connected, packaging and print can also be used to start the process of guiding set-up steps.

"Designing a good onboarding flow requires a combination of good UX design practice, coupled with authentic and approachable information to educate and motivate users."

Onboarding Flows

One key consideration when thinking about onboarding is not showing too much of the system up-front before a user becomes familiar, and engaged, with its use. Good digital onboarding often starts with an onboarding flow; a specific set of screens or UI elements that are not part of the regular app interface. Onboarding flows can be particularly useful for drug delivery companion apps due to the following components (Figure 2):

- Personal information will typically be required, therefore users will be expected to create an account and confirm their identity to view and manage their data.
- The app functionality is likely to be tailored to the user's context and goals. A brief survey or questionnaire may be required to capture lifestyle information, pre-existing conditions or health history.
- Important app features or workflows that may be unique to the app should be highlighted, especially for connected drug delivery devices that may be completely new to users.

Persuasive Design

Designing a good onboarding flow requires a combination of good UX design practice, coupled with authentic and approachable information to educate and motivate users. Communicating effectively and using persuasive design principles helps to ensure users feel confident and informed. In the context of companion apps for drug delivery, persuasive design is not about trickery or improper influencing; if applied carefully and ethically, with the interests of the user at heart, persuasion can help to gain a user's trust and focus their attention and effort towards specific topics and goals. Key concepts in persuasive design include:

- **"Tunnelling"** is a pattern to support easy and efficient onboarding, using a predetermined sequence of steps to encourage a certain outcome, with the focus on one task or goal rather than many during an onboarding flow.
- **"Tailoring"** can help an experience feel more personal and is key to customising app functionality to a user's context and goals.
- **"Social proof"** helps to encourage adoption and acceptance where users see evidence that other people in a similar situation to their own are benefiting from the use of the product or service.

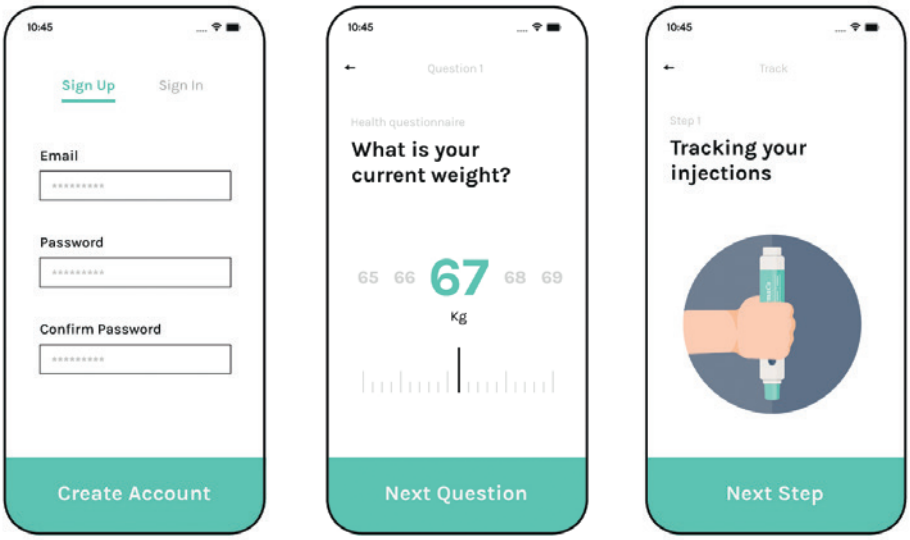

Figure 2: Onboarding flow components.

- **"Chunking"** is the practice of breaking down information into small, memorable parts and can be used to avoid overloading users with feature descriptions.

Data Privacy

When asking users to sign up to a new companion app, privacy concerns must be addressed at the earliest opportunity. A recent study in the US found that the majority of Americans believe that data collection poses more risks than benefits.[6] The simple communication of privacy controls and justification for entering personal information should be included in sign-up or onboarding screens.

External Triggers

The final part of the equation for onboarding and the early stages of adoption is the use of external triggers to prompt behaviour. These may include prompts and reminders, pop-ups or tooltips highlighting new features, or message notifications from the app community or healthcare provider. The key is to use these sparingly to avoid fatigue. The goal is to help a new user become a repeat user as smoothly and as quickly as possible, so that they become less reliant on external triggers and more on internal triggers, and start to build habits and adopt the product as part of their routine.

> "The goal is to help a new user become a repeat user as smoothly and as quickly as possible, so that they become less reliant on external triggers and more on internal triggers, and start to build habits and adopt the product as part of their routine."

When compared with popular consumer apps where a user's objective can be achieved by completing a few simple tasks, such as purchasing an item, companion apps for drug delivery devices are intended to address issues that can take months or

Figure 3: Example of a friendly app persona.

years to manage. Therefore, onboarding must be carefully considered. It is the front line of a user's experience and everything from adoption, engagement and retention can be positively impacted.

APPS FOR HUMANS

Human conversation is about exchanging meaning in ways that make sense in a current situation. In many scenarios, companion apps augment the role of a carer or clinician, effectively "talking" to the user. Designers should listen to what users say and take account of the type and tone of conversation they may wish to have with a companion app, even for screen-based UI. Both system and user personas should be considered to ensure a consistent, authentic and approachable experience (Figure 3).

Looking at emerging design systems from Amazon and Google for voice and multimodal UI, now is the time to start shifting our thinking around the systems and situations we already design for; modelling human interactions as a way to develop more compelling and individualised digital interfaces and interactions. Designers should focus on creating more personal experiences and avoiding robotic or sterile interactions.

THE FUTURE OF DIGITAL HEALTH

There is significant work underway to develop new health apps, build an evidence base, validate functionality, create standards for development and design frameworks for app evaluations. As a result of covid-19, health has been brought to the forefront of many people's minds. In light of this, there have been reports of a rise in patient adherence, with many people looking to ensure they remain fit and healthy. This is partly due to the limited in-person access to GPs and hospitals over the past year, leading many people to look into tools for self-managing their conditions and taking their existing medication more seriously. As the pharmaceutical industry continues to explore digital solutions such as companion apps to capitalise on this trend, building effective onboarding and persuasive user experiences will be an important step towards ensuring their adoption.

ABOUT THE COMPANY

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

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

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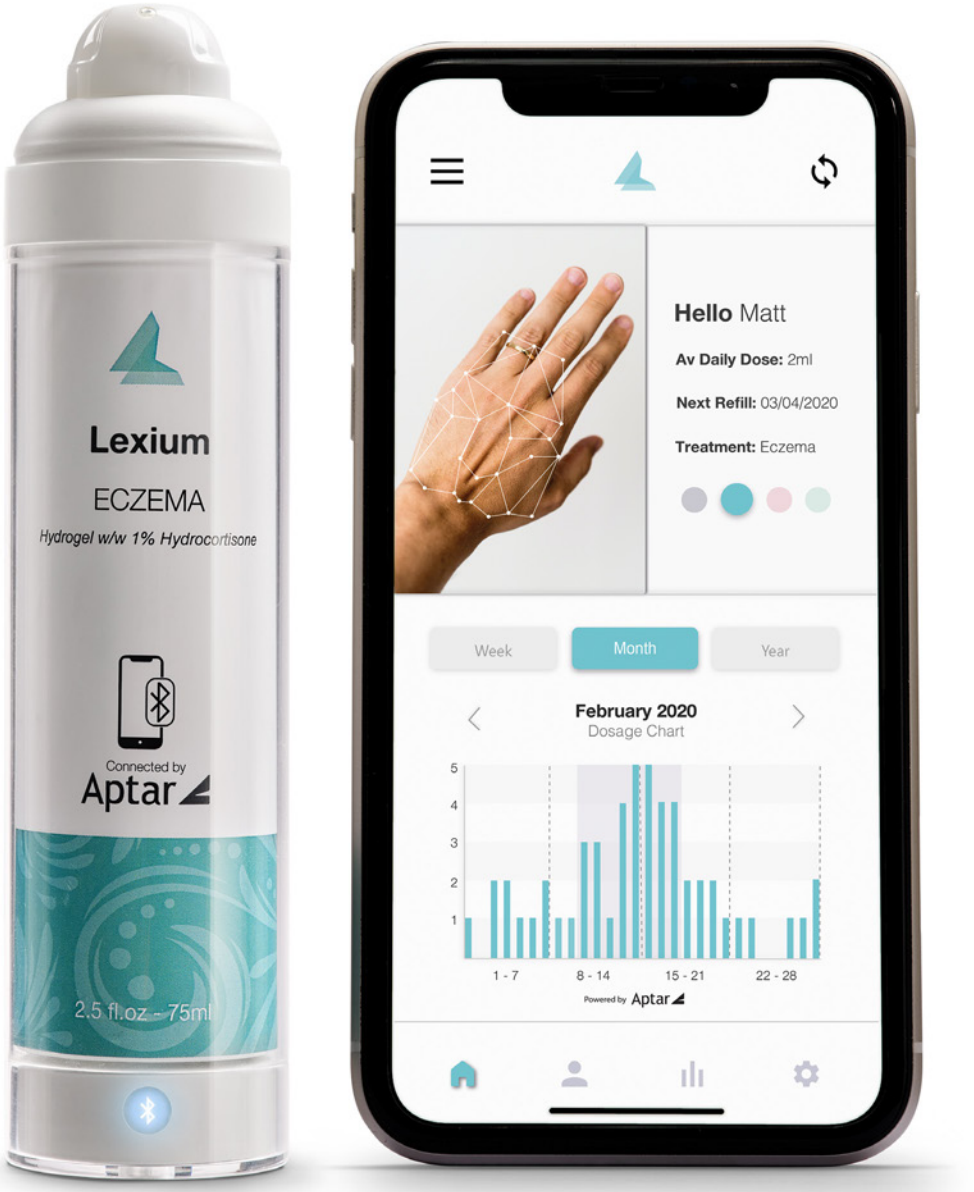

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