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CONNECTING DRUG DELIVERY

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Image:
Scanning electron micrograph of Fesoterodine Modified Release Coated Bead

Gary Nichols, Material Characterization, United Kingdom

THE COVID-19 CATALYST: HOW A GLOBAL PANDEMIC IS ACCELERATING THE NEED FOR DIGITAL HEALTH

In this article, Marcus Bates, Business Development Director, Digital Health, Aptar Pharma, discusses the positive impact covid-19 has had on the digital health industry, including the acceleration and development of remote patient services.

On 11 February 2020, the World Health Organization (WHO) made an announcement regarding the official name of a new respiratory illness thought to have originated in Wuhan, China, and now found to be spreading among populations across the globe.

At that exact moment, covid-19, the disease caused by infection with the SARS-CoV-2 coronavirus, had been responsible for just over 1,000 deaths in China, but among the 395 cases confirmed elsewhere across the world, just a single fatality had been recorded.

Fast forward to near the end of 2020 and the picture is very different. Covid-19 has struck populations throughout the world, and with previously unimaginable consequences. Almost everyone has had to adjust their life in some way to adapt to levels of social distancing, whether through enforced lockdowns or government guidelines. For most people, working from home has now become the norm and soaring demand for e-commerce sites, business and personal, has underlined the pandemic's role in driving digital service provision.

These enforced, dramatic changes in behaviour have inevitably impacted the healthcare space. Prior to the pandemic, digital health was building momentum, with many sharing Aptar Pharma's vision of a connected future where technology is increasingly integrated into an intelligent patient-care ecosystem. In the space of just a few short months, this trend has shifted several gears, with early adoption accelerated by the need to continue to provide high levels of patient care while also limiting person-to-person contact as much as possible.

REACHING A DIGITAL TIPPING POINT

While many changes to everyday life have been enforced, research carried out pre-pandemic shows that consumers were already displaying a readiness for digital health services. One such example, is a study that showed a nearly unanimous 97% are mostly willing to try one or more digital health innovations and 58% of consumers find the vision of digital health exciting.[1]

These figures reflect an increasingly positive sentiment among some patients. At the same time, this group also hints at a level of frustration that healthcare is only now coming into line with many other aspects of life where digitisation is bringing significant benefits. Retail, media and travel, for example, are all sectors that have transformed their consumer offerings through digital technologies, and consumers have now come to expect these higher levels of immediacy, convenience, flexibility and control across other aspects of their lives.

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"Conceivably, the outbreak of covid-19 has created the perfect storm of conditions to force healthcare over its digital tipping point."

Conceivably, the outbreak of covid-19 has created the perfect storm of conditions to force healthcare over its digital tipping point. Systems that have been in development for many years were suddenly pushed to the forefront as the protection of staff and patients through social distancing became a key priority. Telehealth and telemedicine services, which demonstrated compound annual growth rates (CAGRs) between 2014 and 2018 of just 13% and 4%, respectively, became vital tools for facilitating ongoing patient communication as many surgery centres closed their doors or severely limited access (Figure 1).[2]

This evidence is further supported by data from the UK publication, NHS Digital. Overall, the figures show a stark decline in the total number of consultations carried out as patients retreated from a health service becoming overburdened by covid-19, but they also give evidence of the marked increase in the number of consultations conducted remotely.

In April 2020, the number of remote consultations carried out in England reached 7.7 million – an increase of 120% on February's figure. This represented a share of 49% of all consultations, while just a year previously this figure stood at 14%. Among these numbers, there are marked rises in the number of patients from older demographic segments, who are at higher risk from covid-19, seeking medical advice through telehealth. Rather than being left behind by technology, these groups have embraced it and found it a valuable way to decrease their risk of exposure.[3]

CONNECTING ON A DIGITAL LEVEL

Further evidence can be obtained from a PharmaVoice special publication into telemedicine.[4] The covid-19 pandemic has dramatically reduced in-office medical encounters among both primary providers and specialist caregivers by up to 80%, moving these interactions online. Hospitals and other healthcare providers are increasingly using telemedicine to lower costs, increase satisfaction and better protect both patients and practitioners. Telehealth is similarly growing, providing nurses with the opportunity to guide patients remotely about self-care and treatment plans. To best support these rapidly emerging areas, the tools and technology must enable a connectivity of data so that the most effective care can be delivered.

The conclusion of the report projects a fascinating future landscape, full of opportunity for the entire ecosystem in digital health: "Telehealth will continue to grow and improve in areas where it has already been implemented, and it is likely to expand into areas that have not yet reaped its benefits. Digital health options will accelerate in all areas of healthcare from product distribution to surgical procedures. We are likely to expect innovations in drones and robotics in healthcare. It is important that the healthcare industry is committed to this growth and improvement. Implementing telemedicine into medical curriculum and offering extensive continuing education courses involving telemedicine, especially in rural communities, will improve the use and function of telemedicine in both urban and rural areas, and will help improve overall patient care and treatment."

"Covid-19 has fundamentally altered the nature of the relationship between healthcare providers and patients."

REMOTE CONTROL IN CLINICAL TRIALS

Covid-19 has fundamentally altered the nature of the relationship between healthcare providers (HCPs) and patients, accelerating the rise in remote interactions through digital health. This acceleration can also be seen in clinical trials. Prior to the pandemic, remote trials were already a feature of the drug-development landscape, but restrictions within physical settings and limits on movement imposed by covid-19 means greater focus is now being applied to remote trials.

Remote trials have the advantage of being naturally more patient-centric as everything takes place in an individual's home, rather than in unfamiliar and perhaps intimidating medical environments. The patient can receive all drugs, materials and diagnostic equipment directly to their door or via local healthcare providers, such as pharmacies. Communication and data transfer are managed via supporting software applications to provide an intimate, real-time, real-world view of the candidate's experiences.

As with all clinical trials, the key challenge is in controlling the many variables that have the potential to influence results. This, of course, represents more of a challenge when trials are conducted in individual homes rather than being led from centralised, controlled environments. This change in environment and respective impacts create a greater importance on the need for digital health solutions that can minimise these variables and support a flow of accurate, high-quality data. Telehealth and user-friendly apps become crucial in supporting the onboarding and training process. Furthermore, robust connectivity to the clinical monitoring site is essential to satisfy the need for transparent tracking and traceability via secure data transfer.

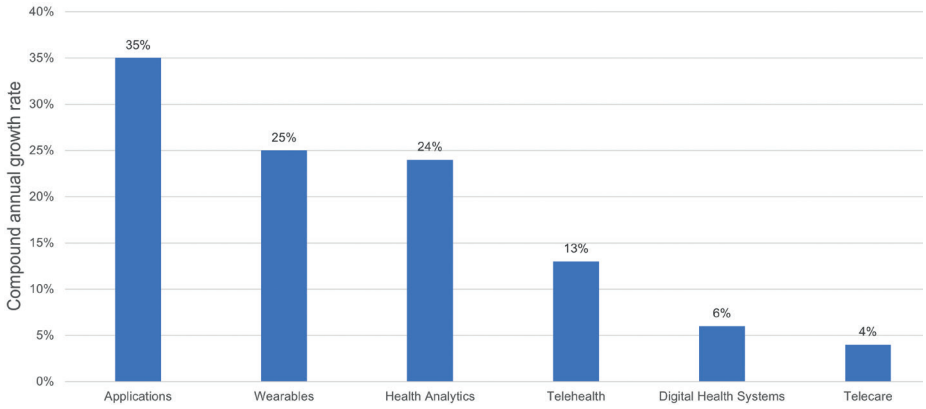

Figure 1: CAGR 2014–2018 in UK market shows year-on-year increase in telemedicine/digital health.

ADDRESSING COMPLEX PATIENT ONBOARDING

Whether looking at candidates in a clinical trial or patients managing long-term conditions, technology alone can only go so far in tackling the challenges presented by the shift to remote healthcare relationships. Digital capability is only truly effective if it is married to a clear understanding of the various behaviours of a specific cohort of patients and the challenges of their diseases, which may result in non-adherence or non-compliance. Like any technology platform, the outputs are only as good as the user and their conscientiousness in data entry.

Noble, which became part of the Aptar Pharma family in October 2019, is a leader in drug delivery training devices and patient onboarding. Its service offering includes providing pharmaceutical partners with deeper insight into the clinical trials environment, by addressing and optimising the pre-launch planning process for medical devices. When applied to the patient onboarding process, Noble's patient-centric approach helps to overcome non-adherence in the use of autoinjectors, prefilled syringes and on-body and respiratory devices. This novel approach not only negates drug product wastage but also combats poor disease management by ensuring patients are properly administering their medicines.

According to Noble's proprietary research, levels of adherence are correlated strongly with the amount or quality of training received. A total of 49% of HCPs do not train patients to use their self-injection devices correctly[5] and 84% of patients do not use an autoinjector correctly.[6] Rather shockingly, 90% of treatment information is forgotten within a week if patients do not practise at home, a phenomenon attributable to the "forgetting curve" theory, which is without practise and repetition, retention and recall degrade over time.[7] Without sufficient support, patients are likely to be less engaged and more likely to suffer from poor confidence and experience higher levels of anxiety. The prescribing rate for devices requiring self-administration has not declined because of covid-19, however, the pandemic has hampered patient training in two essential ways. Firstly, the already limited resources available within healthcare systems have been placed under further strain by the pandemic, resulting in cancelled appointments. Secondly, the widespread anxiety caused by the threat of infection has led patients to avoid medical settings.

AN IMMEDIATE AND IMPORTANT ROLE FOR DIGITAL HEALTH

The combination of a lack of healthcare resources and anxiety about meeting people in close proximity leaves a dangerous vacuum, where patients in need of HCP guidance are not engaged with the system and are failing to manage their own health effectively. Noble's innovative AdhereIT® system is an example of a digital health solution capable of filling this void (Figure 2). AdhereIT® is a complete ecosystem that trains and guides patients that are self-administering the self-injection process while sharing data in real-time with a designated HCP for ongoing monitoring and management. The result is more accurate dosing, less wastage and an overall improvement in the patient experience to help build confidence and ease anxieties.

BECOMING A "MUST HAVE"

Aptar Pharma has been a leading advocate for the creation of a digital health ecosystem for some time now, demonstrating the clear benefits for patients, HCPs, payer and pharma partners.

Patients benefit from greater control and better outcomes. HCPs can take advantage of more flexible and effective treatment models. Payers should see costs reduce. Lastly, pharma partners are able to create points of differentiation, provide disease management solutions and deliver new, sustainable revenue streams through potential digital therapeutics applications.

Figure 2: AdhereIT® is a complete ecosystem that trains and guides patients.

The benefits are clear, but it is probably fair to say that, to date, it has been the innovators and early adopters that have been most excited about the evolving digital landscape. And then came covid-19, which has proved to be a potent catalyst for digital health, accelerating the development and implementation of remote patient services by a factor of years.

> "The rules around healthcare engagement are being rewritten. AdhereIT® exemplifies how technology has the potential to augment patient care and deliver better outcomes for all stakeholders in a more connected future."

As a result, the rules around healthcare engagement are being rewritten. AdhereIT® exemplifies how technology has the potential to augment patient care and deliver better outcomes for all stakeholders in a more connected future. For pharmaceutical companies looking to adapt to this rapidly evolving digital-health ecosystem, success will depend on an approach that balances sustainability in all its guises, from cost management and regulatory compliance to environmental impact and long-term support for patient-disease management.

In our opinion, digital health is becoming a must have whereby a seamless ecosystem generates the data necessary to support patients remotely and safely, while delivering greater adherence and enhanced outcomes for all.

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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ABOUT THE AUTHOR

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

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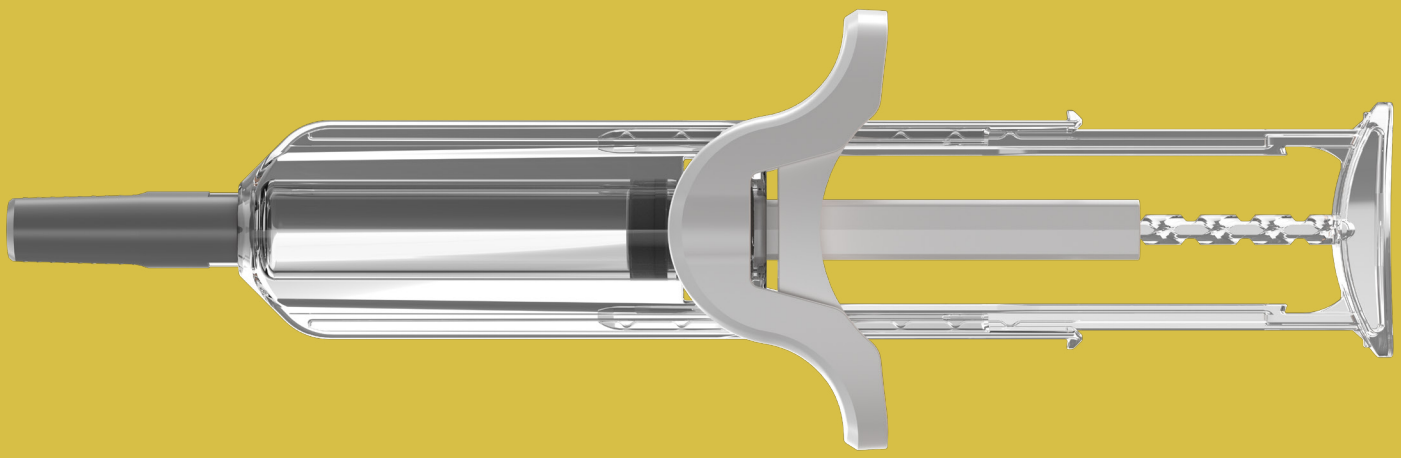

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MEDICAL DEVICE DESIGN STRATEGY FOR A CONNECTED FUTURE

Today's medical device market demands the most up-to-date technology, with connectivity to the cloud now considered a "must have" capability for digital healthcare product solutions. In this article, Michael Kiely, Senior Device Development Engineer; Laura Marsden, Senior Market Research Manager & Digital Health Lead; Peter Stringer, Technical Program Manager; and David Boyle, Senior Design Engineer, all of Jabil Healthcare, discuss the design challenges at the electromechanical interface and encourage manufacturers to adopt a standardised approach for connecting medical devices to the cloud.

The Internet of Things (IoT) refers to the billions of everyday devices that are now connected to the internet. Our cars, home appliances, phones and fitness armbands have all been transformed into smart devices, capturing data and delivering analysis in an holistic feedback and analysis loop. In healthcare, this combination of digital-sensing technology and cloud computing has dramatically accelerated growth in the Internet of Medical Things (IoMT).

Today's connected medical devices enable new models of engagement between patient and provider, enhancing the exchange of vital metrics and health information at both the personal and population level of healthcare delivery. Better informed, time-efficient, safe and clinically effective outcomes are at the heart of the promise in digital healthcare. The numbers bear this out: the global connected healthcare market is expected to reach a market value of around US$6.6 billion (£4.9 billion) by 2027 and is anticipated to grow at a compound annual growth rate (CAGR) of around 11% in terms of revenue from 2020 to 2027.[1]

> "With millions of devices potentially impacted, it's vital that both engineers and developers establish comprehensive system-level understanding of how these components will come together at assembly."

Manufacturing variability is always a primary concern within the tightly regulated healthcare industry. Medical device product development, at minimum, requires subject matter expert (SME) input for both

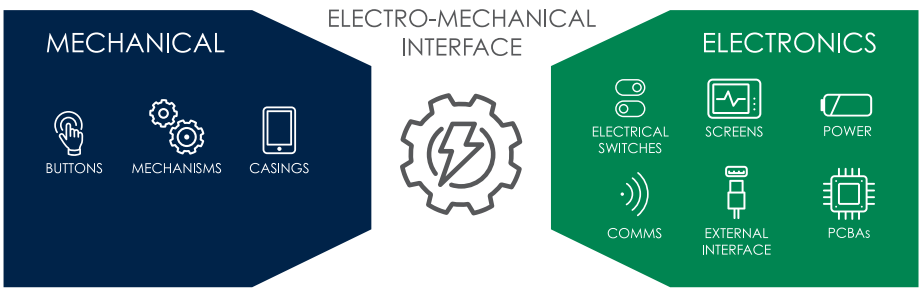

Figure 1: The electromechanical interface.

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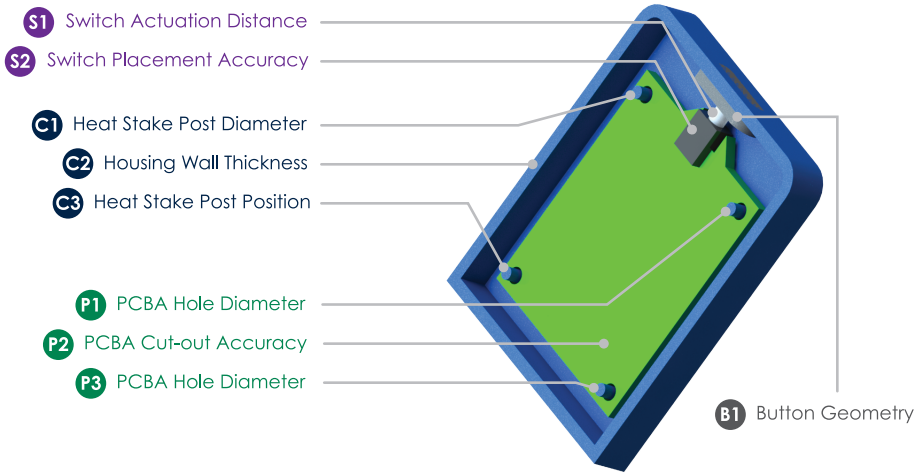

Figure 2: Factors contributing to button actuation profile accuracy.

electronics and mechanical componentry. Connected devices also require expertise related to software, automation and user experience. With millions of devices potentially impacted, it's vital that both engineers and developers establish comprehensive system-level understanding of how these components will come together at assembly (Figure 1).

DESIGN CONSIDERATIONS FOR HIGH-VOLUME MANUFACTURE

Let's consider the mechanics of a push button as an example. As one of the primary interfaces for the user with the device, it is important that the button achieves the correct tactile and visual feedback. This gives the user confidence that the action has been carried out correctly and is important for the overall quality and "feel" of the device. How many times have you been frustrated by buttons getting stuck or having a sticky action? Your initial reaction to the product is to question the quality of its build. Consistent button action doesn't just happen; it requires thorough design work up front and an excellent understanding of both the electrical and the mechanical component specifications – particularly when manufacturing at high volumes.

The example shown (Figure 2) is a simplified rendering of a switch mounted on a printed circuit board assembly (PCBA). Actuation of the switch is accomplished by a mechanical button positioned at the top of the device. Design requires that it is flush to the surface of the outer case. To achieve the correct tactile feedback and continuous surface appearance, controlling the distance between the electrical switch and the button is critical.

Mounting the switch on the board itself (S2 in Figure 2) is another consideration, and accuracy is paramount. This position may have a large tolerance band in a typical reflow soldering process which is used for high-volume PCBA manufacture. For post-soldering inspection purposes, a larger contact pad and solder amount is preferable to confirm correct electrical connection. However, this will require a large tolerance for the end position of the surface-mounted switch post reflow, as it may land anywhere in the large contact pad. Therefore, the smaller the contact pad, the better the positional accuracy. There is a trade-off with inspection requirements and the placement accuracy of the automated line to land on a smaller contact pad. For fine placement accuracy, a mechanical mounting can be used but this will add to PCBA cost and complexity. In a real-world example, there are likely to be many more interacting components, such as sensors and connections ports, that will only add to this complexity.

Cut-out tolerances must also be accounted for: PCBs may be manufactured to a range of tolerance standards, and it is challenging to achieve fine tolerances at high volumes. The accuracy of the cut-out will be largely dependent on the routing process used. Typical cut-out tolerances here can be in the range of ±0.1–0.2 mm, which can be significant in the stack up of tolerances. One potential solution for reducing offset inaccuracies could be drilling the PCBA mounting holes at the same time as the panel tooling holes.

SWITCH INTERACTIONS

Tolerance of the switch itself is another primary factor. Achieving tighter tolerances typically requires integration of expensive, high-end or bespoke switches. Tolerances are dependent upon the materials used, the design of the tool (injection-moulded parts) and the distance to the measurement datums on the parts. All of these must be optimised, for example by applying design-for-manufacturing (DfM) principles, and addressed to meet end-tolerance requirements (Figure 3).

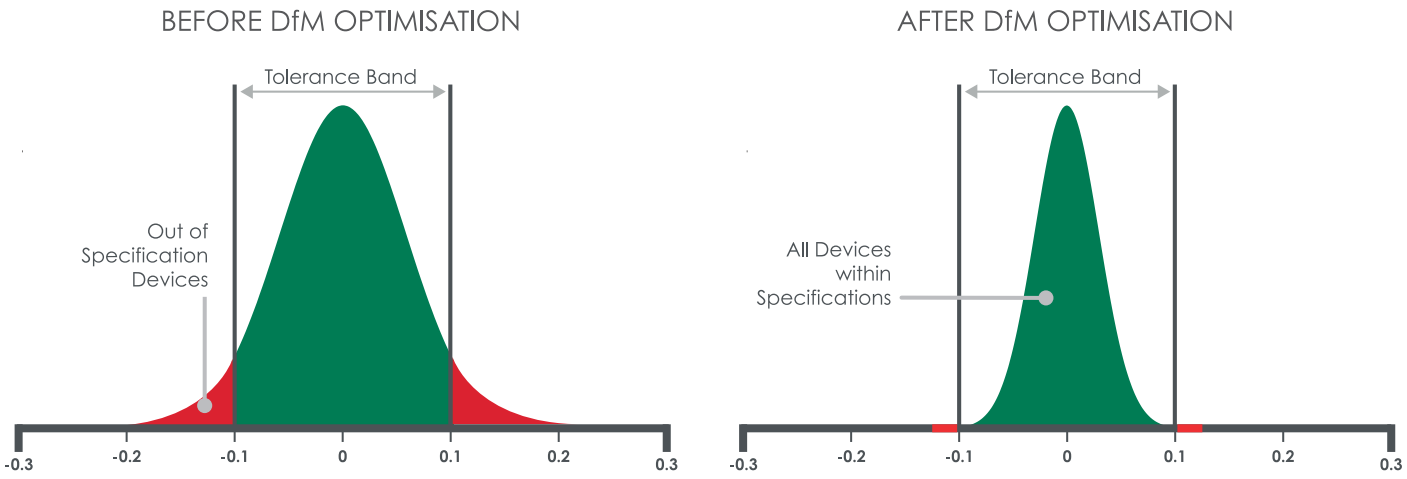

Figure 3: Reduction of out-of-specification devices after the application of design for manufacturing (DfM) principles.

"One can begin to understand how critical it is to have cross-functional expertise when optimising a connected device design for high-volume manufacture."

A checklist of considerations is:

- Moulding tolerances of the plastic casing
- Relative position of PCB retention features
- Geometry of the PCB retention features
- Position of the button mounting
- Thickness of the button
- Wall thickness of the housing.

At a system level, when all these sources of variation from both the electronic and mechanical components are taken into account, one can begin to understand how critical it is to have cross-functional expertise when optimising a connected device design for high-volume manufacture.

SENSING THE PLUNGE – WHAT'S MEASURED AND HOW?

Data collection is at the heart of design strategies for connected devices. It's critical to optimise a sensor's placement – or an array of sensors – in tandem with the device electronics and firmware. For example, in a connected autoinjector there's a wealth of insight to be gleaned through tracking and measuring plunger travel. Depending on the level of detail and accuracy required, plunger travel data can be captured by sensors in a variety of ways. In a previous ONdrugDelivery article, we discussed sensor integration in a trial smart inhaler.[2] What can be detected by plunger travel?

- Needle shield removal
- Contact with skin
- Start of plunger travel
- End of plunger travel
- Incomplete delivery of medication
- Full dose administration (when coupled with a skin contact sensor – e.g. capacitive or push switch)
- Occlusion detection
- Delivery rate
- Anomalies in the delivery profile.

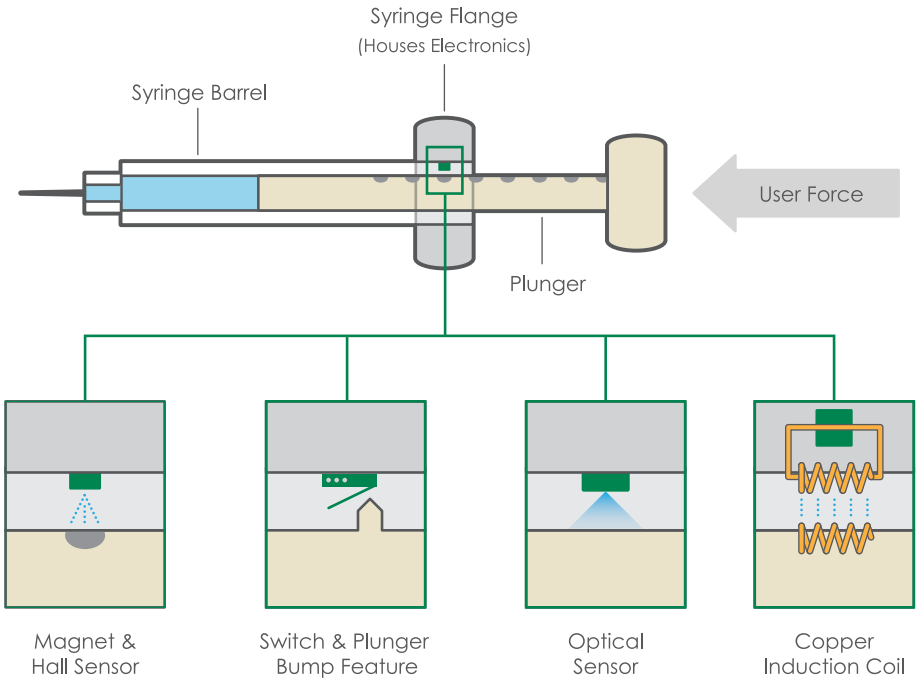

Figure 4: Examples of sensor options for measuring plunger travel.

Once the items to be detected have been identified, it is necessary to understand the technology requirements and how to incorporate them into the design of the device. The range of technologies for tracking plunger position include mechanical switches, hall sensors, inductive measurements and optical sensing (Figure 4).

Whichever method is selected, it is important to understand the challenges and limitations of the measurement technology and the potential impact on accuracy. Direct measurement of the stopper position within the syringe is not usually feasible, so an analogue must be used – e.g. the back of the plunger or movement of another part of the system. The sensing method chosen must be precise enough to provide accurate dosing information, while also allowing for a reasonable tolerance in accuracy of placement of the sensor itself.

Available locations within a device to site and integrate electronics may be limited. The integration of electronics to the area of least sensitivity to variation should be prioritised in the design. A detailed tolerance analysis will be critical at this stage to understand if the accuracy requirement can be met, taking into account the sensor accuracy, the sensor placement accuracy and the variation within the device itself.

Component tolerances, component interactions and assembly all contribute to potential variations in autoinjector product performance. Some sources of variation that should be considered and optimised prior to sensor selection are:

- Drug fill volume
- Syringe barrel internal volume dimensions
- Syringe barrel mounting area dimensions
- Needle dimensions
- Plunger stopper dimensions
- Plunger stopper assembly position
- Change in plunger stopper position due to transport
- Change in properties of all device elements due to temperature and humidity
- Mechanical position of the syringe in the device
- Mechanical position of the plunger component
- Injection mechanism forces
- Frictional effects.

"Whichever method is selected, it is important to understand the challenges and limitations of the measurement technology and the potential impact on accuracy."

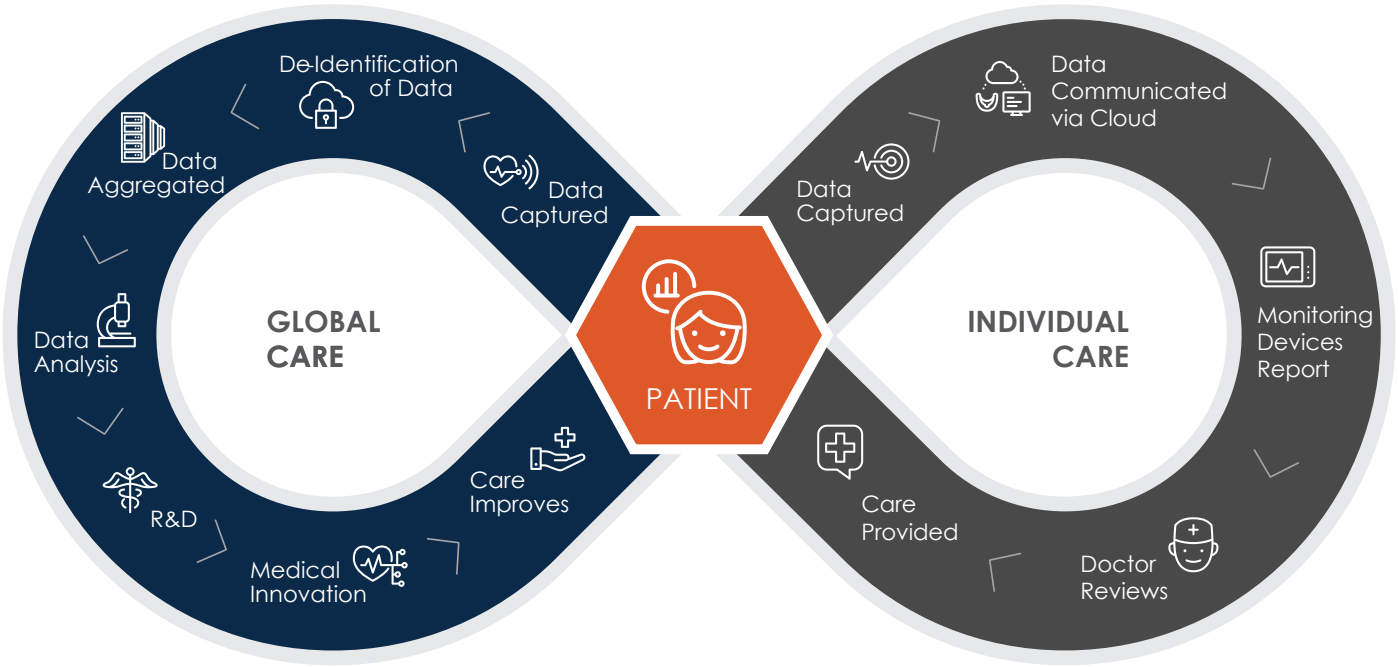

Figure 5: Communications handshakes among potential players of the IoMT.

> "Component tolerances, component interactions and assembly all contribute to potential variations in autoinjector product performance."

Accommodating all these considerations will ensure collection of the most accurate drug delivery information from the autoinjector, which sets up the next step: connecting the device for communication to the cloud.

DESIGNING FOR CONNECTIVITY – A STANDARDISED APPROACH IS BEST

Connected devices serve a wide array of use cases and purposes. As with the device's electromechanical design, a breadth of SMEs with different skillsets should be engaged to work across the full solution, over different timelines and phases. Variability is again a primary challenge and must be accounted for across the design and development workflow.

A standardised approach is ideal; without it, each device solution becomes a time-intensive and bespoke effort, requiring the creation of new firmware for every device. Backend development must be accommodated from the start – not delayed – as that would risk the need to solve connection issues when the devices are connected to their solution. These issues can include needing to use code workarounds and patches to address unanticipated connectivity problems or require a return to the device firmware embedded code. This can be challenging at the best of times and too late to address at others.

There are many benefits to be gained from a standardised approach and it is in fact a differentiator across many industries. In the plumbing industry, for example, some professional plumbers will only quote and engage in a job if the homeowner or designer will be installing Grohe faucets. Grohe has become known for its "quick connect coupling" system throughout its portfolio of products. This standardisation allows installation time, tools and other connection supplies to become reliably predictable. The professional is prepared every time. The accuracy of quoting a job becomes a seamlessly smooth transaction and potential pitfalls or lost time and money are mitigated.

Taking this approach with connected devices involves the creation of a firmware architecture that is scalable to different microcontrollers and maintains reference code libraries of different sensors and device types. A communication protocol is required to enable the device and solution to communicate the telemetry and attributes of the device and what they require to interface and communicate with the solution.

Not long ago, getting a personal computer up and running had users scrambling for installation instructions for the drivers for each unique device, (mouse, keyboard and printer) to enable connection and operation. Today, all of this happens by simply plugging in the device or pairing over a WiFi connection. It's become as simple as a handshake. The devices communicate a representative model of their capabilities and this allows the operating system to reference a known model and understand how to interact with the device (Figure 5).

Microsoft's Azure is an excellent example of a service product that has the power to standardise across the industry for connected medical devices. Its service removes the requirement for extensive embedded code in exchange for a common open modelling language between IoMT device and IoMT application. Just as described with peripheral devices, this creates a model for compatibility across the platform.

Azure's plug and play modelling language is based on JSON-LD and RDF.[3] Each device model has a unique identifier or digital twin model identification (DTMI) number. Each model identity (ID) in the library has a set of interfaces. The device and cloud solutions interface at the different levels. At each level, the communication protocol enables the devices to "advertise" their attributes. In other words, they are able to answer all

the questions about the device regarding on-board sensors, how they communicate and what they need to connect.

Interactions, such as the device's digital twin model running "search" functions to query and understand the device's attributes, how it functions and communicates, enable the system to self-regulate and improve. These solutions also help create an appropriate environment, dashboards or insights from the device's data, enabling users to send management commands to the device, ultimately, guaranteeing a seamless ease of connection to any compatible platform solution using this approach.

Ease of connection is a huge advantage. Not only does it remove the burden of complex embedded code, it also simplifies calibration of life-sciences diagnostics instrumentation. In today's communication protocols, software maintenance and calibration are built in, freeing the lab technician to focus on understanding and applying laboratory results, not software upgrades. IoMT designers and developers can apply the bulk of time and effort where it will provide the greatest impact and value: the use cases and insights that data and applied analytics provide.

The ability to model interactions and build libraries and protocols enriched by metadata will only increase with the volume of devices added and integrated. All these data collection and communication enhancements will provide more leverage in the pursuit of improving individual wellness, disease state management and population health.

Our future, and increasingly our present, has us working with connected and interoperable ecosystems, providing a clearinghouse of shared and structured data. Devices connected to patient, provider and the cloud are building out networks of complex connections and applied analytics – enabling deeper insights and problem solving for improved patient care.

ABOUT THE COMPANY

Jabil Healthcare (formerly Nypro) is one of the industry's largest, most comprehensive healthcare manufacturing solutions and capabilities providers. Its customers have access to an array of engineering, design and manufacturing solutions across multiple sectors in the healthcare industry. The Pharmaceutical Delivery Systems (PDS) business within Jabil continues to accelerate leadership within the industry, with disciplined and innovative execution on design, engineering, product development and manufacture across multiple platforms including autoinjectors, inhalers and dosing.

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ABOUT THE AUTHORS

Michael Kiely is a Senior Device Development Engineer at Jabil Healthcare. Since joining the company in 2012, he has guided the development of an array of mechanical, electromechanical and connected medical devices, from initial concept through to design transfer and production support. Mr Kiely has an Honours Bachelors' degree in Applied Physics from Dublin City University (Ireland).

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Peter Stringer is a Technical Program Manager within the Jabil Healthcare Engineering & Technology group based in Bray Ireland. Since joining Jabil in 2017, he has been working on a wide range of mechanical and electro-mechanical medical devices. Mr Stringer has been working in medical device R&D for more than 12 years, he has an Honours Bachelor of Engineering Degree in Mechanical Engineering from University College Dublin (Ireland).

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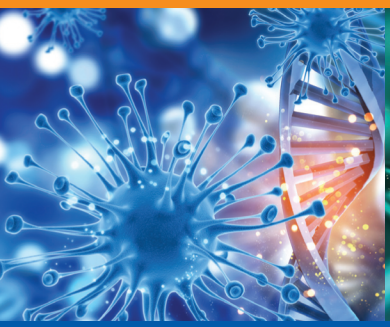


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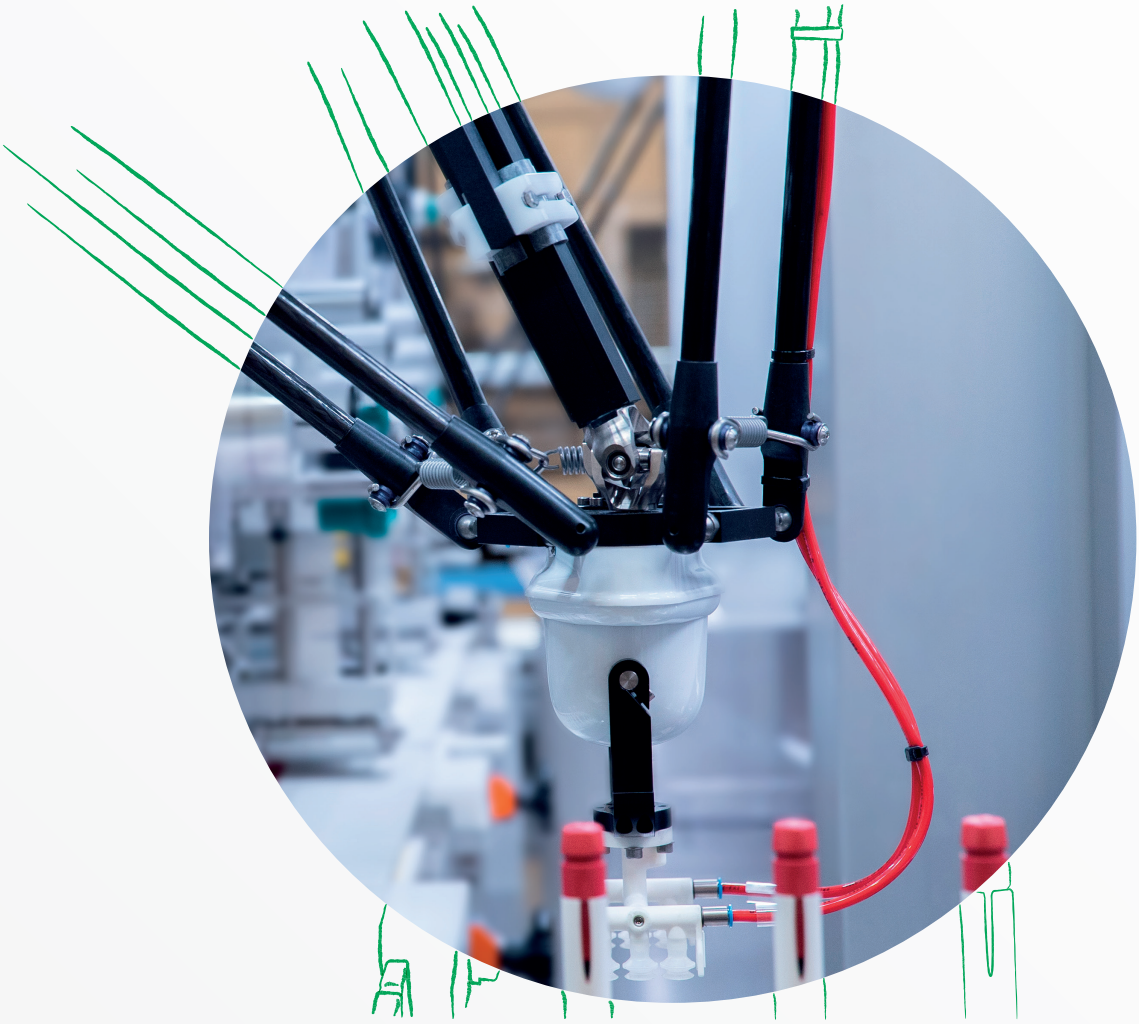

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RS01X – BERRY GLOBAL HEALTHCARE'S SINGLE-DOSE DPI GOES DIGITAL WITH AMIKO'S RESPIRO

In this article, Mauro Citterio, Director, R&D and Industrialisation; and Marco Franza, Sales & Business Development Director – Global Inhalation & Medical Devices, both of Berry Global Healthcare; and Martijn Grinovero, Chief Commercial Officer and Co-Founder of Amiko, discuss Berry Global Healthcare and Amiko's partnership to develop the RS01X connected single-dose dry powder inhaler, based on Berry Global Healthcare's commercialised RS01 inhaler and Amiko's Respiro digital health platform.

DIGITAL HEALTH – BENEFITS AND CHALLENGES

Digital health is fast becoming a well established concept in the drug delivery industry. The benefits to all stakeholders in the industry is a well-discussed topic, frequently the subject of conference talks and industry articles. For patients, digital technology can improve their quality of care with apps associated with their device to track usage, provide reminders and potentially offer guidance in correct usage of their device, which is an especially pertinent benefit in the respiratory sector, where patients' difficulties mastering their devices is notorious. For the healthcare provider (HCP), digital technology can give them insights into how their patients' medication regimens are proceeding using data direct from their drug delivery device. This increased level of insight not only has the benefit of being real-time, allowing HCPs to pre-empt potential crises, but also of being remote, not requiring a patient to make a journey into the clinic. For pharmaceutical companies, there's the significant benefit of digital devices allowing them to collect data on the performance of their medications, as well as saving them money from increased patient adherence.

However, alongside these myriad benefits, there are novel challenges for the drug delivery industry when it comes to developing and deploying digital technology in medical devices. These challenges are varied, including the additional costs and expertise required for developing connected technology, regulatory challenges from both the usual regulators, such as the EU EMA and US FDA, and data protection regulations, such as the EU GDPR. There is also the potential for friction between technology companies moving into the healthcare space, coming from a world that gave us the mantra "move fast and break things", and established pharmaceutical and medical device companies investigating digital technologies, who often have more cautious and risk-averse approaches.

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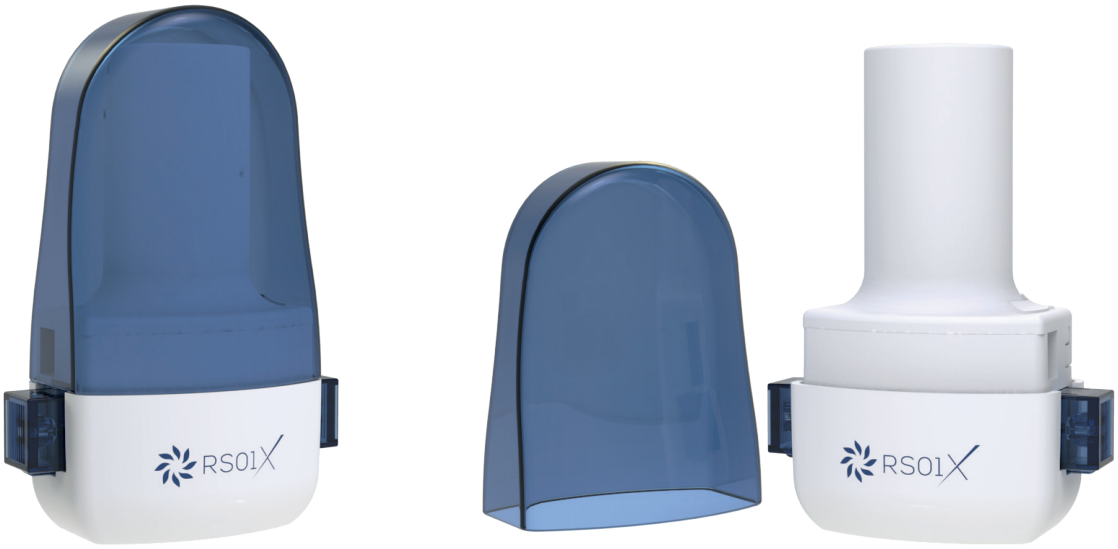

Figure 1: The RS01X connected and intelligent single-dose DPI.

Therefore, on this frontier of drug delivery device development, a successful partnership between a digital technology company and established drug delivery device manufacturer is hugely valuable. Such a partnership has come to fruition between Berry Global Healthcare, developer of the internationally successful RS01 dry powder inhaler (DPI), and Amiko, the digital technology company behind Respiro, a digital medicine solution for respiratory devices built on proprietary sensing technology, data science and elegant digital user experience design. Together, Berry Global Healthcare and Amiko have combined their expertise to produce the RS01X, a connected, intelligent single-dose DPI (Figure 1).

BERRY & AMIKO – A PARTNERSHIP FOR SUCCESS

The partnership between Berry Global Healthcare and Amiko marks a significant milestone in Berry Global Healthcare's stated commitment to bring innovation to the healthcare market that advances and improves the quality of patient care. With Amiko, Berry Global Healthcare has found a technology partner that shares its dedication to the cause of advancing respiratory care with technology. Both companies bring a key element of the RS01X DPI to the table.

Berry Global Healthcare provides the expertise of a well-established player in the respiratory drug delivery device industry. The RS01's intuitive patient-centric design provides ease of use and short administration time. It is also a most versatile device to work with, being designed to function with a wide variety of powders and capsules, as well as being available with different airflows to maximise the scope of its application. With its excellent reputation, broad applicability, and established and proven place in the market the RS01 was a natural fit for adaptation to digital technology.

Amiko brings its proprietary digital respiratory technology: Respiro, a proven digital health product specifically designed for the respiratory market. Respiro combines connected sensors built into an inhaler with artificial intelligence (AI), data science and digital experience design to help deliver better patient outcomes. Along with Amiko's sensing technology, Respiro features a patient-facing app providing personalised guidance and feedback to patients to assist them in managing their condition, and a provider portal for HCPs, giving them data, insights into the progress of their patients' conditions and treatments, and predictive analytics to further enhance the quality of care they can provide.

Through their partnership, Berry Global Healthcare and Amiko have combined their expertise and products to bring the RS01 DPI into the world of digital healthcare, as the RS01X, made smart by Respiro. Commenting on this achievement, Vincent Clauzel, Managing Director, Berry Global Healthcare – Care Unit, said "The introduction of the RS01X is a significant milestone for Berry Global Healthcare globally, as well as for innovation in respiratory devices. We are very excited to have established a successful and very close partnership with Amiko to achieve this." From Amiko's perspective, the company is thrilled to have in Berry Global Healthcare a partner with vision, ambition and market experience, and excited about the RS01X and Respiro becoming available to patients and care providers at scale.

> "Through their partnership, Berry Global Healthcare and Amiko have combined their expertise and products to bring the RS01 DPI into the world of digital healthcare, as the RS01X, made smart by Respiro."

RS01X – CONNECTED & INTELLIGENT DPI

The RS01X tracks a patient's inhaler use via inbuilt sensors, and connects to Amiko's Respiro app using Bluetooth wireless technology. The data captured by

> "The RS01X automatically captures, stores and encrypts objective inhaler-use data, covering various metrics of user-generated inhalations, such as inhalation flow rate and duration, to power its predictive analytics and personalised user advice."

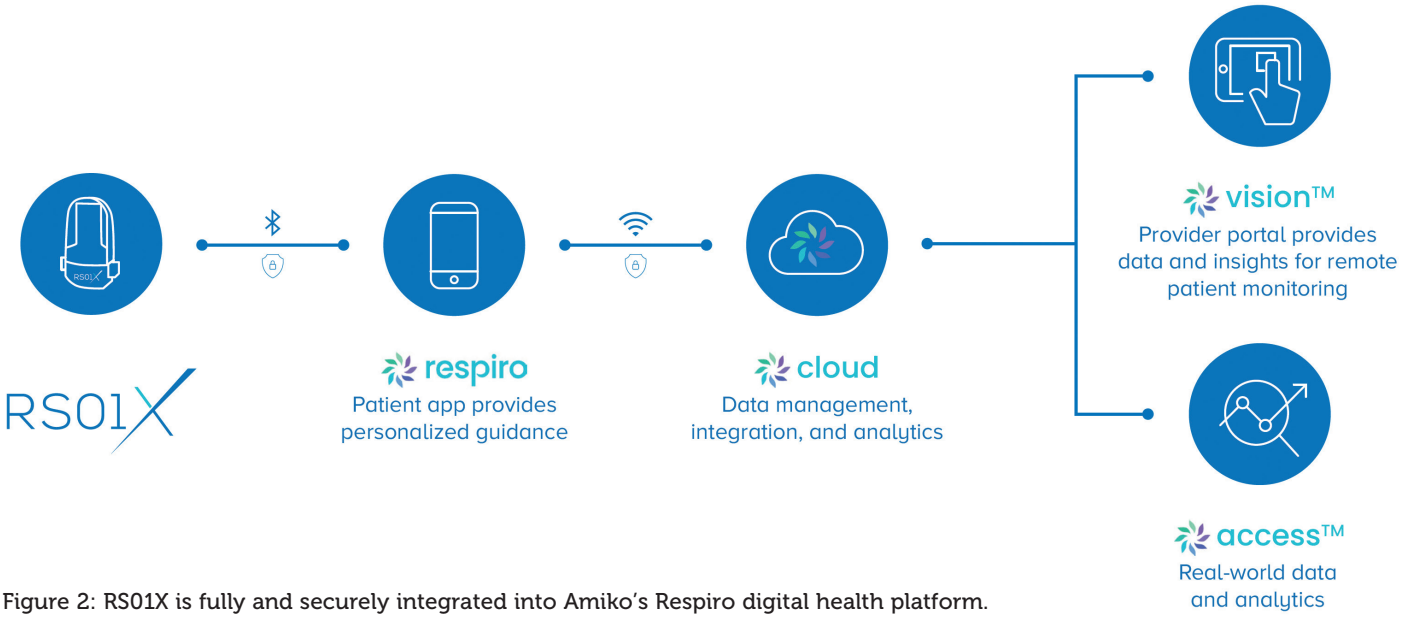

Figure 2: RS01X is fully and securely integrated into Amiko's Respiro digital health platform.

the RS01X's sensors enables the companion app to provide patients with personalised feedback on their care.

The Respiro companion app can provide guidance and feedback on proper usage technique to a patient for their inhaler, as well as adherence-improving tools, such as personalised feedback and reminders for when they are due to take their medication. Such tools improve the overall quality of patient care because, with proper technique, patients are able to get the full efficacy of their treatment, which leads to better health results. In turn, better results lead patients to adhere to their prescribed medication regimen more reliably, resulting in improved long-term treatment results.

The Respiro app is powered by AI to better assist patients and enable them to self-manage their conditions more effectively. This has been demonstrated with Respiro in clinical studies and over 30 commercial programmes; the percentage of patients showing proper medication adherence and correct inhalation technique improved remarkably amongst patient populations using Respiro-powered inhalers.

The RS01X automatically captures, stores and encrypts objective inhaler-use data, covering various metrics of user-generated inhalations, such as inhalation flow rate and duration, to power its predictive analytics and personalised user advice. The inhaler's sensors monitor the patient's inhalation without requiring a mechanic or pneumatic connection to the inhaler air flow path.

Being powered by Respiro, the RS01X is seamlessly integrated into Amiko's digital health platform (Figure 2). RS01X and the Respiro app incorporate the latest industry-standard security and privacy protections. However, if a patient is willing to share their data with their HCP they can gain access to a wealth of further advantages in the form of collaborative decision making and data-driven treatment adjustments. Data from the RS01X can be shared either in person using the Respiro PDF reports, or digitally, and in real-time, using the Respiro digital health platform.

All of this technology has not changed the familiar design of the RS01. The RS01X is just as easy to use, familiar and functional as the original. This includes the RS01's internal medication delivery geometry, ensuring that the medication delivery of the RS01 and RS01X is completely equivalent. In addition to the familiarity and versatility of the RS01 base, the RS01X includes a built-in battery so that no additional charging is required for the duration of its usage.

CONCLUSION

The RS01X combines Berry Global Healthcare's 50 years of experience in inhaler design, development and manufacturing with Amiko's expertise in developing hardware enabled, AI-powered digital health technology. The RS01X builds upon the globally recognised RS01 design without sacrificing any of the original device's simplicity, usability or versatility to provide a device that offers advantages to all stakeholders, and advances inhalation technology into the digital age.

ABOUT THE COMPANIES

Berry Global is a worldwide supplier of a broad range of innovative non-woven, rigid, and flexible products used every day in both consumer and industrial end-markets. Berry is a Fortune 500 company with operations that span 290 locations across six continents. Berry Global Healthcare's mission is to have a positive impact on disease management and the environment. Berry Global Healthcare offers a wide number of specialisations in drug administration, including oral, nasal, pulmonary and ophthalmic, as well as an extensive range of pharmaceutical packaging.

Amiko is an AI and advanced data analytics company that provides Respiro, a digital medicine platform that combines connected inhaler sensors, apps, and data analytics to enable enhanced respiratory care. Respiro is a certified medical device and has been used in clinical studies and over

"All of this technology has not changed the familiar design of the RS01. The RS01X is just as easy to use, familiar and functional as the original. This includes the RS01's internal medication delivery geometry, ensuring that the medication delivery of the RS01 and RS01X is completely equivalent."

30 commercial programmes across Europe. Amiko, which is ISO 13485:2016 certified, serves patients, healthcare providers and pharmaceutical companies.

ABOUT THE AUTHORS

Mauro Citterio is a Member of the Board of Plastiape SpA (a Berry Global company), where he leads R&D and industrialisation activities. Since joining the company in 1998, Mr Citterio has had various responsibilities, including technical and economical evaluation of new business opportunities, costing and pricing, development of new design concepts, project management, equipment industrialisation and maintenance. He founded the company's core team dedicated to regulatory compliance for medical devices. He is named as inventor or co-inventor on multiple international patents and has been an invited lecturer at various international conferences. Mr Cittero holds an MSc in Management, Economics and Industrial Engineering.

Marco Franza is Sales & Business Development Director – Global Inhalation & Medical Devices, at Berry Global Healthcare. He was previously Director, Sales, Marketing and Key Accounts at Plastiape, until it was acquired by Berry in 2019. Mr Franza has extensive experience in the commercial side of the drug delivery industry, having held roles related to sales, business development and marketing. His roles have had a particular focus on inhalation devices, which are both a key growth factor for the company and a passionate personal interest.

Martijn Grinovero is the Chief Commercial Officer and Co-Founder of Amiko. He is responsible for leading Amiko's commercial go-to-market teams, including sales, marketing, commercial relationships and business growth. Mr Grinovero has an MSc in Strategic Management from the Rotterdam School of Management (Netherlands).

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2021 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 31, 2020
February	Prefilled Syringes & Injection Devices	Jan 14, 2021
March	Ophthalmic Drug Delivery	Feb 4, 2021
March /April	Drug Delivery & Environmental Sustainability	Feb 18, 2021
April	Pulmonary & Nasal Drug Delivery	Mar 4, 2021
May	Delivering Injectables: Devices & Formulations	Apr 1, 2021
June	Connecting Drug Delivery	May 6, 2021
July	Novel Oral Delivery Systems	Jun 3, 2021
August	Industrialising Drug Delivery	Jul 1, 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 5, 2021

IMPROVING INHALATION THERAPY ADHERENCE WITH CONNECTED DEVICES

In this article, Edgar Hernan Cuevas Brun, Marketing Manager at HCmed, discusses the role of connectivity in improving adherence to medication and introduces the company's mesh nebuliser smart cap, Pulmogine+.

PATIENT ADHERENCE ISSUES

Non-adherence has been reported as a major issue in the treatment of most chronic diseases, affecting approximately 50% of patients, a large proportion of which are elderly people. Research has also shown that the implications of non-adherence can lead to critical problems, such as a decrease in treatment efficacy and an increase in the cost of medical care.[1] In the past, clearly identifying groups of patients that presented non-adherence behaviour based on socio-economic or pathologic factors was difficult to achieve.[2] However, finding effective methods to improve these behaviours still remains an important issue.[3]

Throughout the past decades, several platforms to monitor adherence have been introduced. The main goal is to educate and encourage patients who suffer from chronic diseases to follow their treatment. Nonetheless, awareness about the consequences of non-compliance and adverse scenarios of discontinuing treatments should be further reinforced in order to overcome the current challenges.

> "Awareness about the consequences of non-compliance and adverse scenarios of discontinuing treatments should be further reinforced in order to overcome the current challenges."

NON-ADHERENCE IMPLICATIONS IN CHRONIC RESPIRATORY DISEASES

Chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis bronchiectasis are among the chronic respiratory diseases in which a significant number of patients have been reported as not complying with their treatment. When it comes to bronchiectasis, one study stated that only half of the total patient sample completed 80% of their prescribed inhaled antibiotic medication to treat their condition.[4] Similarly, although there is currently a wide range of options to treat COPD patients, a significant number of patients remain symptomatic, with no improvement in their condition, due to non-adherence issues that could be traced to the patients' health-related experiences, behaviours and beliefs.[5,6] In a different study, it was reported that both COPD and asthma patients prefer to reduce their inhalation treatment to a single daily dose.[7] This is a factor that should be taken into consideration when looking to improve treatment adherence in this group.

Low adherence in the treatment of respiratory diseases is not only related to patients not taking their prescribed medication – the mishandling of inhalation devices is another major factor. This results

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in even lower adherence levels when using inhalation therapy for the treatment of chronic respiratory diseases than other types of treatment.[8] Intending to mitigate this problem, a guideline to optimise adherence for inhaled medications has been proposed. It describes three adherence process phases: initiation, implementation and persistence, and proposes a list of specific solutions for some of the main groups of issues. For example, receiving proper training on the handling of inhalers or switching to another, easier-to-use inhaler are ways to mitigate the patients' lack of knowledge.[9]

INTRODUCING ADHERENCE DEVICES

With the aim of helping patients achieve better levels of adherence to their treatment, several non-digital and digital devices have been introduced in recent years.[10-12] Non-digital devices include inhalers that incorporate counters in their design so that patients can keep track of the number of treatments that have been taken or that remain. Digital or connected devices, on the other hand, offer a wider range of features that rely on connectivity functions to allow patients to set reminders for their daily treatment, receive feedback on their inhalation profiles, and even have access to educational sections.[12] In most cases, these connected devices, which are part of the smart device category, are able to collect and store data in a secure data cloud to record treatments. The information can be readily accessed and reviewed by patients, and monitored by medical professionals, thus improving treatment efficacy.

While some smart devices are attached to products for inhalation treatment as add-ons, others have embedded components to the inhalation devices that create the smart functions. When it comes to add-ons, there are several commercially available smart caps that can be used with pressurised metered dose inhalers (pMDIs), as well as a few others that are suitable for dry powder inhalers (DPIs) and soft mist inhalers. On the other hand, most smart devices with incorporated connectivity components are smart nebulisers because their mechanism requires the integration of several other functions to measure parameters and collect information from aerosol-generated performance.

> "After analysing several factors needed for a nebuliser smart cap, such as ergonomics, connectivity, functionality and interface, the initial prototype of the smart cap Pulmogine+ has been completed and presents a number of components to become an important player in the field."

MESH NEBULISER SMART CAP – PULMOGINE+

As awareness of improving adherence to treatment continues to grow, the need for new adherence devices has become crucial in the development of inhalation devices. With the aim of contributing in this field, in 2019, HCmed Innovations began to develop a connectivity accessory that could be suitable for the Pulmogine Vibrating Mesh Nebuliser. After analysing several factors needed for a nebuliser smart cap, such as ergonomics, connectivity, functionality and interface, the initial prototype of the smart cap Pulmogine+ has been completed and presents a number of components to become an important player in the field.

Figure 1: Pulmogine+ smart cap attached to Pulmogine vibrating mesh nebuliser.

Pulmogine+ is a smart cap that is attached to the bottom part of the Pulmogine device (Figure 1). It is an easy-to-operate add-on that counts with a single on/off button and an LED light that indicates the status of the device (Figure 2). The technology used in Pulmogine+ comprises a Bluetooth system that is able to transmit data to a mobile app to collect information about the patient's nebulisation treatment. To use the smart cap, it should be first paired with a smartphone, through the mobile app. The smart cap is then able to transmit the collected information about the time, date and duration, which could be further translated by the mobile app by detecting the beginning of the treatment, and the end when the nebulisation treatment is complete. The recorded data makes it possible to keep track of a patient's treatment and compliance. This smart cap was designed to offer a simple but reliable mechanism, along with the mobile app, as a well-rounded connected platform.

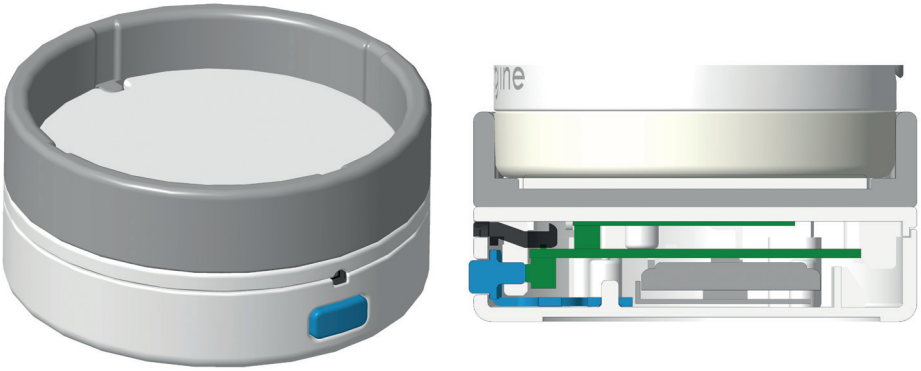

Figure 2: Outer and cross-section views of Pulmogine+.

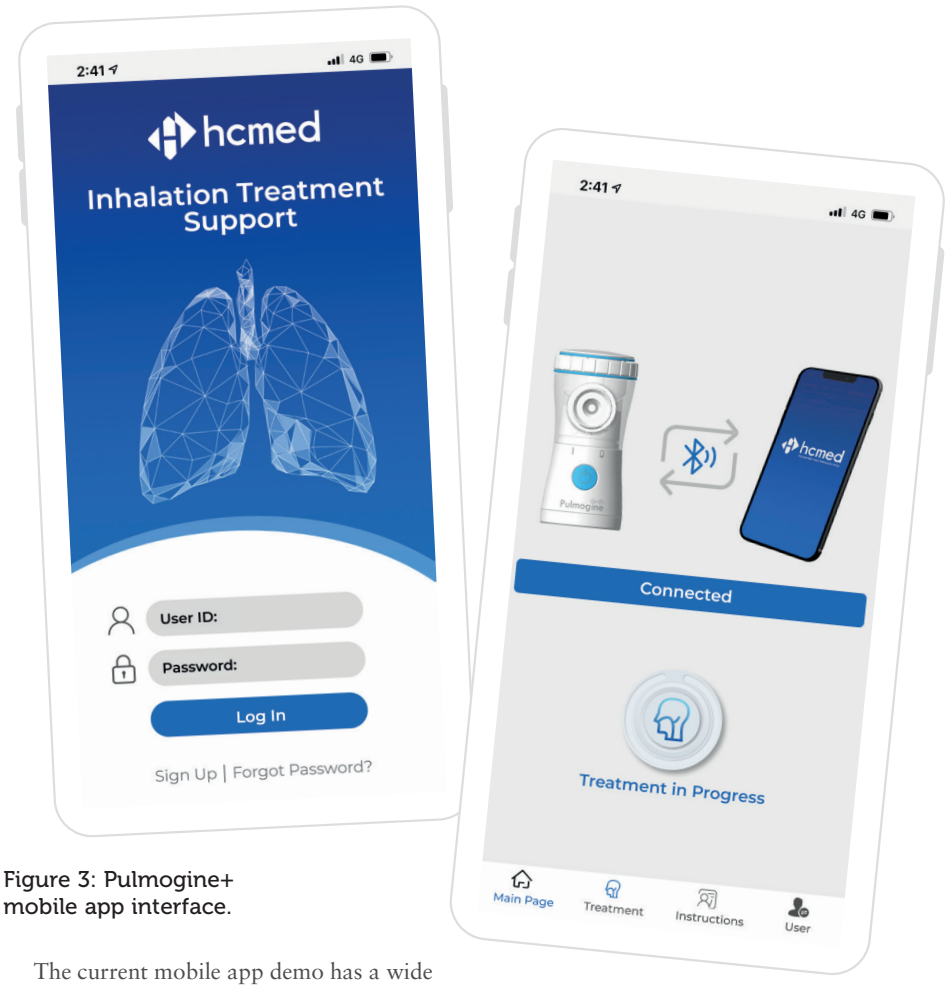

Figure 3: Pulmogine+ mobile app interface.

The current mobile app demo has a wide range of options and functions. Starting with a slick interface, patients are required to register before the first treatment (Figure 3). Data about the patient is filled out in the patient information section. The next step involves the insertion of the treatment type (Figure 4). At this point, patients can programme the indication and medication for their nebulisation treatment, including the treatment period and the specific time at which the patient should nebulise their prescribed medication. The calendar option allows patients to add the complete length of the treatment that serves as a reminder.

Once all relevant information has been completed, the treatments are recorded and displayed on a simple interface that organises data about the type, time, date and duration of treatment. The smart cap is also able to collect and retain up to 30 sets of treatment in an embedded memory. By doing this, records can be stored and later downloaded into the database of the mobile app the next time it is connected to the smartphone through Bluetooth connectivity. The inclusion of this function adds flexibility to patients to track their treatment data. Moreover, the mobile app has been designed to collect information in a subsequent connection, even if the Bluetooth is accidentally disconnected during the treatment.

Intending to further enhance patient compliance, a test evaluation page has also been included, which allows patients to track their condition throughout the entire treatment course. Asthma Control Test (ACT) for adults, Childhood Asthma Control Test (C-ACT) for children, and Chronic Obstructive Pulmonary Disease Assessment Test (CAT) questionnaires are embedded into the mobile app to perform the tests when required by physicians, while keeping records of previous tests (Figure 5). Last but not least, a page comprising instructions for use has also been built in to ensure patients have access to all relevant information that could help them to achieve higher levels of adherence. The cloud system is currently under development and is expected to be ready in 2021 as collaborations with pharmaceuticals companies and other partners are established.

IMPORTANCE OF DATA SECURITY AND OTHER ISSUES

Data security has become a big concern in the development of connected devices. As stored treatment and personal data of patients is intended to be shared between patients and medical practitioners, the assurance that all private data is securely stored has become one of the main pillars of connected medical devices. Regulatory

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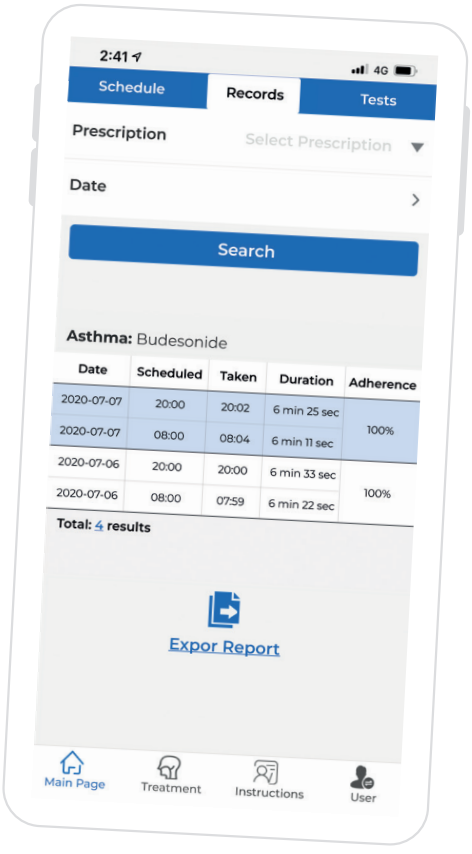

Figure 4: Treatment and indication page of mobile app.

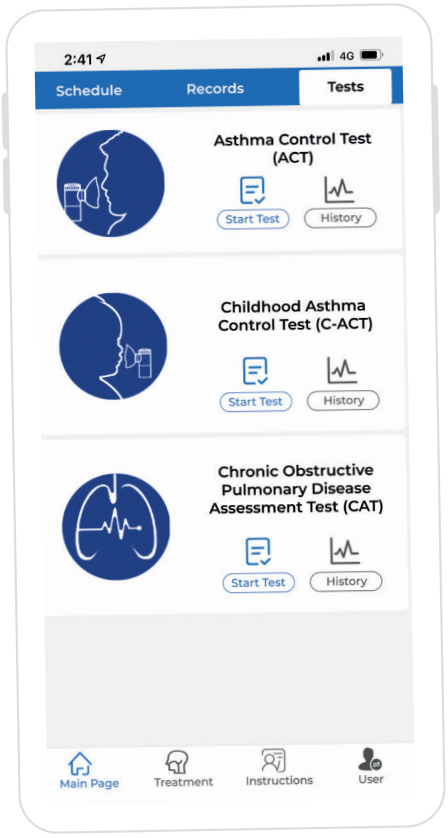

Figure 5: Test evaluation section of mobile app.

compliance for the hardware and software elements of connected devices, such as compliance with the Health Insurance Portability and Accountability Act (HIPAA) and ISO 13485, are fundamental for the development of smart devices.

As new technological advancements and the implementation of existing technologies are included in the development of connected devices for inhalation therapy, there are other issues that should also be addressed in order to keep up with the evolution of these devices for improved patient adherence. Among them, providing affordable products is indispensable to allow more patients to have access to these technologies, while properly instructing patients and physicians on the device operation is fundamental, and constitutes a major factor to be considered in the future.[9] Moreover, sufficient levels of investment in the development process are also required to properly deliver products that fulfil hardware and software standards.

"HCmed's next step is to expand collaborations with medical cloud partners and pharmaceutical companies for the future commercialisation of its connected products; ensuring a secure storage network is the next milestone in achieving commercialisation of connected devices."

FUTURE DEVELOPMENTS IN CONNECTED INHALATION THERAPY

Existing smart caps for inhalation devices and smart nebulisers are already capable of storing valuable data regarding the treatment of patients, supporting patient adherence. HCmed's next step is to expand collaborations with medical cloud partners and pharmaceutical companies for the future commercialisation of its connected products; ensuring a secure storage network is the next milestone in achieving commercialisation of connected devices.

Besides the smart cap Pulmogine+, HCmed is also working on a wider range of functionality for its smart breath-actuated nebuliser AdheResp. The AdheResp platform comprises a drug-device combination platform that will allow more data to be collected, such as breathing patterns, to provide insights into the condition of patients and improve adherence. Furthermore, it contains a lock-and-key function that activates the device with the use of a specific drug to reinforce compliance, while ensuring optimal drug delivery.

It is predicted that the next five years will be of great importance in the development of connected devices; therefore, companies should be prepared to play a bigger role in the development of connectivity functions for inhalation therapy. Only by building solid partnerships will it be possible to provide better solutions to patients and help solve current adherence issues.

ABOUT THE COMPANY

HCmed Innovations is focused on the development of drug-device combination products for inhalation therapy. It develops and manufactures portable vibrating

mesh nebulisers that offer a mature customisation platform. This technology enables efficient and reliable nebulisation of different types of medication, including small molecule synthetics and large molecule biologics, as either solutions, suspensions or even difficult-to-deliver high viscosity drugs. The newest products include the incorporation of breath actuation and connectivity features to enhance drug delivery and reinforce patience adherence.

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Edgar Hernan Cuevas Brun, Marketing Manager at HCmed Innovations, is responsible for the marketing analysis and research of new products as well as the branding of HCmed's commercially available mesh nebulisers. He has more than five years of experience in the drug delivery field, holding a degree in biomedical engineering and an MBA. He is also in charge of co-ordinating HCmed's participation and publications at major conferences, such as the European Respiratory Society International Congress and the American Thoracic Society Conference.

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THE CHANGING FACE OF CONNECTED HEALTH IN THE TIME OF COVID-19

In this article, Neil Williams, Director of Front-End Innovation and Head of Connected Health, and Angela R Eder, PhD, Healthcare Content Creation Manager, both of Phillips-Medisize, discuss how the current pandemic is transforming the adoption of connected health.

Three years ago, it was recognised that, while technology and data analytics had the ability to revolutionise healthcare, and that major technology companies were making investments in this area, the entire healthcare industry was resistant to changing in a way that adopted and integrated these technologies.[1] At the time, technology readiness, patient acceptance, data security, regulatory challenges and the difficulty of justifying financial investment in connected health devices were all key impediments to the adoption of connected health technologies.

However, the emergence of SARS-CoV-2 (Figure 1),[2] the virus that causes covid-19, has changed nearly every aspect of modern society, including the way healthcare is delivered, emerging medical needs and the acceptance of connected devices by both patients and healthcare providers. In response, the US FDA[3] and other regulatory bodies have modified guidance around the use of telehealth and connected devices, for the duration of the pandemic at least. Despite the emerging availability of vaccines, leading economists are emphasising that other covid-19 prevention measures, including social distancing and mask wearing, will be with us for a long time,[4] in all likelihood making telehealth and medical device connectivity permanent fixtures in the way we provide and receive healthcare.

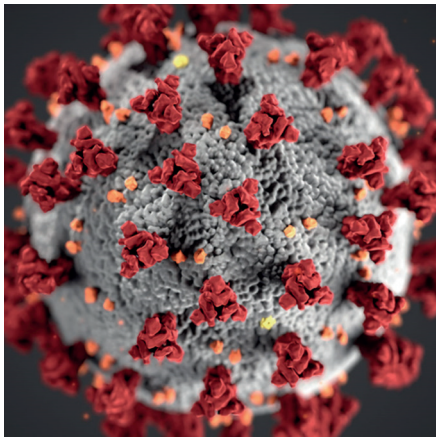

Figure 1: Rendition of SARS-CoV-2.

At the time of this publication, there have been more than 64 million cases of covid-19, with over 1.49 million deaths attributed to the virus globally.[5] The deaths have been tragic, but the impact of covid-19 on the health of patients, both those affected by the virus and those who have not contracted it, has extended well beyond mortality figures and has been profound. For the nearly 64.5 million global survivors of covid-19, chronic health conditions will persist. "Long covid" syndrome and "long haulers" are widely accepted in the medical community, even as the full range of effects are only now being understood. Even mild cases of covid-19 create a cascade of symptoms that will require long-term management: headaches, gastrointestinal issues, cardiac arrhythmias, fatigue and pulmonary dysfunction.[6]

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While the full nature of covid-19-related chronic health conditions is not completely understood, there is widespread acceptance in the medical community that covid-19 will have chronic effects for many, if not most, survivors of the acute illness. These patients will require both short- and long-term care to monitor symptoms and recovery, and to evaluate the efficacy of physical therapy and medication regimens, preferably in a remote care setting.

Beyond patients recovering from covid-19, those who have not contracted the virus will still require remote care for long-term health conditions – those that existed prior to covid-19 and those that resulted as secondary conditions stemming from the effects of living through a pandemic. Prior to covid-19, it was estimated that nearly half of all adults manage one or more chronic health conditions, for which there is no cure, but which are managed through daily medication and/or treatment.[7,8] Common examples of long-term conditions include: diabetes, certain mental health conditions (e.g. depression, PTSD), respiratory illness (e.g. COPD, asthma), cardiovascular disease, osteoporosis, HIV/AIDS and Alzheimer's disease. Increases in the incidence of cardiovascular diseases and respiratory illnesses are expected for covid-19 survivors; for those who care for these patients, it is anticipated that chronic mental health conditions will increase in the coming months and the post-covid-19 era. In one study, Mount Sinai Hospital (NY, US) estimated that 25–40% of medical personnel and emergency workers will suffer from PTSD due to covid-19, requiring long-term management of associated symptoms.[9] Symptom tracking, adherence to medication regimens and counselling will all be critical elements of successful recovery for affected medical personnel.

COSTS OF MEDICATION NON-COMPLIANCE

Adherence to medication regimens is a critical component of managing symptoms and effects from these chronic conditions. When patients do not take medications as prescribed, it can lead to A&E visits, hospitalisations, adverse health outcomes and death. The effects of medication non-adherence and lack of effective remote healthcare have been particularly stark with the advent of covid-19. In 2020, to date, more than 299,000 Americans and 70,000 citizens of the UK have died due to ordinarily preventable illnesses and chronic health conditions that were left untreated or were improperly managed due to patient fear of entering healthcare facilities.[10,11] The majority of these excess deaths occurred in the age bracket of 25–44, which corresponds to a significant negative economic impact.[12]

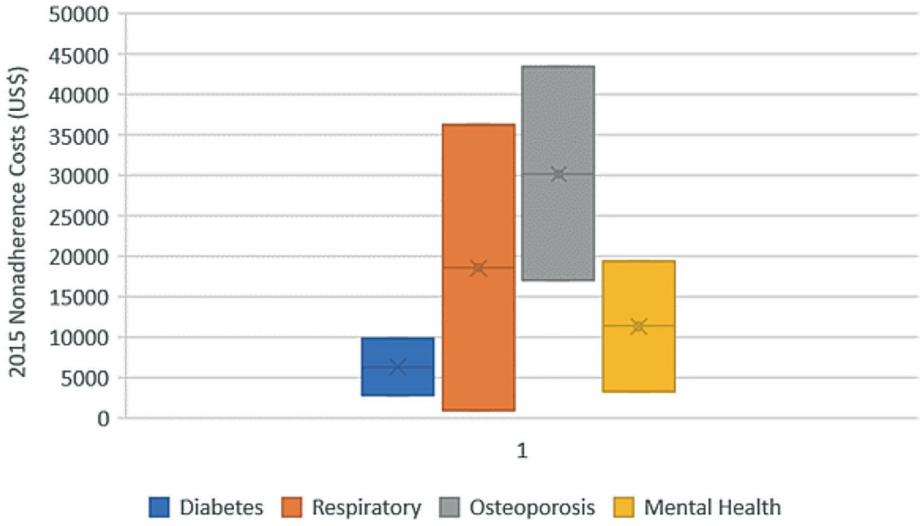

Figure 2: Non-adherence costs of select chronic healthcare conditions.

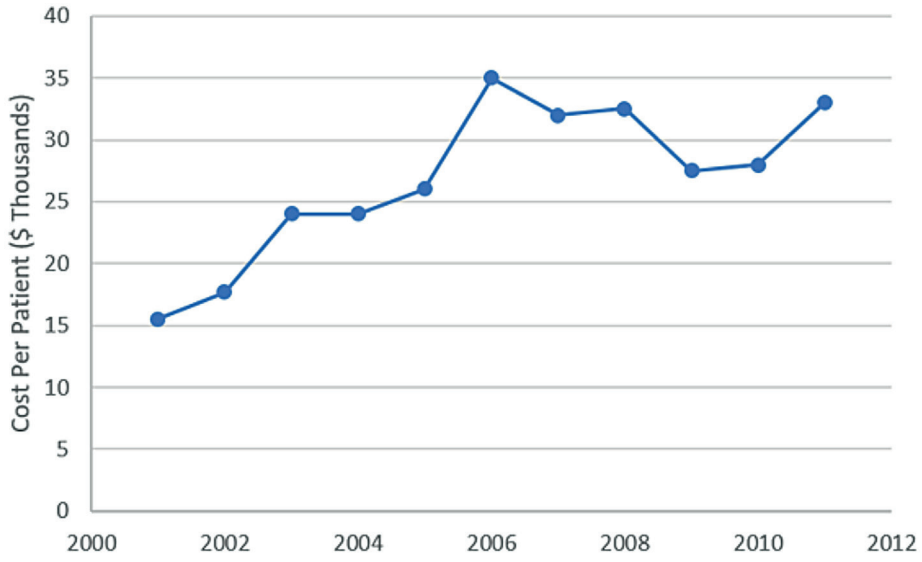

Figure 3: Cost per patient of hypoglycaemic events for unmanaged diabetes (US dollars).

The financial cost of non-adherence to a medication regimen is variable (Figure 2), and can cost as much as US$43,000 (£32,000) in per-patient costs for unexpected treatment stemming from a patient failing to take medication.[13] While no single chronic health condition is more important than another, diabetes serves as an illustrative example of the importance of medication adherence, irrespective of the current pandemic. Within the US and UK, diabetes is one of the most common chronic medical conditions in adults. It is estimated that 34.2 million Americans have diabetes and another 88 million Americans have pre-diabetes.[14]

According to the International Diabetes Federation's Diabetes Atlas, by 2030, worldwide, diabetes is predicted to affect 7,578 million people.[15] Patients living with diabetes can experience both hyperglycaemic and hypoglycaemic events, although it is hypoglycaemic events that are more common when patients do not take medication as prescribed. Per patient, it is estimated that each hypoglycaemic event caused by medication non-adherence costs around $30,000, with the costs only increasing over time (Figure 3).[16] Each year, total costs for non-adherence for diabetes alone are over $5 billion; for all chronic illnesses, costs of non-adherence are approximately $290 billion.

"The importance of remotely monitoring patient well-being and medication adherence is increasing – since March 2020, in-person medical appointments have decreased by 60%, whereas telehealth appointments have increased by 14%."

Clearly, a means of helping patients to better manage medication for chronic conditions is critical to not only improving patient health, but to ensure they don't miss doses of their medications, saving both patients and healthcare payers significant sums of money by preventing non-adherence A&E visits and hospitalisations. The importance of remotely monitoring patient well-being and medication adherence is increasing – since March 2020, in-person medical appointments have decreased by 60%, whereas telehealth appointments have increased by 14%.[17] It is likely that connected medication delivery devices and home health monitoring will not only improve the quality of life for patients and health professionals conducting telehealth appointments, but may additionally serve to bridge the gap of the current ~46% of patient appointments that are not being served either in person or via telehealth.

PATIENT INSIGHT

Patient behaviour has been a key stumbling block, both in terms of medication non-adherence and the willingness to adapt to connected device technologies. However, even prior to 2020, key technological changes have occurred that were leading to significant mindset changes towards connected device technology. Since 2017, adults have been increasingly turning to smart, or connected, devices to help manage their daily routines. It is estimated that half of all homes will be connected by 2020.[18] Often controlled through smartphone apps, these connected devices manage everything from grocery lists and lightbulbs to summer reading lists and thermostats.

"Due to increased familiarity with connected devices in daily life, adults managing chronic health conditions are beginning to turn to this technology to manage their own health."

Due to increased familiarity with connected devices in daily life, adults managing chronic health conditions are beginning to turn to this technology to manage their own health. Devices are now able to monitor heart rate, pulse oximetry, peak flow and tidal volume, blood glucose, body temperature and much more.[19] Improved engagement in individual health management has been demonstrated through adoption of covid-19-tracking application programming interfaces (APIs) recently launched in the UK,[20] Ireland and Germany,[21] among other countries; powered by Google and Apple healthcare technology, 20 of 50 US states have, or will have, APIs for contact tracing by the end of 2020.[22,23] In the UK, the NHS contact tracing app is the most popular download to smartphones, second only to Zoom.

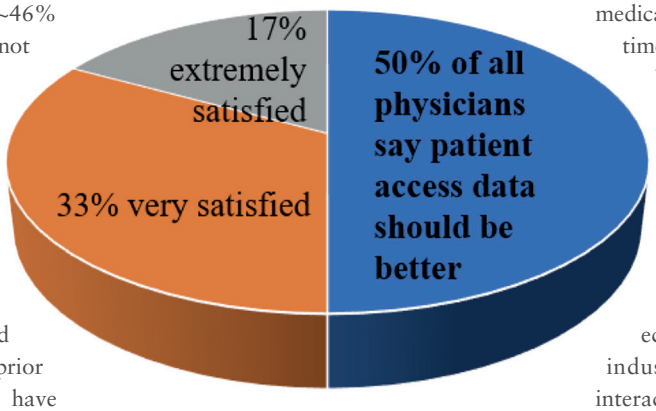

Figure 4: Physician satisfaction with patient data access.

Complementing changing patient views on remote health monitoring, physicians are likewise increasingly demanding connectivity to their patients. In a 2018 survey, 50% of all physicians felt their access to patient data could be much better (Figure 4); of those, 83% cited patient medication adherence as a priority need.[24] Understanding the relationship between medication adherence and healthcare outcomes, physicians wish to be able to provide more meaningful healthcare advice and earlier interventions, if required. Obtaining patient medication data, communicating that data and using it in a timeframe commensurate with when it is obtained, in order to make informed and timely healthcare decisions, are critical to providing meaningful healthcare advice. Connected devices, that communicate directly between the device and the patient's medical file, are a key means to achieving timely data collection and use – and are becoming increasingly cost effective (Figure 5).

CONNECTED HEALTH – IMPROVED OUTCOMES AND DECREASED COSTS

Delivery of medication is a complex ecosystem within the healthcare industry, relying on streamlined interactions between patients, healthcare providers (nurses and physicians) and pharmacists. Related to these primary

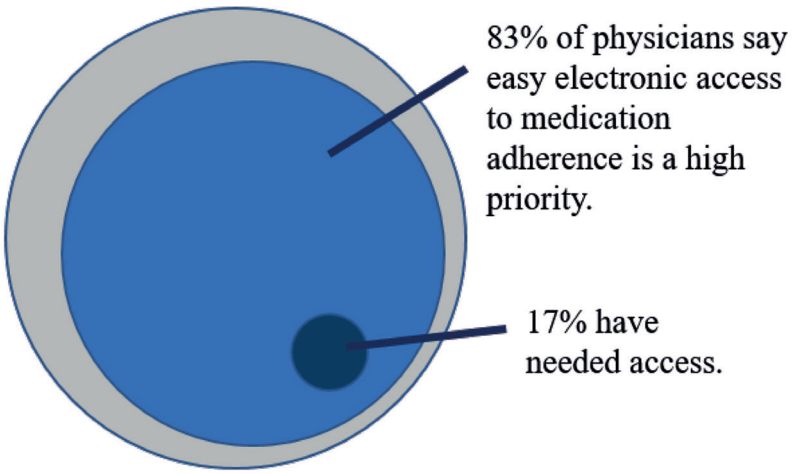

Figure 5: Physician access to medication adherence.

interactions are healthcare payers and pharmaceutical and medical-device developers and, for patients with memory care conditions (e.g. Alzheimer's disease, moderate-to-severe traumatic brain injury), caregivers who directly oversee or check in on medication adherence.[1] Anticipating patients' need for security, and data retention for all dosing events regardless of temporal connectivity, are important features for connected devices to ensure the many data pathways are protected and that all participants in the data interactions have immediate access when the device is connected.

The ideal connected device should be thought of as a system, comprised of both a device and a data storage and transmission method; each aspect of these systems requires regulatory checks to safeguard data and guarantee patient and data fidelity. Effective connected devices ensure no patient-identifiable data is held on the medication delivery device, but rather transmitted securely over Bluetooth to an app or over a network directly to a secure cloud platform. These systems encrypt all data, maintaining a full record of every event over the course of the device lifecycle. Data generated by the medication delivery device or patient input should be stored outside of the smartphone, so that it is not at risk from operating system upgrades or cyber attacks on the operating system. For web access to the patient view or health professional view, all data should be encrypted at rest and in transit. Any data cached on the medication device or mobile app should be secured until the next connection to the cloud platform, at which point the data can be synchronised between device, app and cloud.

Such a system has many benefits to the patient. First, it avoids the need to manually record the data, which may translate to lost data or data that lacks a temporal tag. Second, it allows for the collection of empirical data and for systems to simultaneously correlate symptoms, results and medication. Particularly in light of covid-19, the ability to track and correlate symptoms to medications that are new and under emergency use authorisation allows physicians, pharmaceutical companies and regulators to gain insight into the efficacy of novel medication regimens used on a novel disease vector.[25,26]

	Range ($ per unit)
Conventional	3.00–5.00
Current Technology	1.20–1.45
Next Gen Tech	0.85–1.05
2nd Gen Tech	0.75–0.95

Table 1: Price models for adding low-cost connectivity to existing devices.

Important features of any connected device are the cost of both the device and the service, as well as increased revenues due to medication adherence, and the reduction in healthcare costs due to "healthier" patients. Traditional connected devices increase the per-unit cost of a standard device by $1.20–5.00 (Table 1). However, with emerging demand for connected devices due to covid-19 and subsequent increases in chronic health conditions and the need for remote medical care, increased manufacturing volume and emerging technology trends in the field of connected devices are expected to drive the per-unit cost down by between 22% and 80% compared with the technology of just two years ago.[27] Even if medication adherence translates to a mere 15% in healthcare cost savings, this translates to approximately $43.5 billion in annual savings, based on pre-coivd-19 data. Given that covid-19 is expected to permanently alter healthcare – requiring increased care for chronic health conditions and a permanent shift to remote healthcare monitoring – these savings are only expected to grow in the coming months and years.

Figure 6: The smart, reusable autoinjector can handle multiple drugs through a syringe radio frequency identification (RFID) reader and has an intuitive user interface with illuminated user graphics and audible feedback.

SUMMARY

Connected drug delivery solutions (Figure 6) have demonstrated their potential to revolutionise medication adherence in the community, but the aspirations of a pre-covid-19 era are increasingly becoming a necessity now, and will likely continue to be an essential healthcare tool in the near and long term. Incremental cost is minimised by manufacturing in volume and increased demand for a more engaging digital experience – driving down the cost of care, improving medication adherence and lessening the need for costly urgent and emergency care.

ABOUT THE COMPANY

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

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ABOUT THE AUTHORS

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

Angela R Eder, PhD, is a Healthcare Content Creation Manager at Phillips-Medisize, where she is responsible for bringing scientific and engineering innovations to a wider audience. She has more than 20 years' expertise in research and development in both healthcare and consumer products, bridging the specialties of medical device, food safety, microbial disinfection and drug delivery systems. Dr Eder has augmented her professional experience by serving in academia: teaching collegiate chemistry, volunteering as industrial liaison to graduate programmes and mentor for young female scientists, and developing science and engineering outreach programmes to cultivate future generations of scientists and engineers.

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D-FLEX® ECOSYSTEM – FROM DATA TO VALUE

Here, Fred Metzmann, PhD, Vice-President Sales and Marketing, and Frank Leipold, Business Developer Digital Solutions, at Haselmeier, discuss the benefits of connected medical devices in clinical trials and describe the advantages of Haselmeier's D-Flex® Ecosystem for improving adherence and reducing the dropout rate in clinical trials.

In recent years, interest in, and adoption of, connected technologies has grown significantly within the drug development industry, due to their potential for improving healthcare delivery, research and the patient experience. The use of connected digital products, such as those that capture physiological and behavioural metrics, in formal clinical research has also been steadily gaining in prevalence and importance for several years.[1]

Currently, many pharmaceutical companies are exploring how connected digital devices can be incorporated into their clinical trials to improve the data foundation and, potentially, to assist in securing a faster time to market and improve patient retention. However, one of the biggest challenges that remains to doing so is the creation of a work structure that is robust enough to allow the output data from connected devices to be accepted as evidence for the trail.

To this end, Haselmeier has developed the D-Flex® Ecosystem, a flexible digital solution that works with Haselmeier's D-Flex® disposable injection pen. The D-Flex® Ecosystem presents significant advantages for improving the robustness and data quality of clinical trials (Figure 1).

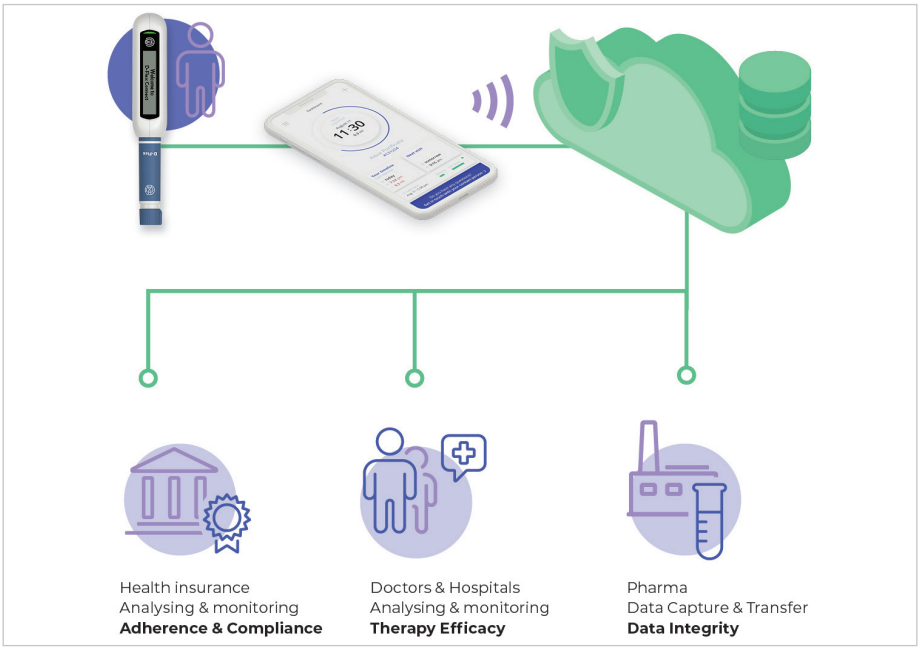

Figure 1: Adaptive data capture in clinical trials using the D-Flex® Ecosystem enables real-time monitoring and reduces the time between data collection and analysis.

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"eCRFs have many advantages over their paper counterparts. For example, data entry can be verified directly by the CRO, which provides a better overview of patient recruitment and the quality of data entry."

FROM DEVICE TO CONNECTIVITY

Healthcare is perhaps the best place for the application of the Internet of Things, here called Internet of Medical Things (IoMT). Connected medical devices have the potential to expand access to providers, improve the quality of care through more accurate patient information and enable patients to gain more control over their overall health. In addition, the IoMT can change the process of clinical trials, making them more efficient and cost-effective, thus reducing the time needed to research new treatments.[2,3]

Electronic data capture (EDC) in clinical trials is a contemporary way of capturing medical data digitally with the patient via an online database, instead of using the more traditional paper-based format. The case report forms (CRFs) used with EDC are called electronic CRFs (eCRFs).

eCRFs have many advantages over their paper counterparts. For example, data entry can be verified directly by the contract research organisation (CRO), which provides a better overview of patient recruitment and the quality of data entry. eCRFs also result in significantly fewer queries, as problems with illegible handwriting are eliminated. Furthermore, EDC can also be programmed with numerous plausibility checks, so that many incorrect entries, such as entering the current date instead of date of birth, are impossible.

Figure 2: The disposable D-Flex® injection pen is easy to configure for a single dose or multiple fixed dosages. It is easy to adapt to a customer's dosage requirements and ensures that a fixed dose is delivered, increasing patient safety.

The eCRF format also enables online monitoring, in which the data entered is checked for correctness and completeness, while monitoring in the study centre focuses on source data verification, i.e. the comparison of database entries and source documents. Due to the resultant time savings and its user-friendliness for investigators and study nurses, EDC has established itself in recent years to become the standard in clinical studies.

FROM TECHNOLOGY TO THERAPY

The D-Flex® Ecosystem comprises hardware, software and service-enabling data capture in clinical trials. In particular, the D-Flex® Ecosystem consists of the disposable D-Flex® injection pen, a digital cap, a mobile app and the Haselmeier data platform. The digital cap enables data capture at the point of input from the proband, patient and/or healthcare professional and subsequently the secured transfer of this data to the Haselmeier data platform. The platform works as a transient vector for transferring the captured data to healthcare provider or the CRO in their preferred eCRF format or directly into their own data system.

D-Flex® Injection Pen Product Platform

The D-Flex® injection pen product platform for use with 3 mL cartridges can be easily configured, from a single fixed dose to multiple distinct fixed doses on a single pen, bridging the gap between fixed and variable dose pens (Figure 2). The D-Flex® technology does not allow any intermediate steps between the distinct fixed doses, reducing the risk of an incorrect dose and therefore increasing patient safety.

The dose levels of the D-Flex® injection pen can be freely adjusted as part of a customer-specific adaptation programme by modifying only one component of the D-Flex® product platform. This is particularly interesting for dose-finding trials and the rapid approval and marketing of combination products for subcutaneous self-administration.[2,3]

Thus, the D-Flex® product platform offers innovative technical features that enable customers to accelerate the development of their combination product for subcutaneous self-administration by synchronising the drug development and device development processes at an early stage. In this way, device development can begin as early as Phase II trials, instead of the usual sequential start of device development after completion of Phase III trials.

The D-Flex® technology allows for optimal adaptation to the titration scheme of clinical trial design through all phases, providing important information on the therapeutic efficacy window of the drug. In addition, the technology allows for easier self-administration by the patient during the treatment phase. The handling of multiple devices, which would generally require further training or hospitalisation, can thus be eliminated, while at the same time allowing easy adaptation to the individual needs of the patient. These possibilities are of course also of increasing interest to the treating physician.

D-Flex® Connect – Data Capture and Transfer

The digital cap of the system measures the expelled dose, time and temperature; is able to transfer this data via Bluetooth Low Energy (BLE); and contains embedded firmware for its specific user interface (Figure 3). Depending on the study requirements, the app associated with the D-Flex® Ecosystem can be either minimalistic or used to collect additional data, such as patient questionnaires. The health data platform is the cloud system used to transfer

"The D-Flex® Ecosystem comprises hardware, software and service-enabling data capture in clinical trials. In particular, the D-Flex® Ecosystem consists of the disposable D-Flex® injection pen, a digital cap, a mobile app and the Haselmeier data platform."

Figure 3: The D-Flex® Connect cap works seamlessly with the D-Flex® injection pen to provide easy data collection and transfer, and facilitates analysis of data sets and dosage adjustments.

data to eCRFs, or to be used by a CRO for data validation, statistical analysis, safety and efficacy summaries, or final study reports. This means that, if desired, D-Flex® Ecosystem can provide pharma companies with an all-in-one solution, which is flexible, secure and efficient.

D-Flex® Ecosystem App

The administration-specific app transfers relevant data directly from the patient to the Haselmeier data platform, which is used primarily for data transfer to the eCRF while ensuring data security and integrity. As the mobile app can also provide essential services, such as reminders to ensure that medications are taken on time, it can also improve the patient experience. An optional feature is the possibility to enable real-time feedback from the patient if electronic patient reported outcomes (ePRO) are among the collected data points in the study. Compared with scheduling clinic visits, this can allow for faster and more regular check-ups on patients to help ensure relevant input from them, such as side effects, is not missed (Figure 4).

Mobile devices have proved to be a very useful tool for capturing data from patients in a trial, with the area of mobile health (mHealth) services seeing significant growth. Using mobile devices as a therapy management solution, patients can engage in regular surveys pertaining to their treatment and be notified about medication regimes. Additionally, other mobile capabilities, such as feedback options, gamification of the application and medication reminders, can be channelled to support behavioural change and improve clinical data collection.

If the patient does not apply the pen correctly this will be registered, and a notification can be sent via the app to ensure the correct dose of the medication is taken. This enables the organisers of clinical trials to ensure that only high-quality data and results from patients who adhered to the therapy scheme correctly are analysed, because non-adhering participants can be flagged in the system by the CRO in real-time.

Figure 4: The D-Flex® Ecosystem app not only serves to transfer data to the Haselmeier data platform, it can also improve the patient experience.

FROM CLINICAL TRIALS TO COMMERCIALISATION

Missing data and patient drop-outs in a clinical trial impacts the quality of its results and therefore its significance. Study volunteers terminate their participation prematurely for various reasons, such as side effects, lack of efficacy or because they find it simply too much effort to participate. The D-Flex® Ecosystem enables convenient digital data capture for patients at home, contributing to increased adherence, reduced drop-out rates, and a higher quality of study results (Figure 5).

The D-Flex® product platform can be easily adapted to specific customer requirements or clinical trial designs. This allows early integration of commercial device development to begin in Phase II and continue into Phase III by simply adapting the product platform. In general, only one component of the pen needs to be modified, which saves both costs and time.[4]

When setting up a clinical trial that uses connected digital devices for data collection and management, there are both opportunities and challenges for everyone involved. For starters, depending on where the clinical trial takes place, organisers must obey local data protection and data security regulations. Ethical and legal concerns regarding data collection will naturally permeate all layers of the trial. Organisers planning a clinical trial with a new medical device that allows direct data collection must consider the security of the participants' data from several angles.[5,6] Unlike the introduction of a medical device or a drug, this does not just entail whether the hardware itself adheres to the laws of the local market.

Certain questions must be answered before and while setting up the trial. The organisers must decide which data points need to be collected. Everyone involved needs to have all the hardware, software and internet access required to play their part in the trial. If participants are unable to use the device or software, is there somebody else who can and is legally allowed to? Participants have to be trained on how to use the device and/or software needed for data collection, while the medical and research staff need to know how to work with the incoming data, i.e. the software the data will be analysed with. If doctors are

Figure 5: The D-Flex® injection pen can be easily adapted to a specific customer clinical trial designs by changing just one part.

> "Participants in clinical trials need to feel that that are being taken seriously, included, involved and informed. Uncertainty or uneasiness can lead to a lack of adherence or discontinuation."

the ones training patients to use the device or app, this will be perceived as an extra effort on their part. For this reason, it should be clearly communicated how the device or app can reduce the time and effort a doctor has to spend on a patient further down the line of a clinical trial.

In relation to data integrity,[7] points that need to be addressed before the start of the trial include the format in which the data will be saved and transferred, whether all data transfers from device to collection points are sufficiently encrypted, and who will have access to which data. Additionally, all the collected data and trial information has to be stored in a secure fashion that not only protects patients' privacy, but also follows the applicable guidelines concerning long-term data storage.

Prior to the start of data collection, roles with specific rights to view, amend and/or input data must be assigned to everyone involved. To avoid data security breaches, patient data has to be de-identified. It is important to note that the extent of anonymisation required also depends on local data security regulations. For this reason, organisers of multinational trials need to be even more careful when setting up, taking into account the requirements of regulations in effect in all the locations the trial will take place in.

Participants in clinical trials need to feel that that are being taken seriously, included, involved and informed. Uncertainty or uneasiness can lead to a lack of adherence or discontinuation. Thus, healthcare providers should ensure participants are adequately informed about how their data is used and what is done to protect their privacy, as well as reassuring them that their concerns are taken seriously. This is also important with respect to the fact that, preceding the trial, participants should agree in written form to their data being collected, stored and used for research to avoid legal repercussions for the organisers.

Analogue work processes cannot be simply transferred into a new digital environment. Therefore, a lot of processes must be redesigned to create an efficient workflow. Digital transformations take a lot of effort and it can be a challenge to get everyone onboard. New systems for data collection and management are initially perceived as a burden, adding more work. Therefore it is not sufficient to simply supply and train users with new medical devices and software without creating an awareness for the benefits for themselves. This can create an initiative that makes people want to "go digital".

FUTURE OUTLOOK

The IoMT has already begun to permeate clinical trials.[7] It is not as mainstream as it is in other sectors because the technology is still evolving and advances still need to

> "New systems for data collection and management are initially perceived as a burden, adding more work. Therefore it is not sufficient to simply supply and train users with new medical devices and software without creating an awareness for the benefits for themselves."

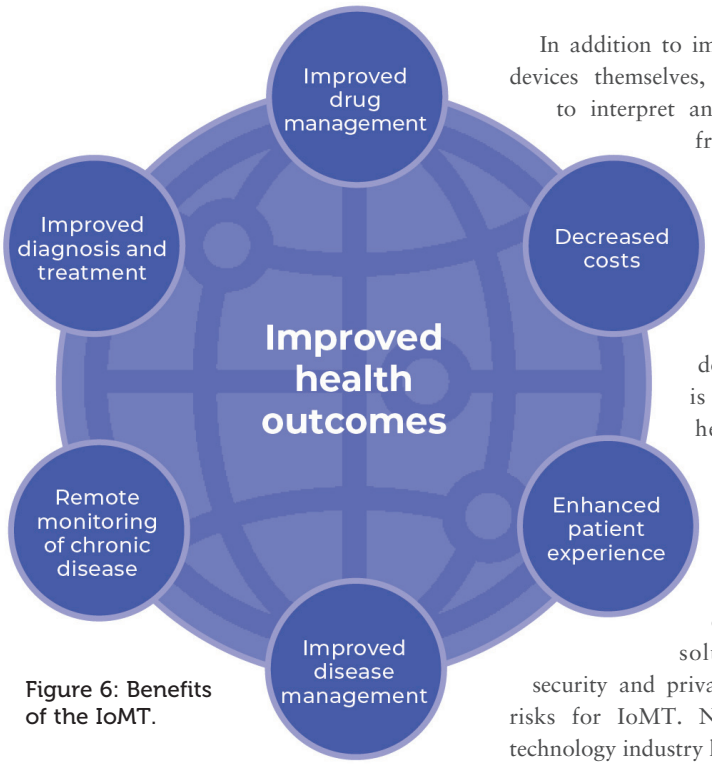

Figure 6: Benefits of the IoMT.

be made. Clinical researchers have also had a history of being hesitant to adopt new technology, as the accuracy of the data collected in clinical trials is critical and without room for error. With time, we will see its presence grow exponentially as more clinicians begin to realise the immense benefit derived from using digital devices and the IoMT,[2–4] which is significantly greater than simply speeding up data collection (Figure 6).

Of course, new technologies are not only of interest to healthcare professionals and researchers. Since some therapies can have a drastically lower efficacy if medications are taken irregularly or have to be restarted from the very beginning after a treatment discontinuation, data about patient adherence to a therapy would be of great interest to insurance providers as well. Better adherence means that there is no need to pay for an expensive treatment regime twice, after all. Having real-time access to participants' data all presented in the same format can also allow sponsors of clinical trials to be more flexible and adapt protocols or dosing schemes more easily if the need arises. At the same time, a system that collects all the relevant data without fail, and that can be accessed at any time during the trial, can be extremely helpful for the parties involved in continuous quality controls or audits. The D-Flex® Ecosystem has the potential to help monitor and improve patients' adherence to a treatment.

In addition to implementing the digital devices themselves, companies will need to interpret and use data streaming from these devices properly, with skilful data scientists and analytic tools creating value from the captured data. There is no doubt that the IoMT is transforming the healthcare industry completely by redefining how apps, devices and people interact and connect with each other in delivering healthcare solutions. However, security and privacy remain the biggest risks for IoMT. Nonetheless, since the technology industry has come a long way in providing solutions in this area, this should not be a reason not to adopt new technologies. New tools, including the D-Flex® Ecosystem, will help to form a secure integrated healthcare system with the view of ensuring patients are better cared for, healthcare costs are significantly reduced and treatment outcomes are improved.

Ultimately, remote data collection will become part of the normal therapy regime, where patients can administer drugs themselves and monitoring can largely be done via health apps and devices that measure specific biomarkers and relate patient feedback to healthcare providers. This is especially of interest in fields where patients receive care from nurses in their own homes. Having the option to document a treatment, the patients' progression and other important data points by simply transferring and saving patient data digitally, via a verified and validated system, could save a lot of time and inconvenience for healthcare providers. In theory, doctors could even provide feedback or medical advice to their patients via an app, after checking their patients' data.

Clinical-led improvement, enabled by digital technology, is transforming the implementation of clinical trials, but strategic decisions about investment in digital technology can often be a footnote in board discussions. This needs to change. These decisions need to move centre stage. Leaders in the healthcare industry need to widen their understanding of the digital health terrain and the possibilities integrated digital systems can offer, particularly to meet the immense productivity challenge ahead, and to gain practical insights, such as real-time feedback or the synchronised development of drug and device, that will help avoid expensive mistakes.

ABOUT THE COMPANY

Haselmeier, a part of Sulzer AG, has been established in the healthcare market for over 100 years. Starting as a family owned business with approximately 240 employees, Haselmeier has been pioneering the development of injection pens for subcutaneous drug delivery since the 1960s. Haselmeier continues to drive innovations in self-injection pens, from design and manufacturing to packaging and delivery. The company has developed solutions in scalable volumes for numerous pharmaceutical partners, always following state-of-the-art engineering practices – and aims to evolve even further.

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MALLYA: ENLIGHTENING PAST, EXCITING PRESENT, PROMISING FUTURE

Arnaud Guillet, Vice-President Business Development at Biocorp, reviews the Mallya connected device platform, from the origins of the project to the current success in diabetes and deployment in other fields, and introduces the promising next-generation Mallya.

Looking back at the Mallya journey, which began in 2014, gives some perspective on the evolution of the drug delivery device and the pharma industry during the last few years. Following the path of other sectors – with a noticeable delay due to regulatory, technical and mental barriers – the rise of digital health and connected solutions has been spectacular in this field, and we are now at the dawn of a new era of value-based care, supported by objective data. This wave has been specifically spectacular in the field of diabetes, initiated by disease management mobile apps, the adoption of continuous glucose meters, digital therapeutics – and now, smart solutions to monitor insulin delivery.

In this context, after six years of intense development, testing and regulatory work, the first version of Mallya – dedicated to insulin pen injectors – has been launched in the fourth quarter of 2020, in a few geographies in Europe and Asia, and is preparing for large-scale distribution in 2021, with orders already secured. But smart delivery devices require continuous improvements and sustained innovation towards an ever-better patient experience and Biocorp is now unveiling the next version of its Mallya platform to be launched within two years. It is time to look back at the origins of the Mallya project and contemplate present and future challenges.

> "Investing in connected solutions to support the management of diabetes seems like an evident necessity."

THE UNMET NEEDS BEHIND THE SOLUTION

When launching its connected initiative in the early 2010s, Biocorp quickly decided to focus on diabetes, as it was the therapeutic area with the most urgent needs for treatment delivery monitoring solutions, and decided to go for the add-on option, considering the characteristics of this area.

From the perspective of both the patients/healthcare professionals (HCPs) and the health industries, investing in connected solutions to support the management of diabetes seems like an evident necessity. Managing diabetes is a complex endeavour and relies on multiple pillars: careful lifestyle management, carbohydrate counting, glucose monitoring, titration, medicine intake, frequent adjustments and interactions with referring doctors. Plus, the structure of the market calls for differentiating factors. Diabetes is a highly concentrated market, specifically for the insulin segment, with a limited number of companies competing for commercial advantage and looking to differentiate through their service offering.

This context explains the spectacular penetration of connected solutions in the field during the past few years, covering almost all parts of the patient journey, with very advanced solutions for glucose monitoring (continuous glucose

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monitoring systems such as Dexcom G6 (Dexcom, Camberley, UK) or Abbot Freestyle Libre 2), successful digital therapeutics (Livongo (CA, US), Omada (Copenhagen, Denmark)) and US FDA-approved insulin titration software (Amalgam RX (DE, US)).

Connectivity emerged as a market standard. But there was one missing piece in this picture: a reliable solution to monitor insulin delivery, for which pen injectors are by far the widely dominant option. Providing reliable smart pen options has emerged as a new frontier for diabetes management, and the only option to provide a truly comprehensive disease management product.

In that context, Biocorp decided to go for the add-on option, as disposable pens are by far the most commonly used option by patients. Integrating electronic components and communication sets into a disposable system was neither economically viable nor environmentally acceptable. Users' habits are hard to break and, to this day, there is no evidence of a significant switch from disposable to reusable pens. This is why Biocorp worked on developing a smart clip-on device, collecting the dose selected and enabling automatic transfer to companion software that can be easily installed on existing pens and removed once they are out of drug, which will also last for a significant time.

Although Mallya was initially developed for diabetes, pen injectors are a common drug delivery system in many other fields, including fertility, growth hormone deficiency, osteoporosis and parathyroid hormone. Engagement factors might be different in those different therapeutic areas but Mallya can provide several benefits – from injection guidance and reassurance to compliance tracking and patient reward initiatives.

THE SOLUTION

Based on these foundations, Biocorp has developed Mallya, a Bluetooth-enabled add-on module composed of two parts – a body, containing an electronic board that is clipped to the pen; and a button, attaching to the dose button of the pen. It turns any conventional injection pen into a connected device and automatically records treatment information (selected dose, date and time of injection). Data is sent in real time to companion software, using Bluetooth technology.

Figure 1: The Mallya device.

"Mallya turns any conventional injection pen into a connected device and automatically records treatment information."

This device was developed following some core principles to ease user adoption and trust, and simplify implementation for pharma companies.

1. Simplicity for Users and all Stakeholders

Providing connectivity to patients is key but it also important to take into consideration that patients are using a "simple" pen injector device already and we have to integrate connectivity into their daily routine without impacting their user experience. To make it seamless for patients, tremendous efforts were made on the mechanical side to work on the form factor and look and feel of the device. The evolution of the platform is testament to the level of commitment from the R&D and usability teams (Figure 1).

On the hardware, firmware and software side, Biocorp's R&D team made the system totally passive from the patient perspective – and the set-up and the onboarding sequence have been streamlined using a proximity pairing system and a quick video sequence to guide patients through the process.

Making it simple for patients also implies a clear value proposal. Biocorp has explored many potential functionalities for the device but, through discussions with HCPs, patients and pharma partners, eventually realised the importance of focusing on a very limited number of key functionalities – type of insulin, dose selected, time and date.

On top of simplicity for users, ease of implementation for pharma partners was a key driver in the design and development of this solution: the implementation of Mallya does not imply any modification of the existing pen, whether internal or external. No mechanical adjustment is needed to make it fit and no addition of small components (magnets, electronics, etc) is required. Following this principle significantly limits the regulatory and industrial impact for Biocorp's partners.

"On top of simplicity for users, ease of implementation for pharma partners was a key driver in the design and development of this solution."

2. Accuracy, Reliability and Robustness

Mallya was initially developed for diabetes and the monitoring of insulin delivery. In this area, accuracy and exhaustivity of information is paramount. Coming from this background, top priority was to work on a system reaching the highest level of accuracy, replicable on any pen platforms, in any therapeutic areas.

The choice of magnetic-sensing technology to track the dose selected was the best technological option to reach the highest

"The choice of magnetic sensing technology to track the dose selected was the best technological option to reach the highest level of accuracy."

level of accuracy. The model accuracy and the algorithm reliability were validated through robust testing, combining bench tests and user testing in real-life settings.

Beyond accuracy, the system provides further guarantee to the patient: exhaustivity of data, visual signals to warn the patient if wrong manipulations or misuses are detected, distinction between dose selected and unselected versus actual injection, and distinction between priming and actual injection.

Furthermore, Biocorp's R&D team worked on the robustness of the system and perfected the choice of materials and the resistance of components to make it compatible with the challenges of daily life. Drops and spills are to be expected, and the device has been developed and tested to face these situations. It can also adapt to different storage conditions, including storage in the fridge. Mallya should adapt to the ways of its users, not the other way round.

3. Agnostic and Replicable

Finally, Mallya has been designed as an agnostic platform, covering different pen platforms with the same solution, to leave the choice of treatment options entirely in the hands of patients and HCPs. For instance, in the field of diabetes, patients can use a specific pen for their basal insulin (e.g. Lantus (insulin glargine injection), delivered by Sanofi's Solostar pen) and a different one for their short-acting insulin (e.g. Novorapid (insulin aspart), delivered by Novo Nordisk's Flexpen). In this configuration, the patient is not tied to a specific brand or pen platform, as Biocorp can offer the same solution for both options.

This agnostic principle has led the Biocorp team to work on different pen platforms – making the Mallya technology easily replicable and expandable to any therapeutic areas.

WHERE WE ARE NOW – DIABETES AND BEYOND

Five years after the start of the project, Biocorp has a fully developed and industrialised Mallya range for disposable insulin pens, with a CE mark Class IIb granted in June 2019, significant distribution and development contracts with major players in the diabetes industry, and active programmes to adapt the technology to further pen platforms in other therapeutic areas such as fertility or growth hormone.

Given the potential of the insulin market for this technology, Biocorp decided to support on its own the development of a complete range of Mallya for disposable insulin pens, covering the most important platforms. Three different variants are now fully developed and industrialised – Mallya for Sanofi's Solostar (carrying insulins such as Lantus, Toujeo (insulin glargine injection) and Apidra (insuline glargine injection)), Mallya for Eli Lilly's Kwikpen (Basaglar (insulin glargine) and Humalog (insulin lispro injection)) and Mallya for Novo Nordisk's Flexpen (Levemir (insulin detemir) and Novorapid (insulin aspart)). From the same technology base, specific stock keeping units (SKUs) for each platform have been developed, with slight mechanical variations on the Mallya cap and the size of the body part. However, overall form factor, look and feel, performance, functionalities and user experience remain exactly the same from one platform to another.

This initiative was the foundation of multiple commercial successes. In July 2019, Biocorp signed a major partnership agreement with Sanofi, including global distribution of Mallya and specific development activities. The scope of the agreement and the level of investment from Sanofi – around €20 million (£18 million) in total – acknowledged the quality and potential of the Mallya technology. This partnership has now reached a new, exciting phase with imminent launches scheduled between the fourth quarter of 2020 and the second quarter of 2021 in various geographies in Europe, the Middle East and Asia, with the US not far behind.

Following this initial success, Biocorp signed another major distribution contract with Roche Diabetes Care France in June 2020. Roche plans to distribute Mallya through French pharmacies and integrate the data into its existing software ecosystem including connected glucometers (Accu-Chek Mobile, Accu-Chek Guide) and a companion app called Gluci-Check. Biocorp is therefore preparing for large-scale production and distribution of Mallya devices in France, starting from the first quarter of 2021.

To boost Mallya distribution and cover all potential geographic areas, Biocorp has also signed deals with local distributors

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in South Korea, South Africa and Eastern Europe. Finally, Biocorp has partnered with software players to integrate Mallya data into existing ecosystems providing broader services to patients, including glucose readings, carbohydrate counting (Health2Sync (Taipei, Taiwan)), basal insulin titration (Amalgam RX) or bolus calculator (SocialDiabetes (Barcelona, Spain)).

In parallel with this intense activity in the field of insulin, Biocorp has initiated partnerships with pharma companies to adapt Mallya technology to other pens in therapeutic areas such as Parkinson's disease, fertility treatment and growth hormone deficiency. Although treatment plans, injection frequency, variability of doses and expectations vary from one therapy to another, accurate capture of the dose dialled always remains the priority of stakeholders. In that regard, Biocorp's proprietary electromagnetic sensing technology, relying on strong intellectual property, can guarantee the highest level of accuracy, regardless of the existing pen platform. Pharma partners can rely on a strong technological basis and leverage Biocorp's expertise, know-how and previous R&D efforts, which reduces development timelines, costs and project risks.

THE NEXT GENERATION

These developments of different insulin pen platforms and customised programmes for pharma companies made Biocorp realise that Mallya had no specific restrictions in terms of form factor. Mallya is about a technology, based on a magnet evolving around the standard position of a magnetometer, and a guarantee of accuracy, robustness and usability.

Biocorp started working on the next generation of the product, not because the existing version was not satisfactory, but for the sake of continuous innovation for the benefit of patients, HCPs and its healthcare industry partners.

One of the reasons why digital, software solutions and connected devices have such difficulties penetrating the pharma industry is due to the pace of innovation. Pharma is used to working for 10 or 15 years before getting a drug approved, and then benefiting from a long patent protection and commercial life, without making any change. The same paradigm applies for traditional drug delivery devices. But the burst of digital health really changed the game. On the other hand, connected drug delivery devices face a difficult dilemma: relatively long development cycles but a short commercial life before they become obsolete, due to the extremely fast pace of innovation in this sector. When a request comes from a pharma partner, the time to design, develop, industrialise and approve such systems makes them already obsolete at the end of the journey.

Figure 2: The next-generation Mallya.

Therefore, players like Biocorp need to anticipate future needs and initiate internal developments to de-risk projects and shorten development time to match the pace of digital health innovation and help pharma companies be successful in this field. To that end, Biocorp has been working – and continues to work – extensively on the next generation of Mallya.

The challenge was simple: making it one piece, with everything contained on the cap. The challenge sounded impossible, given the principles of Mallya technology and the different electronic features and components, but it was met by Biocorp's R&D team by leveraging the very solid know-how the entire team has acquired on magnetic sensing technology – and also thanks to the fast pace at which electronic components are released, thus providing new solutions. Following years of intense design and development activities at Biocorp, the company has now introduced a new version of the Mallya platform, all in one piece (Figure 2).

ABOUT THE COMPANY

Recognised for its expertise in the development and manufacture of medical devices and delivery systems, Biocorp has today 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 AUTHOR

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 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.

CONNECTED DRUG DELIVERY: ACHIEVING OPTIMAL BENEFITS THROUGH SMART COLLABORATION

In this article, George I'ons, Head of Product Strategy and Insights at Owen Mumford Pharmaceutical Services, discusses the challenges developing connected devices presents to key market stakeholders when it comes to successful rollout and implementation. Additionally, he considers the perspectives of these market players, as well as the patients themselves, with respect to how connected drug delivery devices can help them to better achieve their desired outcomes.

The covid-19 pandemic has driven the healthcare industry to make greater use of remote consultations and digital tools, but it is likely that this trend will continue even when cases abate. In fact, a recent poll found that the vast majority of general practice doctors in the UK intend to keep some or all of the new technology they have introduced after the pandemic (Figure 1).[1]

Accompanying this trend towards remote care is a growing market for digitally connected drug delivery devices. Analysis using both proprietary data and published market analyses (such as those from GrandView Research, Acumen Research and Future Market Insights) estimates that the global market for connected drug delivery devices (injection and inhalation) will grow at a compound annual growth rate (CAGR) of over 25%, reaching a total value of US$706 million (£529 million) by 2025.

"In a recent survey of pharmaceutical executives, gaining regulatory clearance was identified as a primary challenge in the development of smart drug delivery devices. The presence of electronic components in a device already makes it subject to additional regulatory requirements, such as compliance with the EU's WEEE."

THE COMPLEX DEVELOPMENT JOURNEY

In a recent survey of pharmaceutical executives, gaining regulatory clearance was identified as a primary challenge in the development of smart drug delivery devices.[2]

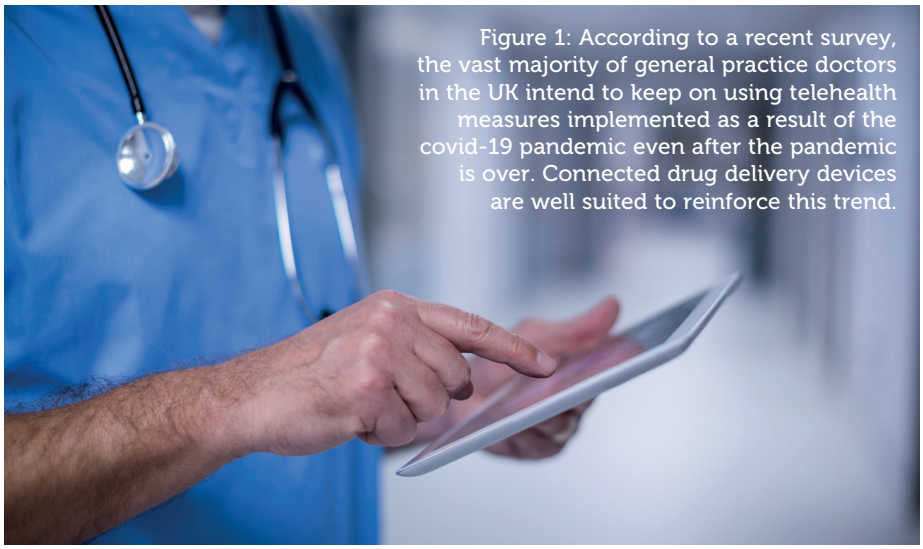

Figure 1: According to a recent survey, the vast majority of general practice doctors in the UK intend to keep on using telehealth measures implemented as a result of the covid-19 pandemic even after the pandemic is over. Connected drug delivery devices are well suited to reinforce this trend.

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"For instance, the US FDA intends to apply its regulatory authority to software applications intended for use on mobile platforms (mobile applications or "mobile apps")."

The presence of electronic components in a device already makes it subject to additional regulatory requirements, such as compliance with the EU's WEEE (the Waste Electrical and Electronic Equipment Regulation). As the digital health industry continues to develop at a rapid pace, it is likely that regulators will increase their oversight accordingly to ensure that patient safety is not put at risk. For instance, the US FDA intends to apply its regulatory authority to software applications intended for use on mobile platforms (mobile applications or "mobile apps"). The organisation's recent guidance specifies that, if a mobile app meets the definition of a medical device, it may be referred to as a "mobile medical app" and therefore would be subject to FDA oversight.[3]

A further obstacle to gaining approval is that regulatory authorities need robust evidence of the value of the data that's gathered by connected devices, and the impact on healthcare outcomes; however, a strong body of hard evidence can only be sourced by testing devices in the field on a wide scale. Recognising the need for a more updated approach, the FDA launched the Digital Health Center of Excellence (DHCE) in September 2020. The DHCE is focused on "helping both internal and external stakeholders achieve their goals of getting high quality digital health technologies to patients by providing technological advice, co-ordinating and supporting work being done across the FDA, advancing best practices, and reimagining digital health device oversight".[4] Given that the regulatory processes for digital health are both complex and still evolving, investing in specialist knowledge and support – whether to write a regulatory submission, pre-emptively identify concerns or carry out human factors testing – may prove invaluable in getting a new connected device to market.

Regulators will also be closely scrutinising data protection measures, since connected devices raise a host of concerns around patient confidentiality. Medical device manufacturers with products on the US market must note that they "are responsible for remaining vigilant about identifying risks and hazards associated with their medical devices, including risks related to cybersecurity". The FDA further states that healthcare delivery organisations (HDOs) should evaluate their network security and protect their hospital systems.[5] For their part, pharmaceutical companies must clarify how data will be stored and who is responsible for it, as well as who owns the data generated by connected devices in their portfolio. They will also need to work with other stakeholders, including medical device manufacturers, governments and healthcare providers, to standardise data transfer protocols; implementing the use of connected devices will be doubly difficult without interoperability across standard clinical systems. It is important that a range of devices can be used seamlessly by different healthcare providers to realise their maximum potential.

Addressing these factors across the varied array of disposable drug delivery devices already comes at a significant cost, so may not be financially viable for single-use products. Moreover, such a solution would be detrimental to the environment. Though the cost of embedded electronics is decreasing over time, they use rare-earth metals, of which as little as 1% are recycled.[6] One solution is to take a hybrid approach to designing devices that tend to be single use. This means designing the device with two components:

- A reusable, connected "shell" device that includes the embedded electronics
- A traditional autoinjector or prefilled syringe that sits within the shell and can be disposed of and replaced.

Looking at the overall environmental impact of patient care and therapy, connected devices can reduce this impact if implemented effectively. Improved patient adherence may reduce the need for visits to healthcare centres or on-site procedures, and therefore also reduce the use of energy, pharmaceutical products and equipment required for treatment. In fact, one study found that overall greenhouse gas (GHG) emissions were reduced by around 50% when a patient with poorly managed paediatric asthma improved their adherence by using a smart inhaler.[7] The most significant environmental effects of switching to a smart inhaler were reduced reliever use and reduced hospital admissions.

"Though the cost of embedded electronics is decreasing over time, they use rare-earth metals, of which as little as 1% are recycled."

STAKEHOLDER PERSPECTIVES AND OBJECTIVES

The aforementioned factors make it clear that the actors involved in developing and implementing connected devices cannot work in silos, which makes it difficult to overcome challenges and find solutions. It is in the interests of each stakeholder to take the initiative, as improved patient adherence can help each to achieve their respective aims. This article focuses specifically on the attitudes to digitisation of payers, clinicians, pharmaceutical companies and patients.

Payers are increasingly focusing on reducing overall costs by helping to create healthier societies and reduce the consumption of healthcare services. Allowing for greater patient involvement in treatment and enabling teleconsultations leads to wider benefits for the healthcare system as a whole. For example, in the US, the Centers for Medicare & Medicaid Services (CMS) found that their telehealth chronic care management programme improved patient satisfaction and adherence to recommended therapies, improved clinician efficiency and decreased hospitalisations and emergency department visits.[8] These cost-saving benefits can be further enhanced by using connected device technologies.

Connected devices equip clinicians and healthcare professionals with data they would not otherwise have in a timely manner, meaning that they can provide more informed advice, take quicker action when needed and adjust treatments to specific patient needs. Currently, embedded electronics and sensors within connected devices allow clinicians to see when a patient has administered medication, the volume of the dose and the site of administration. In future, it is likely that monitoring and reporting capabilities will become more

Figure 2: Connected drug delivery devices provide clinicians with readily accessible, timely patient data. If used as part of patient support, this can increase effective drug efficacy and lead to significantly improved treatment outcomes.

sophisticated. One example is a closed-loop system for blood glucose monitoring, which not only monitors blood sugar levels but also regulates insulin delivery accordingly to maintain target levels. In the more distant future, it may be possible for clinicians to interact with connected devices, remotely adjusting dosage according to incoming patient data.

Therefore, combined with support from clinicians, treatment data can strengthen drug efficacy (Figure 2). For pharmaceutical companies, this data can help to build a concrete case regarding the benefits of their products, which is becoming increasingly necessary as healthcare providers and payers are more stringently assessing drug performance. Additionally, as pharmaceutical and medical device companies increasingly provide additional support services, such as patient training and education programmes, adherence information generated by connected devices would help to make such services more effective. Greater insight and engagement would allow companies to actively contribute to improving adherence, and thereby reduce waste of costly medications.

Patients themselves may not be particularly concerned with any connected capabilities in their drug delivery device. The factors most important to patients, according to an injection-focused qualitative human factors study with a 120-strong focus group, are comfort and ease of use. If these elements are not thoroughly considered throughout the design process, it will be a challenge to encourage adoption of the final connected device. Since patients may already struggle to remember to administer medication, or with the administration procedure itself, new products should ideally avoid introducing new challenges or complexities. Similarly, if a device is perceived to be complicated to use, it may lead to resistance from clinicians or carers.

Digital features, such as downloading and using mobile apps, can be confusing for some patient groups, so this will need to be considered during testing. The novel access to patient treatment data may also be overwhelming or distressing for some, especially if they receive frequent notifications. Training and support programmes may help to address some of these concerns and demonstrate the benefits of introducing digitisation in drug delivery.

CONCLUSION

There is still much room for development and innovation in the area of connected drug delivery devices, and there are significant gains to be made. Empowering patients to take a more informed and active role in their own treatment can improve outcomes for both patients themselves and the wider healthcare system. As remote healthcare becomes more prominent, smart devices will play a pivotal role in optimising treatment, sharing data and providing communication. Intelligent partnerships are critical to the future of the connected drug delivery market, whether to strengthen data protection measures, assess environmental impact or facilitate device use.

ABOUT THE COMPANY

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

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