CONNECTING DRUG DELIVERY

ON drugDELIVERY

JUNE 10TH 2019 • ISSUE Nº 98

ONdrugDelivery Issue N° 98, June 10th, 2019

CONNECTING DRUG DELIVERY

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

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Jun	Connecting Drug Delivery

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Digital subscription is always completely **free**.
Print subscription costs **£99/year + postage**.

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ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd

Registered in England: No 8348388
VAT Registration No: GB 153 0432 49
ISSN 2049-145X print / ISSN 2049-1468 pdf

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DON'T DEVELOP A CONNECTED DRUG DELIVERY DEVICE WITHOUT READING THIS

Here, Matt Jones, Senior Sector Manager, Medical and Scientific, DCA – along with colleagues Richard Gledhill, Aidan O'Hare, Tony Smith, James May, Daniel Jenkins and Rob Veasey – summarises some of the key challenges and opportunities in the development of connected drug delivery devices, focusing in detail on deciding what a connected drug delivery device should do, designing for a coin cell, direct cellular connection and antenna design.

The market for connected drug delivery devices (Figure 1) is in its infancy but many predict that it will grow at an astonishing rate.[1] At DCA, we think this is likely to happen – but only if these devices can demonstrably improve the lives and outcomes of the patients who use them.

> "The advent of new and exciting technology has brought with it a temptation to connect anything to everything, providing features that sometimes offer little real benefit."

The advent of new and exciting technology has brought with it a temptation to connect anything to everything, providing features that sometimes offer little real benefit. In this context, we believe the value proposition for new connected drug delivery devices must be clearly established at the outset.

One school of thought is that new connected objects should be created and launched to see what emergent behaviours

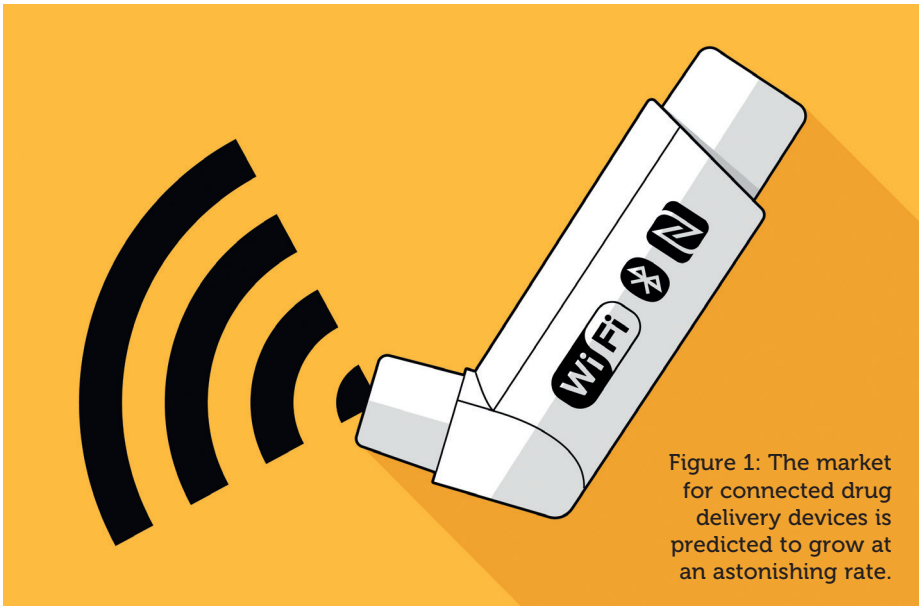

Figure 1: The market for connected drug delivery devices is predicted to grow at an astonishing rate.

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develop and which products win in the market. Some manufacturers opt to develop a minimum viable product by simply connecting an existing product and exploring how users respond to the new proposition. This gets products to market fast – increasing the likelihood of taking early market share and even of establishing a new connected ecosystem.

This "fail fast" approach has many success stories, particularly in the consumer products market, where development time, development costs, product lifespan and inherent product risk are often low.

For drug delivery devices, the picture is different. To make it to market, new products need to be demonstrably safe and effective. Regulators demand extensive evidence of this and fears around data security and privacy are often far more critical than with consumer products. This creates challenges that are in turn compounded by the rapid evolution of underlying connectivity technologies.

So what's the alternative to this "suck it and see" approach? As obvious as it may sound, we think the best answer is found by first explicitly considering and defining the need before developing the product.

WHY CONNECT?

The ability to pass information to or from a drug delivery device enables features that can train and guide patients, monitor their usage, record side effects or assist in managing regimen changes. All of this can allow interventions to improve patient compliance and reduce risks. It is also likely to change business models by providing data that facilitates outcome-driven payments.

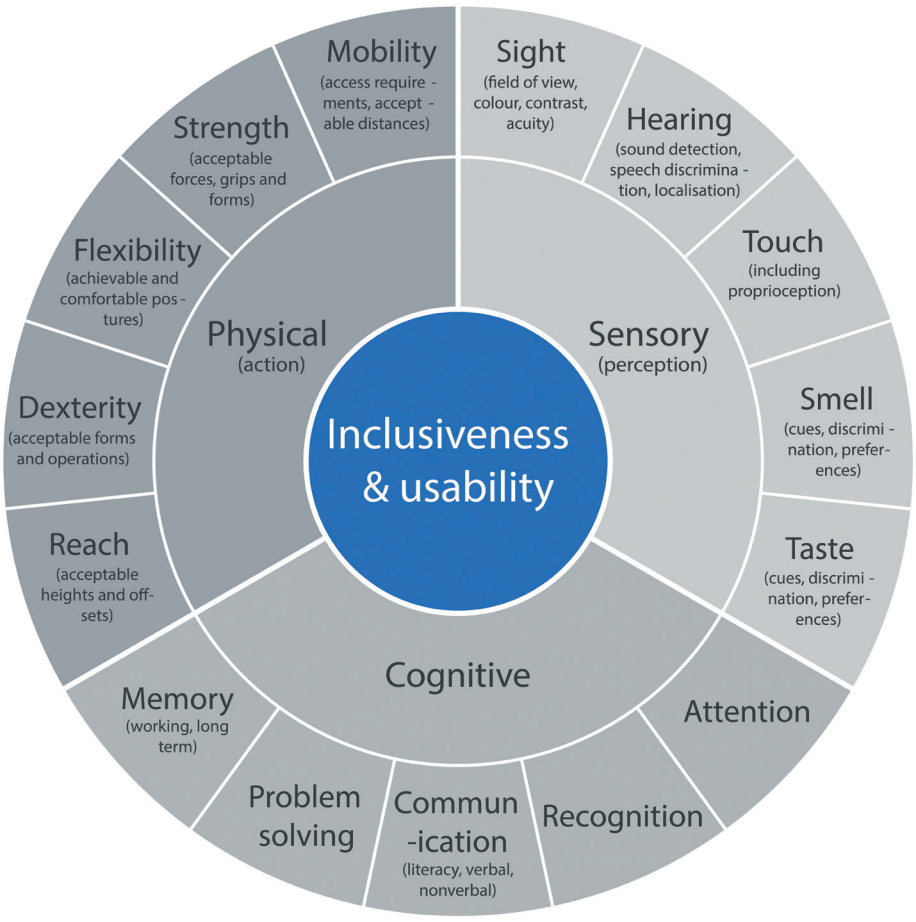

Figure 2: Breaking down inclusiveness and usability.

WHAT SHOULD A CONNECTED DRUG DELIVERY DEVICE DO?

It can be tempting to collect and present data simply because it is accessible. However, in the context of a medical device, it is imperative that the data is relevant, useful and accessible to everyone who will interact with it – whether they be a patient, carer, doctor or payer.

Information	Current product system					Connected system		
	User	Device	IFU	Pack	Diary	User	Device	App
Did I take my dose today?	■				■		■	■
Is this the right device?	■	■		■		■	■	■
How do I prepare the device?	■		■			■		■
Sufficient medicine remaining?		■	■				■	■
How do I deliver a dose?	■		■			■		■
Did I receive the dose?		■					■	■
When do I need my next dose?	■				■		■	■

■ Existing information source
■ Potential new information source

Figure 3: Comparing an existing system to its connected equivalent.

The functionality of connected devices should be informed by a detailed understanding of the conditions that they need to support. One place to start is by considering the use of the non-connected legacy version of the product. Observing and interviewing stakeholders can reveal rich insights.

The international standard for medical device usability (ISO 62366-1) advocates the use of task analysis to evaluate activities. This involves breaking down the activity into sub-tasks, which are then themselves broken down until base-level operations are reached. Each base-level task can be examined to assess the demands it places on the user at a sensory, cognitive and physical level (Figure 2).

This usability analysis will often throw up where new features or information can help support the user in carrying out a particular task. One approach is to then map the functionality of the system in a tabular form, comparing the legacy system with the proposed new connected system (Figure 3). The alternative or additional features or information sources can then be explored, assessed and filtered based on the benefits and potential risks to the stakeholders.

Generating a reasoned, useful and safe set of features is more likely to yield a successful connected drug delivery device if the development team follows a structured process aligned to the relevant standards (e.g. ISO 13485, EN 62304, EN 62366 and ISO 14971). This should support an understanding of the needs and limitations of all stakeholders and help establish the device feature set at the start of the design process. This can then be reviewed and iterated through development.

The next step is to translate this design input into a successful device concept. For a connected drug delivery device, the development process often revolves around a few key challenges, first among which is usually the power source. There are many options available to the developer of a connected drug delivery device – off-the-shelf batteries, bespoke and flexible batteries, energy harvesting, printed batteries, etc. But for reasons of size, cost and availability, a simple, non-rechargeable coin cell is often selected (Figure 4).

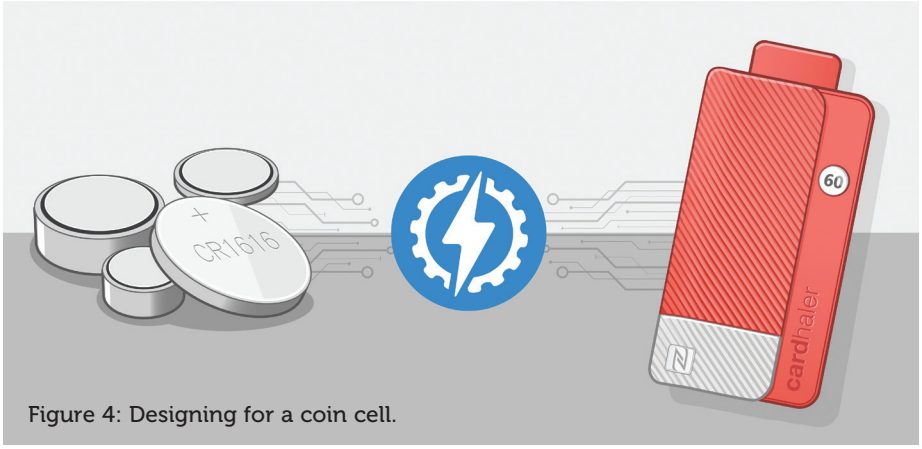

Figure 4: Designing for a coin cell.

DESIGNING FOR A COIN CELL

For all its benefits, the very limited current capability and capacity of coin cells pose challenges that affect every aspect of the device design.

Sensors and Storage

In one example, measuring physical characteristics such as pressure changes in a connected inhaler might be accomplished by using an optical transmitter and receiver. However, running an optical transmitter such as an LED continuously takes more current than the battery can provide. Pulsing the transmitter with short bursts of energy is an option. However, this can only go so far; if the pulses become too short, the transmitter no longer acts like a simple on/off switch and analogue side effects begin to make readings unreliable. At this point, a more sophisticated approach is required, such as pre-charging a capacitor to improve the turn-on speed of the LED and make the best use of the pulse length available.

> "For all its benefits, the very limited current capability and capacity of coin cells pose challenges that affect every aspect of the device design."

Once this problem has been solved, it is possible to take readings. Storing this information to non-volatile data storage would, in normal circumstances, be considered a relatively trivial exercise. However, when the memory is full, erasing data can use up considerable power, depending on the specification of the storage component. One potential solution is to dimension the storage memory to prevent the need to erase any records.

Data Transmission

Once the measurements have been stored, this data often needs to be sent to a paired mobile device. The tiny current capability of a coin cell can generally be managed by the use of suitable capacitors between the battery and the RF transmitter chip. However, the leakage current through these capacitors can drain the battery. Therefore, the amount of data transmitted must be minimised to limit the number of capacitors and consequently the cost, printed circuit board (PCB) space required and background current drain.

Similarly, care needs to be taken when transmitting (relatively) large amounts of data. Sending a single reading may only be a small number of bytes but synchronising a device with a user's new phone could easily result in a few thousand records being requested by the app. Sending that much data too fast could drag the battery voltage down, so intelligent throttling of the flow of data may be required.

The User Interface

With the widespread adoption of mobile phones and their large displays, developers often decide to use a more basic interface on the device itself, such as a flashing LED or a sounder. This seems simple, yet the coin cell's low voltage may mean it's not capable of directly driving the LED. It may be necessary to pulse the LED using a charge-pump system, for example, and vary the pulse duty cycle and speed depending on the battery voltage to achieve a consistent brightness.

Start-up

To achieve the battery life required for a disposable device, the microprocessor must require an incredibly low current while the device is not in use. This means in most cases that the device is effectively coming out of reset each time, rather than a standby mode, and has to go from a standing start to taking the first measurements very quickly. This can be challenging and may drive the selection of an appropriate microprocessor.

Battery Life – Beginning and End

At the beginning of its life, microprocessor programming during manufacture can use up too much of the coin cell's valuable energy unless carefully handled. As the battery comes towards the end of its life, its nominal (unloaded) voltage may appear reasonable but as soon as any current is drawn from it, it may drop significantly, potentially below the minimum operating voltage of the microprocessor. This could affect references and ranges for analogue inputs, the performance of sensors, and Bluetooth transmissions. Switched-mode power supplies will have to work harder to generate stable voltage supplies, further increasing the load on the battery and exacerbating the problem. If these issues are not handled gracefully, various parts of the system may spontaneously reset or misbehave.

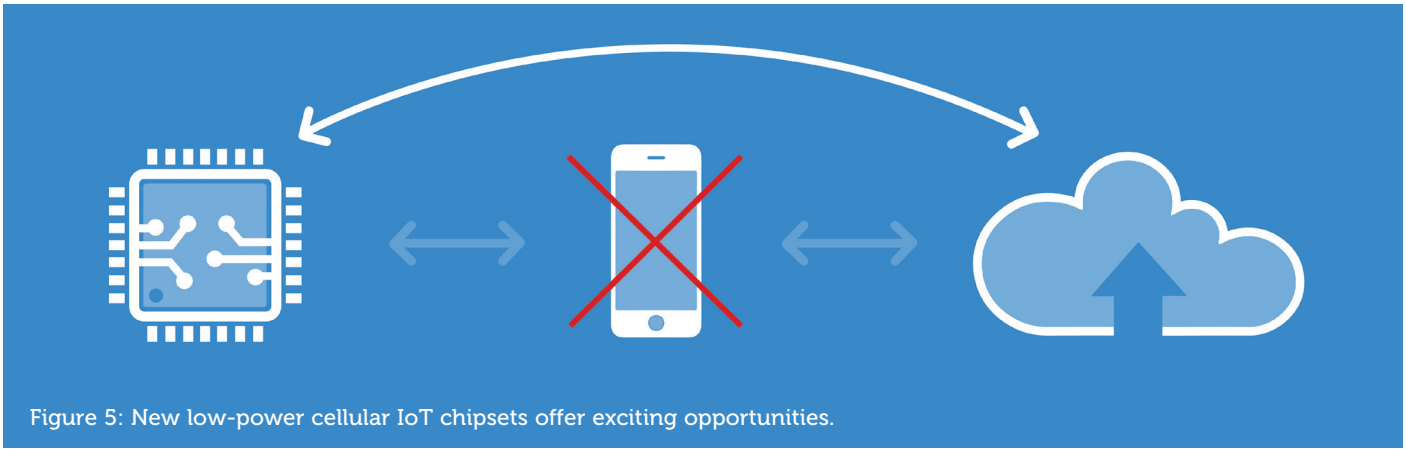

Figure 5: New low-power cellular IoT chipsets offer exciting opportunities.

Finally, there is the issue of managing power "on the shelf" between manufacture and first use. One option is to have a small strip of pull-tape between the battery and its contacts but this risks moisture ingress. It might also be necessary to have some changing data retained from manufacture, such as a real-time clock value. In either case, the current drawn must typically be virtually zero before first use to achieve an acceptable in-use life.

Designing for a Coin Cell: Summary

All aspects of the design of a connected drug delivery device that uses a coin cell are likely to revolve around the coin cell itself. This is fundamentally different from designing devices with larger battery packs or a permanent power supply.

NEW COMMUNICATION PROTOCOLS BRING EXCITING OPPORTUNITIES

A major part of the power budget of a connected drug delivery device is determined by the wireless communication protocol. Bluetooth Low Energy (BLE) and near field communication (NFC) are current favourites but new communication protocols are continually emerging.

Currently, to connect our intelligent devices to the internet, we are dependent on the presence of a local network on our phones and tablets or around our buildings. However, exciting developments are being made in the shape of new low-power cellular Internet of Things (IoT) chipsets that use one of two new radio transmission methodologies: 4G LTE-M and NB-IoT. They replace the current short-range wireless capability (e.g. BLE or Wi-Fi) with a direct cellular connection. This means devices no longer need to be connected through a phone or added to a local network (Figure 5) – opening up the potential for a wide range of new device features, vastly improved usability and greater adoption.

The worldwide network infrastructure to support 4G LTE-M and NB-IoT is currently incomplete but coverage is rapidly increasing. These new communication protocols provide opportunities to redefine the next generation of connected products and user experiences by:

1. Eliminating dependency on phones, Wi-Fi routers, etc. to form the intermediate communications link
2. Enabling lower power location of devices
3. Removing the need for multiple platform apps (e.g. for Apple or Android)
4. Simplifying the process of establishing a connection, which can be problematic for some users.
5. Providing greater opportunities for tighter data security control at the device
6. Improving the host server's connection to the device, offering new feature opportunities (e.g. alerts if emergency medications are used).

The hardware platforms to support this functionality are now being made commercially available. This opens up opportunities to use their functionality to provide new features and benefits to the end user.

ANTENNA DESIGN

The antenna is a key part of the product architecture for connected devices – while it is part of the electronic circuit, it also has a large influence on product packaging and mechanical design. As such, it is essential that the electronic, mechanical and visual design are all addressed simultaneously (Figure 6).

Large metal components near the antenna – such as batteries, motors or PCB ground planes – will reduce wireless communications range. If the product is handheld, poor antenna placement can lead to problems if the antenna can be masked by the user's hands or even touched. Even if an off-the-shelf RF module with an integrated antenna is used,

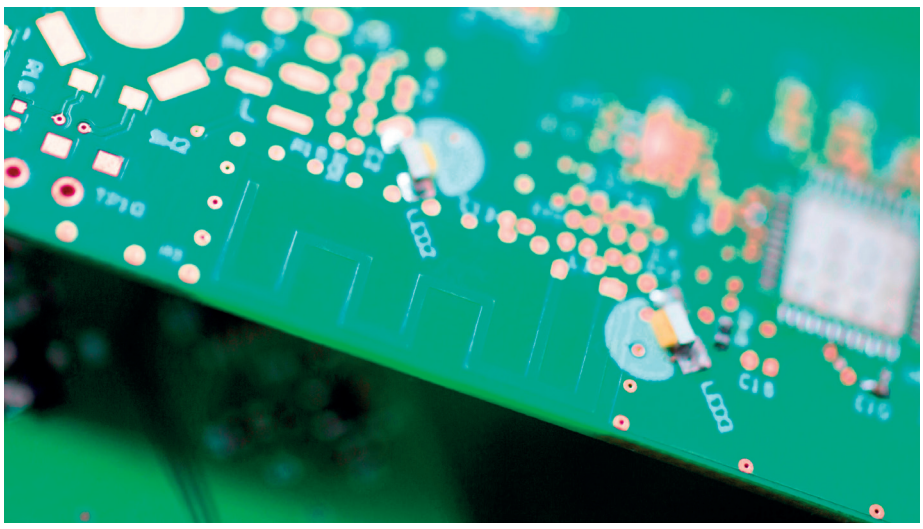

Figure 6: Antenna design is critical for connected devices.

poor location of this within the device can severely reduce range.

Where device cost is particularly sensitive, it is attractive to use a printed antenna on the PCB. However, the board area required for the antenna itself and the necessary separation from other parts of the circuit can be significant and cause the PCB to grow, affecting the overall product size or form factor. A surface mount component can be used with a smaller footprint than a printed antenna but this introduces additional parts and still limits the placement options to locations within the PCB footprint. By contrast, designing a bespoke antenna that is soldered to the PCB but extends beyond the board footprint can improve its location.

There may be an existing metallic part in the device that can serve a dual purpose as the RF antenna – or, conversely, an external finish that degrades performance. The most appropriate approach needs to be evaluated on a case-by-case basis, as effective product design is about striking a balance between all functional characteristics of the device.

CONCLUSION

Connected drug delivery devices offer a huge range of opportunities but come with an equal or greater number of challenges, which must be carefully negotiated to bring them to market successfully. Maximising the probability of success depends on deploying an experienced team and following a structured, evidence-based process. Due to highly constrained design challenges, multidisciplinary development teams must be tightly integrated and focused on common and well-understood goals. In this way, companies can deliver connected devices that really have the potential to improve people's lives.

ABOUT THE COMPANY

DCA is one of the world's leading multidisciplinary product design consultancies, with a history of long relationships delivering commercially successful products for our strategic clients. Our recent record speaks for itself: 100+ products launched, 50+ full-scale drug delivery projects, 1000+ patents granted and 90 major design awards in the last 10 years – as well as approximately 80% repeat business.

REFERENCE

1. *"Connected Drug Delivery Devices Market Worth $717.7 Million By 2025". Grand View Research, 2018.*

ABOUT THE AUTHOR

Matt Jones manages a number of strategic projects within the Medical and Scientific Sector at DCA. A specialist in drug delivery, he has over 15 years' experience in the design and development of a wide range of devices including injection, inhalation, nasal, topical, manual, spring driven, electromechanical and connected.

MIRCEA DESPA & DOUG McCLURE, BD

Mircea Despa, Associate Director, R&D, leads the Smart Device and Data Sciences group within BD Technologies and Innovation, overseeing digital health R&D, which spans early-stage opportunity assessment to evidence generation through clinical studies. Under his leadership, the group has developed and is currently performing clinical research with BD's first prototype interconnected disease management system for free-living patients. This system is composed of hardware, software, and data algorithms, designed using behavioural science principles. Prior to this role, Dr Despa led the department's multidisciplinary efforts to develop smart devices. He has 18 years of experience in the medical, life sciences, and telecommunications industries. Before joining BD, Dr Despa worked at Corning, conducting R&D for optical bio-sensors, biochemical reactors, and specialty optical fibres. He holds a BS in Chemical Engineering from Bucharest Polytechnic Institute (Romania), and an MS in Chemical Engineering and a PhD in Engineering Science, both from Louisiana State University (US).

Doug McClure joined BD in 2016 to help start BD's Digital Health organisation and capabilities. He has been focused on creating product development and operation processes, and commercial models, for BD's digital health products and is currently the Platform Leader for the Digital Health in BD Diabetes Care. Mr McClure has been working in the health IT, telemedicine, and digital health industries since 2001. He began his career at Partners HealthCare at Massachusetts General Hospital and Brigham Women's Hospital (Boston, MA, US) and then worked for a series of companies including a as Co-Founder and Chief Technology Officer of a venture capital-funded startup, Healthrageous. Mr McClure undertook his undergraduate studies at Drew University (NJ, US) and received an MBA from the University of Denver (CO, US).

In this interview, Dr Despa and Mr McClure discuss BD's approach to connecting devices in its portfolio to meet patient, pharma and other stakeholder requirements. Their discussion focuses in particular on safety and security, highlighting the connected wearable injector, BD Libertas™ with Smart Option, as an example.

Q In the last few years, device manufacturers have either developed connected drug delivery or are currently developing this technology. This effort has exposed many benefits and challenges. Where do you see the market currently, and where is it headed?

> "Building connected device technology has become a straightforward engineering task … How you empower the patient and stakeholder ecosystem with the data, and how the data is used, have become the more valuable and commensurately more difficult challenges."

MD One way to describe the market is to think of the acute care and non-acute care spaces. In the acute care space, it is becoming increasingly clear that there is a growing body of data available for analysis with the goal of driving decision making and improving the outcomes and economics of delivering healthcare.

A large and diverse number of participants are actively working to build and capture value from the data generated in clinical settings. Startups and traditional medtech and technology companies are all in the mix. While some take a go-it-alone approach, most pursue partnerships, which are being formed with the understanding that different expertise and skill sets are best combined in pursuit of common goals.

In the non-acute care space, a significant number of participants are focused on using connected drug delivery solutions for chronic disease management, with diabetes as one of the leading areas of participation and perceived opportunity. There is an increased expectation in the level of activity in this space as more evidence is generated showing that connected solutions generate value for a number of stakeholders, including the patient, providers, pharma, and payors.

"Technology developers are in a constant pursuit to resolve risks and improve performance and profitability; in general, the technical hurdles are more obvious and seemingly easier to focus on. In contrast, stakeholder adoption is lagging, likely as a result of a combination of reasons. For example, only now are we beginning to see emerging sets of data demonstrating value."

DM Building connected device technology has become a straightforward engineering task. Building a system that supports and leverages the connected device data is more complex but manageable for organisations with the right capabilities. What these solutions have highlighted is that connecting the data is just the first step. How you empower the patient and stakeholder ecosystem with the data, and how the data is used, have become the more valuable and commensurately more difficult challenges.

As always, the market will reward those devices and systems that best address the unmet needs. In the context of connected devices this is not just about transmitting the data from the device. What we see in the industry is a move to address those unmet needs and expectations of the user once the data is in their control. When we meet those needs we drive engagement, and when we drive engagement we drive adherence – this is when we truly unlock the value of connected device solutions.

Q **The connected drug delivery device market is growing quickly and so too is the Internet of Medical Things (IoMT). What impact is this having on stakeholder adoption, technology and infrastructure?**

"The lines between consumer devices are blurring in the consumer's mind. Today's consumer expects connected experiences for all of the products and services they invite into their lives. The IoT in everyday use is driving expectations for what IoMT must be able to accomplish."

MD IoMT is a term that is being increasingly used to describe a wide range of existing and potential solutions in the hospital, outpatient, home, or other clinical spaces. Increasingly, the participants in this space express optimism that interconnected devices bring with them the opportunity to collect and combine data in order to generate new value. However, there is a clear dichotomy between the advent of technologies and supporting infrastructure and stakeholder adoption. Technology developers are in a constant pursuit to resolve risks and improve performance and profitability; in general, the technical hurdles are more obvious and seemingly easier to focus on. In contrast, stakeholder adoption is lagging, likely as a result of a combination of reasons. For example, only now are we beginning to see emerging sets of data demonstrating value. The known slow pace of adopting novel technologies by a typically conservative industry is also a factor, of course.

DM The lines between consumer devices are blurring in the consumer's mind. Today's consumer expects connected experiences for all of the products and services they invite into their lives. The Internet of Things (IoT) in everyday use is driving expectations for what IoMT must be able to accomplish and this certainly calls for device data to be available to access, use and share as needed. But connected experiences go beyond just device data. Patients will expect connected experiences that empower them to self-support, self-manage and reach on-demand support – anytime and anywhere.

This means that when we are building IoMT products we need to think about the entire stakeholder experience. When the patient needs help with their connected medical device, they want to know how they can they leverage those same connected device technologies in the same way and with ease as the other technology tools they are using today.

IoMT devices also carry the challenge that expectations go beyond those IoT devices. IoMT must meet the expectations that people put on medical and health technology. The infrastructure we deploy for these patient-centric IoMT solutions has to be ready to meet those needs of the entire user experience – anywhere, anytime, securely, and most importantly always ensuring safety.

Q **BD has long been a proponent of using connected technology in healthcare. How has BD's approach and philosophy regarding connected technology evolved?**

DM In the last couple of years BD has become more active in connected solution development. BD's businesses that have a much more direct to consumer interaction have led the way in developing an enterprise connected health infrastructure. Today the platform supports the patient experience of our connected technologies with a focus on patient engagement, adherence, and improved outcomes. This platform also supports the use of ecosystem connected devices that are companions to our unconnected devices. These BD businesses are preparing global launches of their connected devices that will leverage the capabilities built. The best way we know that this set of capabilities is ready to be used by our customers is to use it at scale ourselves.

MD BD has advanced its approach in this space by bringing into the marketplace a first mobile app solution for diabetes support and implicitly developing a robust infrastructure that supports safe and secure data transmission and storage, under the strict HIPAA [US Health Insurance Portability and Accountability Act 1996] and GDPR [EU General Data Protection Regulation]. Additionally, we leveraged this infrastructure and learnings when developing the app for the BD Libertas™ with Smart Option app (Figure 1).

Q Drug delivery devices typically incorporate connectivity in one of two ways: through integration or add-on capability. Please describe for us BD's approach and how might this approach be beneficial to pharmaceutical companies seeking connected devices?

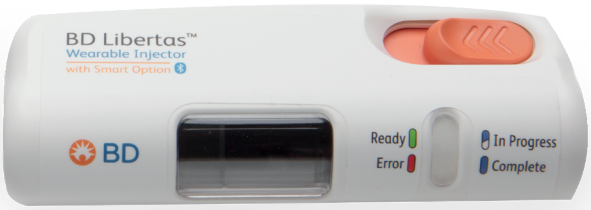

Figure 1: BD Libertas™ wearable injector was designed from the outset with the capacity for smart features, simply by adding a smart element to the core device.

MD At BD, we have pursued both paths to align with the business units' existing portfolios and roadmap strategies. Early on we recognised that add-ons come with the advantages of not impacting the function of the already-marketed base devices and the possibility to amortise the associated costs of add-ons over multiple use events. Unfortunately, add-ons come with the misperceptions of impacting workflow and complex technology requirements needed to add sensors and electronics without impacting device function.

Alternatively, integrated designs alleviate technology complexities while improving performance and reducing cost of the solution. Integrated devices do however require drug-device combination testing, evidence generation, and associated regulatory filings.

DM I completely agree with Mircea. I see our approach being more focused on integration and less so as an add-on. If you consider connectivity early in your device development it helps you to design the proper system architecture around it and this enables a more seamless integration with existing and future infrastructures and devices. For pharmaceutical companies this will mean that BD devices will be compatible with a wider variety of infrastructures, be compatible with each other and will operate with a high reliability, acceptance and use.

> "The best way to manage all of these risks effectively is to approach them holistically and with a systems view. Security and privacy are not just cloud hosting concerns. Usability is not just a physical device concern. Cost is always best managed at scale."

Q There are many risks when considering connected drug delivery devices such as cost, infrastructure, usability, and data privacy to name a few. How does BD mitigate some of these risks with the BD Libertas™ wearable injector with smart option?

DM When building medical technology that will be used in the field by patients and stakeholders the risks can feel overwhelming. The best way to manage all of these risks effectively is to approach them holistically and with a systems view. Security and privacy are not just cloud hosting concerns. Usability is not just a physical device concern.

The BD Libertas™ with smart option is built upon BD's Enterprise Digital health platform. This medical grade platform features a highly scalable and secure cloud infrastructure, cross platform mobile client capability, and mobile wireless radios connectivity. Leveraging this set of platform capabilities, we address entire experience usability while ensuring security and privacy across the entire customer interaction.

MD We have applied a robust approach to innovation bringing life to systems that deliver on unmet needs and providing functionality that truly makes a difference. To arrive at this result, we carefully examined and understood what matters most for patients, pharma and other stakeholders that can benefit from the smart features and associated data.

The primary goal was to design and develop a solution that is both safe and secure and built on enterprise architecture that was developed by many experienced hardware and software engineers. We used an agile approach to product development, constantly iterating to deliver the highest value functionality at the lowest cost. Finally, we designed safety and security into the system and tested to ensure we delivered on all our goals. We are proud that we have accomplished that.

BD

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THE DIFFERENCE OF ONE DRUG DELIVERED

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BD Libertas™ Wearable Injector, BD Libertas™ Wearable Injector with Smart option and BD Intevia™ Autoinjector are products in development; some statements made are subject to a variety of risks and uncertainty.

CONNECTIVITY RESTORING TRUST IN PHARMA COMMUNICATIONS

Here, Napoleon Monroe, Managing Director, New Directions Technology Consulting, analyses connectivity coverage at recent drug delivery conferences and, more broadly, in various publications, to evaluate the current direction, and explore the scope for connectivity to effect changes benefiting multiple stakeholders across a range of treatment categories.

The drug delivery collaboration conference season peaks with three conferences – Partnership Opportunities in Drug Delivery (PODD) in Boston, MA, US (October 7-8, 2019), PDA's Universe of Pre-filled Syringes and Injection Devices (PDA) in Gothenburg, Sweden (October 22-23, 2019) and Drug Delivery Partnerships (DDP) in Orlando, FL, US (February 10-12, 2020).

ONdrugDelivery is a media sponsor for all three, and other related conferences, and often presents highlights of products and trends arising at these events in its publications. It works the other way around too. For example, my February 2019 ONdrugDelivery Expert View, "Connectivity Using Consumer Technology to Create Real Value for Patients"[1] was distributed at Drug Delivery Partnerships in Palm Beach Gardens, FL, US, the same month. Our presentation at DDP was based largely on the article, and so the flow of useful information, insights, and ideas can flow both ways.

At a pre-conference DDP 2019 presenters' dinner, I asked which companies were engaged in connectivity. The response was clear: "Who isn't?" Several highly interesting observations important to connected drug delivery came out of the DDP meeting, and a lot of relevant news has been published since. This article will review some highlights.

One broad observation is about the themes of conference presentations, as shown by keywords in the titles: partnerships, progress, evaluation, sensors, innovation, perspective, treatment, development, commercialisation, marriage, choice, design, requirements, outcomes, evolving, challenges, centricity, approval, management, training, onboarding, value, compliance, adherence and connectivity. All of these words appeared in event presentation titles and ALL are integrally related to communication. To be effective, communications must be trusted.

> "Connectivity can help communicate value to, and help build relationships and instil trust with, patients."

During the DDP 2019 Q&A session in the "Creating Value in Your Patient Centric Platform" panel, Paul Jansen of Haselmeier noted that "Pharma has lost the trust of the patient community as a result of recent pricing policies, especially as it relates to epinephrine". Pricing was, and is, only one key issue, and epinephrine just one example where trust has been impacted by pricing policies. Yes, the EpiPen, a very visible recent poster child for reputationally destructive pharma behaviour, was called "infamous" by a presenter at PDA 2018, and is cited in a March 2019 Pharmaceutical Manufacturing piece, "Pharma's Damaged Reputation".[2] That article discusses some reasons why pharma "has not developed better strategies around ethics and innovation". After DDP, came news that the Pfizer plant which makes the EpiPen is under US federal investigation for quality issues and the news of drug price fixing suits by some >40 states.

Please allow me to note that my colleagues and I were proud of the work we did in the 1970s and 1980s on the nerve agent antidote autoinjectors and developing the original EpiPen, both life-saving delivery systems. The ethics of the time and our corporate management allowed us to focus on the products, not the quarterly financials. However, in my opinion, thus far pharma has not concentrated effort of the widely discussed value to patients. Note that the American Association of Retired Persons (AARP), for example, has

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38,000,000 members all aged 50+, so their members are in the age group for whom the most pharma is purchased. The AARP's May 2019 Bulletin featured an eight-page cover story entitled "A 5-Point Plan to Lower Prescription Drug Prices", which slammed drug pricing.[3] In face of this, how is pharma to recover trust?

Connectivity can help communicate value to, and help build relationships and instil trust with, patients. The loss of trust is far broader than with the pharma industry, but here a focus will be using connectivity in the pharma industry to build trust.

In conversations at DDP, a couple of respected colleagues stated that diabetes is different from all other combination product disease treatment markets as regards connectivity. They opined that the only disease category that made sense for connectivity was diabetes. I agree in so far as diabetes is the only category where connectivity has already achieved broad patient and profitable pharma success. There are good reasons why diabetes is where treatment success and profitability have already been achieved. But that is not to say that the applicability of those reasons begins and ends with diabetes.

> "The characteristics of diabetes treatment that have allowed connectivity to have already been successfully added to combination products are rarely unique to the diabetes market."

While the case for diabetes connectivity is compelling, what has been achieved in past certainly does not represent the limit of future achievements for connectivity. Further, the case for diabetes connectivity does not negate or speak to the possibilities for improving treatment in almost all other disease categories.

The characteristics of diabetes treatment that have allowed connectivity to have already been successfully added to combination products are rarely unique to the diabetes market. Please consider all of the following characteristics shared with other therapeutic areas and treatment categories:

- The large size of the global market
- The mode of administration of insulin is traditionally and most commonly injection. Ongoing R&D in IoT and pens for insulin injection has advanced many designs
- Well-established drug treatment classes for diabetes
- Availability of diagnostic means, also connected diagnostic products
- Patients can often feel the onset of physiological change requiring treatment
- Recognition that failure to treat is a real threat
- Frequency, complexity and variability of the treatment
- Potential for debilitating effects of the disease (loss of mobility and eyesight) from non-adherence / non-compliance
- Potential for life-threatening emergencies (e.g. diabetic ketoacidosis)
- Diabetes triggers many emotions
- Concentration of leadership in a few large companies and their partners who are competing for commercial advantage for their expensive and profitable products and working to lead in and improve their positions in the category.

Expanding on the last point, companies with connected diabetes combination products include: AstraZeneca, Novo Nordisk, Eli Lilly, Roche/mySugr, Dexcom, Abbott, Glooko, and Companion Medical. These companies have secured management support and approvals for large expenditures for connectivity. Some have FDA approvals, many more approvals are pending. The companies believe they have, or can secure, all necessary regulatory approvals and freedom to operate at least in the US. All need to fend off pricing criticisms.

Creative approaches to diabetes treatment connectivity continue to evolve. At DDP, co-operations among Haselmeier, CommonSensing and Flex for a cap for insulin pens and other injection devices was announced. CommonSensing is going forward with clinical studies.[4]

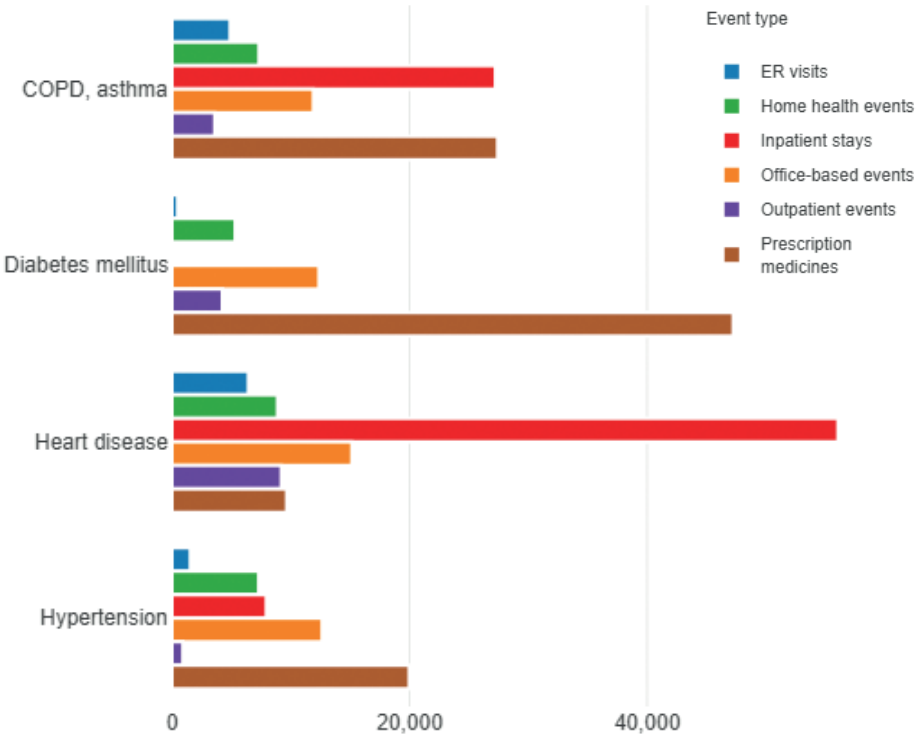

Figure 1: Total US expenditure (US$ million) by condition and event type, from the 2014 Medical Expenditures Panel Survey of the US DHHS Agency for Healthcare Research and Quality.

EXPENDITURES BY DISEASE

Data from the 2014 Medical Expenditure Panel Survey (MEPS) from the US Dept of Health & Human Services' Agency for Healthcare Research and Quality, by service for diabetes, coronary and pulmonary disease are quite interesting and are likely to still be accurate in relative terms (Figure 1).

Let's look at the expenditure for diabetes as compared with COPD and asthma. Note that none of the three diseases is curable. Asthma, like diabetes, has a significant paediatric population. Once diagnosed, patients will likely continue some therapy for life.

There are many longstanding tools providing connectivity for diabetes. Major pharma leaders and their partners in inhaler treatments for asthma and COPD have only recently announced connected inhalers. Companies with programmes for connected inhaler combination products include: AstraZeneca, GSK, Merck & Co, TEVA, Sumitomo (Sunovion), Biocorp, H&T Presspart, 3M, Propeller Health, Adherium and others. Like those with connected diabetes programmes, these companies have secured management support and approvals for large expenditures for connectivity in the area of inhalation, have some FDA approvals with many approvals pending. All need to fend off pricing criticism.

The discrepancies between the figures for diabetes expenditures and those for the two pulmonary diseases are rather fascinating. They may be partly related to the many more years of work on the development of connectivity to improve the effectiveness of diabetes care versus the relatively recent innovations in asthma and COPD.

Analysis

The cost of inpatient stays directly for diabetes are minimal. Proper training and self-treatment can significantly reduce incidence of diabetic retinopathy, diabetic neuropathy and diabetes associated vascular disease.[5] Blindness and amputations of lower extremities are dramatic, but other co-morbidities related to untreated diabetes of diabetes also benefit from patient training and other assistance with adherence. Connectivity represents a tool for such training and assistance.

Two comparisons are most instructive: the US cost of inpatient stays for asthma and COPD was some US$27 trillion as of 2014 and growing. Inpatient stays directly for treatment of diabetes did not register on the charts; and Emergency Room visits for diabetes were minimal compared with those for COPD and asthma.

As covered in my 2019 article for Inhalation[6], and in other articles in ONdrugDelivery, administration by inhalation requires adherence to a difficult technique, reactions may vary by patient, and inhalation therapy can benefit from connectivity.

Whilst US prevalence of asthma in 2016 was estimated to be 26,000,000 diagnosed[7] a large number of individuals, especially children, are undiagnosed. And in COPD, 2010 prevalence was 15,000,000 diagnosed with an estimated 12,000,000 potential cases remaining undiagnosed. For diabetes, 2017 estimates were that 23,000,000 cases were diagnosed with 7,200,000 undiagnosed.[8] Almost twice as many deaths are attributed to COPD as are attributed to diabetes.[9]

The high cost of hospitalisations and ER visits for the other diseases include in the MEPS demonstrates opportunities for improvement. These diseases have similarities with diabetes, such as large markets, recognition that failure to treat is a real threat, potential for debilitating effects, potential for life-threatening emergencies, patients can sometimes feel the onset of physiological change requiring treatment. For asthma and COPD, the fact that patients can often feel the onset of physiological change requiring treatment.

In cardiology, the emerging availability of diagnostic means is important. Heart disease and hypertension are often "silent" diseases until they demand hospitalisation. Patient-use diagnostics for coronary diseases are only recently becoming available with the approvals of AliveCor's Kardia Mobile and the Apple Watch, which has the ability to diagnose the onset of certain abnormal cardiac events. These open possibilities for remote diagnostics for atrial fibrillation and other cardiac anomalies may enable future opportunities for combination product connectivity and cardiac self-treatment.

Broad Treatment Category	Examples / Drug Categories
Treatments subject to abuse	Opioids and other pain management drugs
Emergency, potentially life-saving, rescue medications	Anaphylaxis, asthma, COPD, opioid overdose reversal, acute hyperkalaemia, acute hypoglycaemia, nerve agent antidotes, organophosphate and other insecticide poisoning antidotes
Life-sustaining medication	Diabetes, multiple sclerosis, epilepsy (both human and veterinary), ALS, nonalcoholic steatohepatitis (NASH) (fatty liver disease) treatments, antibiotics and other post-surgical drugs, autoimmune disorders including endocrine deficiencies such as Addison's, haemophilia, drugs to avoid pre-term delivery, cardiac disease management.
Treat to cure	Hepatitis C, tuberculosis, ebola, osteoporosis, some cancers
Enhance quality of life	Sexual dysfunction, growth deficiencies
Control disease severity and prolong life	Cancer, AIDS treatments, psychotropic drugs
Disease avoidance	Vaccines, antibiotics, antivirals, anti-fungals
Predictors of disease progression, exacerbations or other severe conditions	Benadryl or rescue inhaler over-use as a predictor of worsening allergic issues
Adjunctive pharma to enhance or prolong the effectiveness of non-drug therapies	Post-surgical antibiotics, post-transplant immunosuppressants
Control or avoidance of symptoms	Plaque psoriasis, migraine, pain, severe behavioural or psychological dysfunction (schizophrenia being among the most severe), adrenal deficiency diseases such as Addison's
Emergency kits containing drugs for use by untrained individuals	Anaphylaxis
Office-based diagnostic and treatments not currently easily controlled or recorded	Some sequence- and time-sensitive medical and dental products
Veterinary products in some of the same treatment categories	Canine seizure

Table 1: Broad drug / treatment categories with possible benefit from connectivity.

"Having experience with such a product in the hands of many patients should provide a wealth of human factors information. This is in line with FDA's stated objective of securing more rapid approvals and real-world data to provide real world evidence."

A patient-use stroke diagnosis classification (haemorrhagic versus thrombolytic) would be a real breakthrough. Additional research is underway and cardiac self-treatment is likely to be enabled by the approvals of wearable diagnostic devices.

It is clear that connectivity can help meet stakeholder needs. The benefits are often different for different products and for different stakeholders. For example, patient needs are served by making self-treatment possible, making convenient for them to treat themselves, and limiting costs. Medical provider needs are served by monitoring use in order to understand patient response, safety and efficacy. Regulatory expectations for real-world evidence can be met. These have become more important and widespread. Payor desires are served by enabling pay-for-performance models. Societal needs are met for preventing abuse. For all of these stakeholders, connectivity offers solutions.

Table 1 lists numerous disease categories for which connectivity has been explored. Many of the categories have already seen significant investments (asthma and COPD now have connected products approved, for example).

Some listed in the table fit in a super-broad category where connectivity has potential including, for example, expensive treatments for any condition (in particular severe conditions) where compliance is essential to rescue, cure, management, remission or avoidance. With a regulatory acquiescence (regulatory discretion), products falling into this category, providing information to the patient, could be in line with the "C-CONTAINER" approach described in "Connectivity Using Consumer Technology to Create Real Value for Patients".[1] The approach would necessarily limit claims made – companies could enjoy the advantages of early connected product introduction with limited regulatory delay. Having experience with such a product in the hands of many patients should provide a wealth of human factors information. This is in line with FDA's stated objective of securing more rapid approvals and real-world data to provide real world evidence.

BEYOND WHAT'S COVERED AT CONFERENCES

In addition to reviewing the hot topics at drug delivery conferences, it instructive to observe what is not covered. There was little or no mention of the US Drug Supply

"The US ONC recently issued a press release covering guidance on interoperability, transparency, patient access and restrictions on information blocking. If these rules are implemented, they would drive a sea change in how healthcare information systems are used."

Chain Security Act or electronic medical records (EMRs) at either PDA or DDP. My "Connectivity Using Consumer Technology to Create Real Value for Patients"[1] article, for example, pointed out that there were problems with existing EMRs and that there was a need to make more effort to benefit from public initiatives.

After DDP, a Fortune article entitled "Death by a Thousand Clicks"[10] stated that "Ten years and 36 billion dollars later the EMR system is an unholy mess". Soon after that, in an interview with Time Magazine,[11] Eric Topol said: "The biggest problem in medicine is that we use keyboards and screens and it's led to the depersonalisation of the doctor-patient relationship." His views echo those of many other practitioners. His proposed solution is to "have patient data assimilated, slides and scans read and analysed. That liberates doctors from keyboards."

The HHS Office of the National Coordinator for Health Information Technology (ONC) recently issued a press release covering guidance on interoperability, transparency, patient access and restrictions on information blocking. If these rules are implemented, they would drive a sea change in how healthcare information systems are used.[12] The same day, the Trump administration signed an Executive Order on maintaining US leadership in artificial intelligence.[13]

CONCLUSION

I'm hopeful that in the pharmaceutical industry, pharma companies and their partners can overcome the challenges and take the lead in improving communication, building trust, and improving outcomes by making more and better use of connectivity across the important treatment categories highlighted here.

Biotech and other specialty products are generally expensive to manufacture, command high prices, are profitable and sensitive to environmental conditions. The importance of the biotech sector to pharma and patients has driven the development of new delivery devices (combination products) to enable patient home use. Home use is not limited to specialty, but specialty is where the money and in the case of injectables, where the most challenging human factors problems, are. These facts and others discussed here are crying out for connectivity to take an increasing role.

The possibilities for connectivity to bring improvements for all stakeholders are immense and, even though the work has begun, the opportunities connectivity presents that remain largely untapped are vast, to say the least.

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Napoleon Monroe, Managing Director of New Directions Technology Consulting, has a diversified background that extends from developing and producing pharmaceutical product delivery systems, to managing thousands of private brand products for a Fortune 500 company, to building and managing the IP portfolio for a company that is now part of Pfizer. His expertise includes product development, licensing, regulatory processes as business opportunities, risk management and international marketing, with experience managing business relationships in more than 30 countries. Mr Monroe has led teams that have invented and commercialised major products, such as the (pre-Mylan) EpiPen, and nerve agent antidote autoinjectors for the US and allied countries. New Directions holds patents related to medication telemanagement.

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H&T PRESSPART

THE FUTURE OF CONNECTED ASTHMA AND COPD CARE: A NETWORK PERSPECTIVE

In this article, Benjamin Jung, PhD, Program Manager, Connected Devices, at H&T Presspart, uses a network theory approach to look at the ongoing issue of adherence when it comes to the treatment of asthma and COPD, and the players involved in overcoming it.

Adherence to asthma and COPD medication continues to be a problem,[1] with a substantial number of patients not gaining the maximum treatment benefit – which leads to avoidable hospital admissions and even deaths.[2,3] In addition, the economic burden associated with this situation is significant.[4,5,6]

During the introduction of connected devices into asthma and COPD care, which is on its way, one question remains a focal point of discussions with key stakeholders: How will the network of players within connected asthma and COPD care evolve and what implications does this have when it comes to today's decisions and actions? To foster these discussions, this article employs a network perspective[7] on the major stakeholders within connected asthma and COPD care, as well as on the ties they have already established. The article further discusses possible implications for H&T Presspart and our key partners – our pharmaceutical customers.

KEY STEPS TOWARDS A NETWORK PERSPECTIVE

The network theory is becoming increasingly popular in management science and consulting. In a nutshell, it describes the characteristics of networks and discusses resulting consequences, like the consequential flow of data. A network consists of actors (nodes), which have relationships (ties) amongst themselves. A prominent concept within network theory is centrality, which maps out advantages of being connected to well-connected nodes.[7]

> "Patients increasingly demand connected health solutions via their advocacy groups."

In line with common network logic, we will:

- Start with describing major actors within connected asthma and COPD care
- Then discuss ties in terms of partnerships and business relationships between them
- End with compiling potential implications based on consequences from the network, like the flow of data.

MAJOR ACTORS WITHIN CONNECTED ASTHMA AND COPD CARE

To describe major actors within connected asthma and COPD care efficiently, we will subsume whole groups of stakeholders under individual actors, focus on the actors we deem major and concentrate the analysis on the two major markets – Europe and the US. Of course, this is just our perspective. Hence, for example, some of the individual stakeholders listed might recognise themselves as belonging to a different group of stakeholders.

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From our perspective, the major actors are:

- **Patients**, who increasingly demand connected health solutions via their advocacy groups, as these solutions – largely based on recorded data around their device usage – can help them to improve medication compliance.
- **Payers**, differentiated into state-owned and private entities. They show a very diverse approach when it comes to connected care. Some are rather at the forefront, shaping the change. Others are more short-term budget driven and hence not leaning towards preventative spending – even if it can provide significant savings.
- Established **healthcare providers**, which includes a broad set of players like hospitals and physicians.
- **Pharma companies** producing and marketing inhaled drugs for asthma and COPD like beta2-agonists, muscarinic antagonists, inhaled corticosteroids and their combinations. Examples for leading originators in the space are GSK, Boehringer Ingelheim, AstraZeneca, Novartis, Teva and Chiesi. These players have a particular interest in anonymised, real-life patient use and outcome data, as it can foster R&D.
- **Drug delivery device suppliers** producing metered dose inhalers, dry powder inhalers and soft mist inhalers and/or their respective componentry like H&T Presspart and our peers, e.g. 3M and Aptar.
- **Medical device companies** typically producing and marketing medical devices like nebulisers, spirometers and continuous positive airway pressure (CPAP) devices. Prominent examples within connected asthma and COPD care are Philips Healthcare and ResMed.
- **Pharmacies** dispensing drugs to patients.
- Asthma and COPD focused providers of connected platforms, which typically encompass a mobile front end, cloud-enabled services and a database. These companies are often start-ups and tend to market add-ons devices, which are – as far as the inhaler design allows for – generic. This means they can be used with different drugs. Examples are Cohero Health, Propeller Health and Adherium. We will call these players **asthma and COPD platform providers.**
- Non treatment area specific, more general health platform providers. These players tend to focus on cloud-enabled services and the underlying database, rather than on the mobile front end. The activities and respective companies which can be subsumed here are very diverse. They range from the respective activities of the tech giants (e.g. Alphabet, IBM and Apple) to the platform activities of companies such as Phillips-Medisize and Flex. Also, the activities of health record vendors like EPIC fit here. The major aspect to split this diverse group at least into two actors is their approach: some seem to rather have a service provider mindset enabling, for example, pharma companies "to be connected". Others likely aim to build ties to various players proactively and to gather a huge amount of data and therewith value. We will name the resulting actors **platform as a service providers** and **data platform companies**.
- **Care platform providers**, which aim to holistically monitor patient subgroups and which are using connected solutions and underlying data sets as a key enabler to do so. An example is Care Innovations.

Of course, this list could be extended significantly. The following could also be added but have been left out for the purposes of this analysis: regulatory bodies, other policy makers, electronic manufacturing services, electronic component suppliers (e.g. of sensors and chips), pharmacy benefit managers, wholesalers, health systems, design houses, international organisations (e.g. the WHO), specific data providers (e.g. of air quality data), hospital-focused platform providers, software technology providers, server hosts and cloud service providers, consumer/OTC-focused players, patient advocacy groups, employers and so on.

ESTABLISHED TIES WITHIN THE CONNECTED ASTHMA AND COPD CARE NETWORK

We will now describe the ties between the major identified actors. We will focus on the partnerships and business relationships between them, which are public, are rather broadly established and have a connected asthma and COPD care edge. Partly due to the strongly confidential nature of activities in our industry, various ties that already exist may be neglected. This is acceptable, as relationships not yet made public, on average, are less established.

> "The number of established ties of pharmaceutical companies within connected asthma and COPD care is rather small."

As of now, the major ties from the payer's perspective are to:

- Healthcare providers, the Current Procedural Terminology codes for remote patient monitoring introduced in the US being a great example
- Care platform providers, the telehealth efforts in Mississippi – including Care Innovations – are an illustrative case[8,9]
- Asthma and COPD platform providers, where the relationships of Cohero Health and Propeller Health to Blue Cross Blue Shield companies were made public
- Medical device companies, where the reimbursement of ResMed's connected CPAP devices represents a good example.

Patients have established a comparable set of ties: especially to healthcare and care platform providers within telehealth and remote patient monitoring efforts. Furthermore, asthma and COPD platform providers and medical device companies market their solutions directly to patients. Adherium and Cohero Health launched direct-to-consumer solutions. Also, patients can directly register for ResMed's myAir™ online. Patients and payers are, of course, also closely connected, especially when it comes to private payers.

Between the actors being identified as connected to patients and payers (healthcare and care platform providers, medical device companies, and asthma and COPD platform providers) major ties at least exist:

1. Between medical device companies and asthma and COPD platform providers (after the acquisition of Propeller Health by ResMed)
2. Between healthcare providers and care platform providers (as within the telehealth example cited).

So, the following question needs be raised: How are the remaining actors being connected to the dense sub-network identified so far and what kinds of ties have they established between one another?

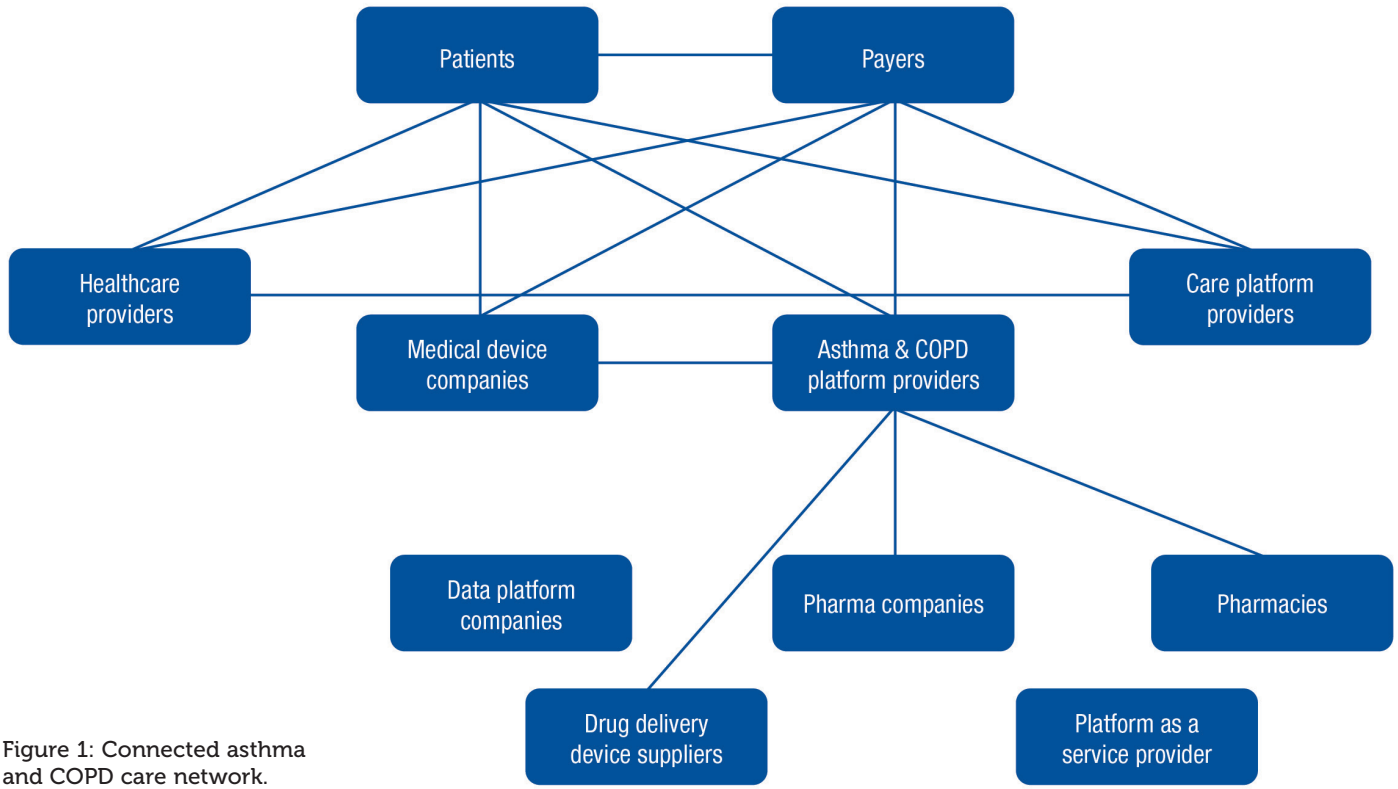

Figure 1: Connected asthma and COPD care network.

The major ties out of the sub-network of patients, payers and medical device companies as well as healthcare, care platform, and asthma and COPD platform providers, are the ties from asthma and COPD platform providers to drug delivery devices suppliers, pharma companies and pharmacies. Good examples are the collaborations of Cohero Health with H&T Presspart, and of Propeller Health with Walgreens and Novartis.[10,11]

When it comes to ties among the remaining players (pharma companies, drug delivery device suppliers, platform-as-a-service providers, data platform companies and pharmacies), we believe, at least based on publicly available information, no ties have yet been established broadly.

POSSIBLE IMPLICATIONS RESULTING FROM THE NETWORK PERSPECTIVE

The resulting network is illustrated in Figure 1. It shows the close-connected sub-network of patients, payers and medical device companies as well as healthcare, care platform, and asthma and COPD platform providers. In addition, the limited ties from the remaining actors into this sub-network and between themselves are illustrated. It becomes clear that data platform companies, as well as platform-as-a-service providers, seem not to have established ties yet.

Let's look at the actual connected asthma and COPD care network described and illustrated in Figure 1, in combination with the possible implications for our key partners – pharmaceutical companies. First of all, it seems fair to state that the number of established ties of pharmaceutical companies within connected asthma and COPD care is rather small so far compared with other actors. Based on the analysis, they also do not appear to be centrally located within the network as of now. From a network perspective[7] this implies that:

- They potentially receive usage and outcome data, which emerges from patients, but also the financial streams emerging from payers later
- Their negotiation position towards players, being more closely connected to patients and payers, is potentially challenged.

This actual positioning of pharmaceutical companies within the network might, at least partly, be traceable back to the following aspects:

- The data platform companies are not positioned clearly yet within the network
- The emergence of a central data player within healthcare is not unlikely, looking at the situation in other networks like retail and communication

> "Connected solutions consisting of embedded devices and customised platforms embracing interoperability are key for pharmaceutical companies."

- The handling and use of real-life patient use and outcome data has, at any point, to be in line with globally diverse, as well as dynamically evolving, data legislation.

Nevertheless, in line with the perspective chosen, building ties to more actors, especially establishing more direct ties to patients and payers, seems critical. Also, doing so via your own connected solutions – consisting of embedded devices and customised platforms with interoperability – is key. These solutions likely offer:

1. A path towards reimbursement of digital therapeutics bundled with pharmaceuticals, which is an emerging reimbursement pattern in other treatment areas
2. More control over data usage.

Figure 2: H&T Presspart's eMDI™ powered by Cohero.

Also, partnerships with other pharmaceutical companies within connected care might be supportive. This pattern is seen within the automotive industry as it progresses towards electric cars and autonomous driving.

From H&T Presspart's standpoint, comparable implications could be derived from a network perspective, e.g. establishing more direct ties to patients and payers. But that is not our business model.

H&T PRESSPART'S eMDI™ POWERED BY COHERO

H&T Presspart aims to enable its pharma partners with its connected devices and with the relationships we build to shape the network. Hence, H&T Presspart and Cohero Health formed a collaboration and, as a result, the first market-ready, fully embedded, intuitive, connected metered dose inhaler was created: The H&T Presspart's eMDI™ powered by Cohero (Figure 2).[12,13]

The eMDI device's connective hardware and software are fully embedded within the actuator design. The actuation of the inhaler and the patient's actuation technique are detected by the electronics with the aid of switches. Then a date/time stamp is added and the data shared wirelessly via Bluetooth Low Energy (BLE) with a mobile phone application – the BreatheSmart® application from Cohero Health. If desired, sharing with other applications is possible and additional features like flow rate measurement can be added.

H&T PRESSPART'S QUANTUM™ DOSE INDICATOR AND APP

H&T Presspart's Quantum™ dose indicator and the respective app interface represent a comparable tool. It aims to give pharmaceutical customers in emerging markets the opportunity to shape the connected asthma and COPD care network. The off-the-shelf Quantum™ dose indicator is an on-can metered dose inhaler indicator solution, ensuring patients don't run out of medication. This is achieved with the aid of an arrow located at the bottom of the can indicating the remaining drug level.

The Quantum™ dose indicator app (Figure 3) can be used to read this arrow almost automatically. The device usage can thus be tracked via combining the can-filling level data gathered during individual arrow readings. Last, but not least, the functionality of the Quantum dose indicator app can be incorporated into a comprehensive respiratory disease management platform to offer additional functionalities, for example data sharing with physicians.[14]

Figure 3: H&T Presspart's Quantum™ app.

CONCLUSION

Analysing the connected asthma and COPD care network, pharma companies seem to not yet be centrally located. Taking on a network perspective and having payers moving from funding medicines to funding care, this position likely comes with disadvantages. Building direct ties to patients and payers seems critical. Therefore, own connected solutions consisting of embedded devices and customised platforms embracing interoperability are key for pharmaceutical companies. With our connected devices and adjacent solutions, H&T Presspart aims to support our pharmaceutical partners across the globe to become the key players within connected asthma and COPD care.

ABOUT THE COMPANY

H&T Presspart offers pharmaceutical customers high-precision injection moulded plastic components and deep drawn metal cans for respiratory drug delivery systems. The company has more than 45 years' experience and a worldwide reputation for competence, quality and innovation in the pharmaceutical and other industrial sectors. H&T Presspart Inhalation Product Technology Centre (IPTC) supports new product developments and strategic initiatives with its customers. Founded in 1970 and acquired by the Heitkamp and Thumann group in 2002, H&T Presspart has three European manufacturing sites in Germany, Spain and the UK, with sales offices in China, India, South America and the US.

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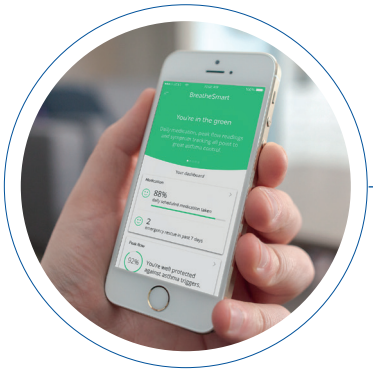

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SHL GROUP

MACRO TRENDS ACCELERATING THE ADOPTION OF CONNECTIVITY IN DRUG DELIVERY

Here, Ramin Rafiei, PhD, Director of Technology at SHL Group, argues that solely relying on the clinical efficacy of medications is no longer adequate for improving patient clinical outcomes. Connected therapeutics – the augmentation of drugs through sensors and connectivity – are now a clinical source for real-world data and provide an opportunity to bridge the efficacy-to-effectiveness gap. This next frontier in drug delivery, powered by connected therapeutics, will be data-driven, personalised, outcomes-based and accessible.

Over the past three decades, SHL Group has partnered with the majority of the world's top 25 leading pharmaceutical and biotech companies to bring more than 30 autoinjector-drug combination products to market. Autoinjectors represent one of the fastest growing segments in drug self-administration, supporting a range of chronic conditions including diabetes, rheumatoid arthritis, multiple sclerosis, migraine and cardiovascular disease.

The increasing prevalence of chronic conditions has amplified the demand for new medication options.[1] As a result, the biopharmaceutical market is growing at double the rate of traditional small-molecule pharma.[2] To cater for the growing pipeline of these macromolecule biologics and biosimilars, SHL continues to invest heavily in the development of drug delivery devices, covering a wide range in both volume and viscosity (Figure 1).

> "Chronic conditions place healthcare systems worldwide under significant stress."

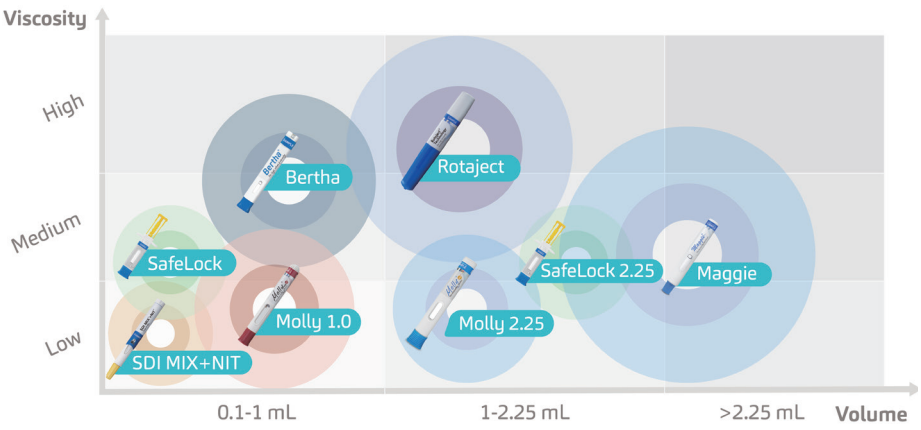

Figure 1: SHL Group develops a range of disposable and re-usable injectors that can accommodate high volumes and high viscosities and can be enhanced through digital implementations.

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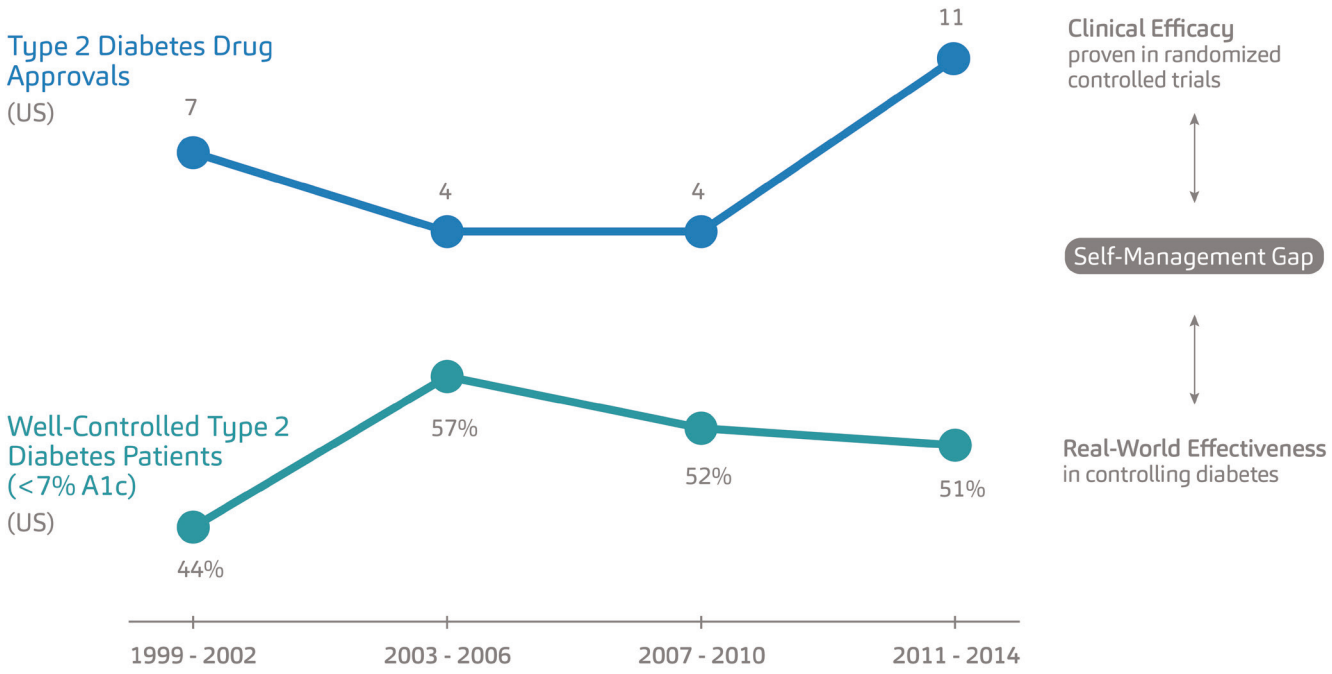

Figure 2: An illustration of the efficacy-to-effectiveness gap for Type 2 diabetes.

EFFICACY TO EFFECTIVENESS

Chronic conditions place healthcare systems worldwide under significant stress. For example, in the US, the number of people with diabetes has grown 20-fold over the past three decades,[3] while costs on a per-patient level have also increased by 7.5% annually.[4] Unlike any other industry, where cost goes down as products and services scale, there is both an increasing prevalence of chronic conditions and increasing cost for managing each patient.

A major reason for this trend is the efficacy-to-effectiveness (E2E) gap. Figure 2 illustrates the E2E gap for Type 2 diabetes. The top line shows the 26 new Type 2 diabetes medications approved between 1999 and 2014, each with proven clinical efficacy.[5] The bottom line shows the percentage of the population with Type 2 diabetes which has the condition under control, specifically defined as a haemoglobin A1c level below 7%. Diabetes patients typically monitor their glucose levels through a mechanism known as the A1c test, which is the average blood sugar level for the past two to three months. A1c levels are an indication of treatment efficacy, therefore, patients are tasked to keep their A1c levels as close as possible to their target percentages, which are typically around 6-7%.[6] While between 1999 and 2003 new therapies, such as Sanofi's Lantus (insulin glargine) proved effective in helping patients reach optimum A1c levels, this trend failed to continue beyond 2003.[7]

> "Clinical trials take place in highly controlled environments whereas, in the real world, the patient needs to self-manage their treatment … Solely relying on the clinical efficacy of new medications is not the solution to chronic disease management."

The E2E gap refers to the separation between the clinical efficacy of new drugs as determined by randomised controlled trials and their real-world effectiveness. Given the intense frequency of follow-up and support for participants, clinical trials take place in highly controlled environments whereas, in the real world, the patient needs to self-manage their treatment. As a result, solely relying on the clinical efficacy of new medications is not the solution to chronic disease management; rather, we need to find ways of helping patients manage existing conditions – what we refer to as the self-management gap.

Bridging this gap demands a systemic focus on medication adherence as typically 50% of people with chronic conditions fail to take their medications as prescribed.[8] The consequences of poor adherence to long-term therapies are poor health outcomes and increased healthcare costs. Non-adherence to medication, however, is a complex and multidimensional healthcare problem and stems from the diversity of patient behaviours and barriers.[8] The fact that non-adherence remains a major problem after decades of research shows just how difficult it can be to identify and address effectively.

> "Once we are able to measure adherence, we can address it through interventions, support and resources."

It has been shown that non-adherent patients cost the healthcare system significantly more in medical costs across all chronic disease states.[9-12] Today, the measured adherence level of 50% or lower across most chronic conditions is typically based on prescription refill claims data.[13-16] It has also been shown that true adherence or dose-level adherence is 15-30% lower when measured with connected drug delivery devices.[17-18] This means the reported avoidable medical costs associated with medication non-adherence are actually underestimations since patients considered adherent based on prescription refill claims data might not be taking the drug as prescribed.[9-12]

BRIDGING THE GAP

Connected therapeutics – the augmentation of drugs through sensors and connectivity – generate real-world data. This data provides a digital representation of the patient's true self-care behaviours and health outcomes outside the clinic. Real-world data from connected therapeutics also complements other traditional sources of clinical data, including electronic medical records as well as pharmacy and medical claims. The fusion of these data sets can now provide an unparalleled view of patient behaviours not formerly possible.

Drug delivery devices, which passively and objectively measure adherence at the point the patient is interacting with their medication, provide the greatest opportunity to bridge the E2E gap. Once we are able to measure adherence, we can address it through interventions, support and resources. If we are able to improve adherence, then we will also indirectly improve both clinical and financial outcomes. Today, Moore's law, the alignment of incentives among stakeholders, and improved regulatory pathways, are converging to pave the way for connected therapeutics.

ACCELERATION BY TECHNOLOGY

In the biopharmaceutical industry, Eroom's law (Moore spelt backwards) refers to the exponentially increasing cost of bringing new drugs to market.[19,20] On the other hand, Moore's law has transformed computing through exponentially decreased costs. As technology continues to get smaller, lighter, more efficient and easier to use, sensors and computers are making their way into drug delivery devices. Here, injectable therapies are still in their infancy when compared with connected respiratory and oral therapies. However, studies across the three connected therapeutic categories have consistently demonstrated improved patient adherence and overall health outcomes.[21-24] Therefore, while bringing drugs to market with proven clinical efficacy is an increasingly costly endeavour based on Eroom's law, the application of Moore's law to drug delivery has the potential to improve the return on investment by bridging the E2E gap.

ACCELERATION BY ALIGNMENT

The second and most important trend driving the adoption of connectivity in healthcare is the alignment of incentives among stakeholders around quality and outcomes. Pharmaceutical companies are increasingly taking on risks through value-based contracts as a way to get more coverage and improve their formulary positions.[25-26] Under these contracts, the price that insurers pay for drugs is tied to either the clinical outcome or an adherence threshold. Interestingly, adherence is a common factor in all the contracts, either as a qualifying event (i.e. only patients who refill their prescription on time are included in the contract) or as an outcome (i.e. the pharmaceutical company is paid less for patients who are non-adherent). Connected drug delivery devices, which generate dose-level adherence data, will become an important tool for pharmaceutical companies in these value-based contracts. Dose-level data will limit exposure when adherence is a qualifier for the contract by identifying patients who refilled their prescription but are not using the medication properly.

The US 21st Century Cures Act of 2016 (Cures Act), signed into law on December 13, 2016, is designed to accelerate the discovery, development and delivery of new cures and treatments for disease.[27] The Cures Act has made it possible for pharmaceutical companies to expand their label into new conditions using real-world data instead of running additional clinical trials for each condition. Since we know real-world adherence is low, connectivity in drug delivery devices will be a necessary tool that allows pharmaceutical companies to generate the evidence from cohorts of patients who are using the medication as prescribed.

Healthcare providers are another important stakeholder driving the adoption of connectivity. Historically, providers have not been on board with remote monitoring primarily due to the absence of a financial incentive. With the 2019 US Proposed Rule, remote care enabled by connected devices has moved to the forefront and providers

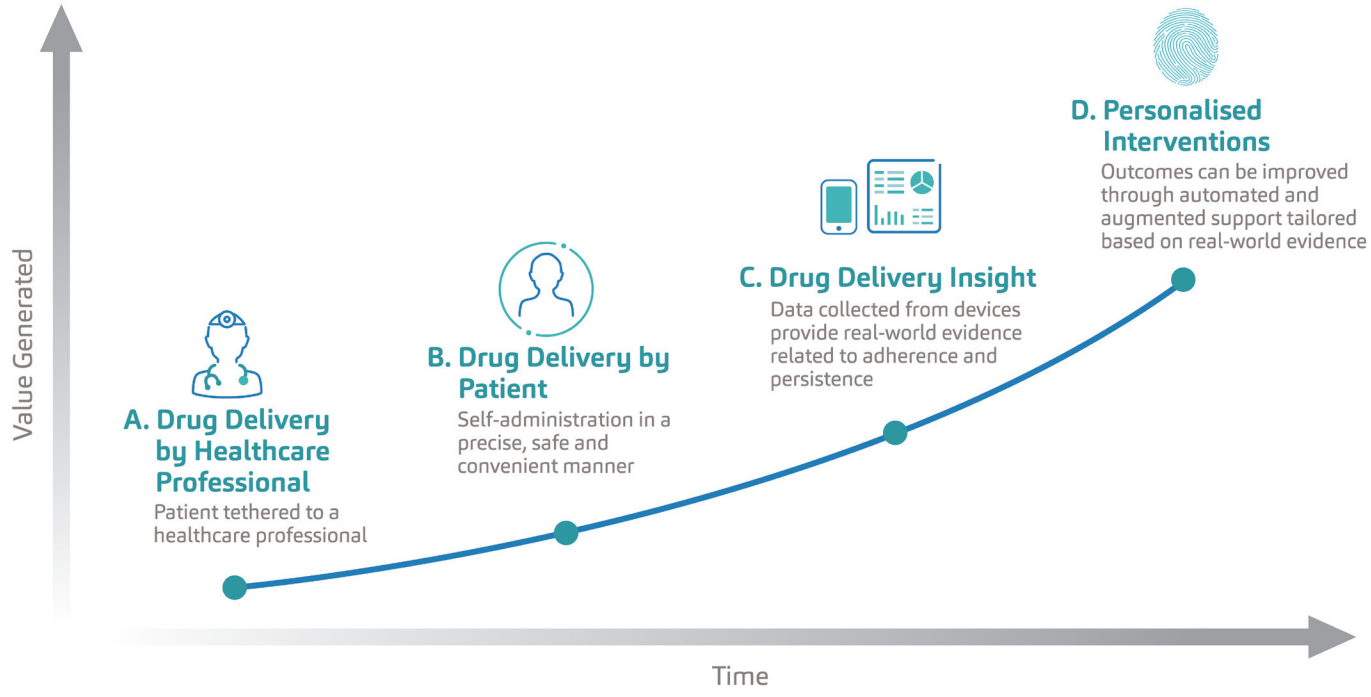

Figure 3: Evolution of the patient experience in drug delivery from clinic-based care to remote personalised care.

> "The next frontier in drug delivery, powered by connected therapeutics, will be data driven, personalised, outcomes based and accessible."

are being reimbursed for high-quality, high-impact care.[28] New Medicare codes now reimburse physicians for remote patient monitoring devices and services. Given there are over 55 million Medicare patients in the US and 80% have multiple comorbidities, this presents a significant market catalyst for the adoption of connectivity.[28]

ACCELERATION BY REGULATION

The US FDA has been proactive in improving the regulatory pathway for managing the data generated by software and connected drug delivery devices. The FDA Software Precertification Program, currently in pilot mode, effectively certifies the organisation developing the digital healthcare product rather than looking primarily at the product itself. This approach stems from the nature of software itself, which undergoes rapid, continuous and iterative improvements. This, according to the FDA, will "provide more streamlined and efficient regulatory oversight of software-based medical devices developed by manufacturers who have demonstrated a robust culture of quality and organisational excellence."[29]

The most recent development is the FDA's artificial intelligence (AI) discussion paper.[30] Here AI refers to software, which can change its mind and improve its learning or decision making based on new data. While there are already a number of so-called "locked algorithms" approved by the FDA and used in the measurement of stroke risk or detection of diabetic retinopathy, this recent paper aims to tailor to AI's adaptive nature. Such efforts by the FDA, which aim to simplify and streamline approvals, are expected to accelerate the adoption of connectivity.

CONNECTIVITY TO CARE

When we look at the evolution of the patient experience in drug delivery, we see that patients have traditionally been tethered to healthcare professionals, typically needing to visit a clinic for the administration of their treatment (Figure 3). As autoinjectors set a new standard in drug delivery, patients were empowered to manage their treatments, and do so in a safe and convenient manner. With the adoption of connectivity, drug delivery devices are becoming an important source of real-world data which is now passively measuring adherence. The true value of this data lies in its ability to improve health outcomes through the personalisation of interventions and care delivery. This next frontier in drug delivery, powered by connected therapeutics, will be data driven, personalised, outcomes based and accessible. Only then will connected therapeutics reach their full value.

ABOUT THE COMPANY

SHL Group is a world-leading solution provider in the design, development and manufacturing of advanced drug delivery devices such as autoinjectors, pen injectors and advanced inhaler systems. It also offers core competencies and services in the fields of medtech and patient care solutions. With locations in Taiwan, Switzerland, Sweden, China and the US, SHL's experienced engineers and designers develop product enhancements as well as breakthrough drug delivery and patient care solutions for pharma and biotech clients globally. This includes advanced re-usable and disposable injectors that can accommodate high volumes and high viscosities and can be enhanced through digital implementations.

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ABOUT THE AUTHOR

Ramin Rafiei, PhD is Director of Technology at SHL Group, leading the organisation's efforts in digital healthcare. His focus is the intersection of connected therapeutics, software and personalised care delivery with the aim of bridging the efficacy-to-effectiveness gap. Over the past two decades, Dr Rafiei has been leading high-stake multidisciplinary scientific and business initiatives globally across established industries such as aerospace and nuclear, as well as next-generation industries such as photonics, autonomous mobility and digital healthcare. Dr Rafiei is a healthcare investor, a healthtech advisor and a published author who holds a PhD in experimental nuclear physics from The Australian National University (Canberra, Australia).

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ADHERENCE TO SELF-INJECTION REGIMENS CAN BE ENHANCED BY CONNECTED DEVICES

In this article, Craig Baker, Executive Vice-President at Noble, looks at the factors contributing to non-adherence and explores how connected devices can help patients follow their self-injection regimens.

A variety of methods of drug delivery, such as autoinjectors, require patients to self-administer medicine as part of their regimen for chronic and acute conditions. Although an increasing number of patients are introduced to these types of devices every year, adherence rates are still less than 50% following six months of treatment.[1] The impact of non-adherence on the pharmaceutical industry can include lower product consumption, suboptimal patient outcomes, lower sales, lower expectations of drug efficacy and lower brand equity.[1]

> "Among the technologies proposed to enhance adherence rates, connected devices have shown a great deal of promise."

The effort to improve adherence rates therefore entails a twofold task. First, it is necessary to understand the nature and scope of non-adherence among patients who self-administer their medicine in general – and via specific devices (e.g. autoinjectors) in particular. This then leads to the second task, which involves focusing on potential solutions—such as new technologies that can be commercialised for the benefit of patients, healthcare providers and pharmaceutical companies.

Among the technologies proposed to enhance adherence rates, connected devices have shown a great deal of promise. These are defined as devices that can be used to capture and transmit information about patient usage, which can subsequently be analysed to gain a better understanding of how patients are using or interacting with their therapies. Noble has recently moved into this space with the development of its AdhereIT™ platform for autoinjector training and injections (Figure 1) to help pharmaceutical companies lower non-adherence rates.

Figure 1: Noble offers customisation of AdhereIT to fit a variety of autoinjector platforms.

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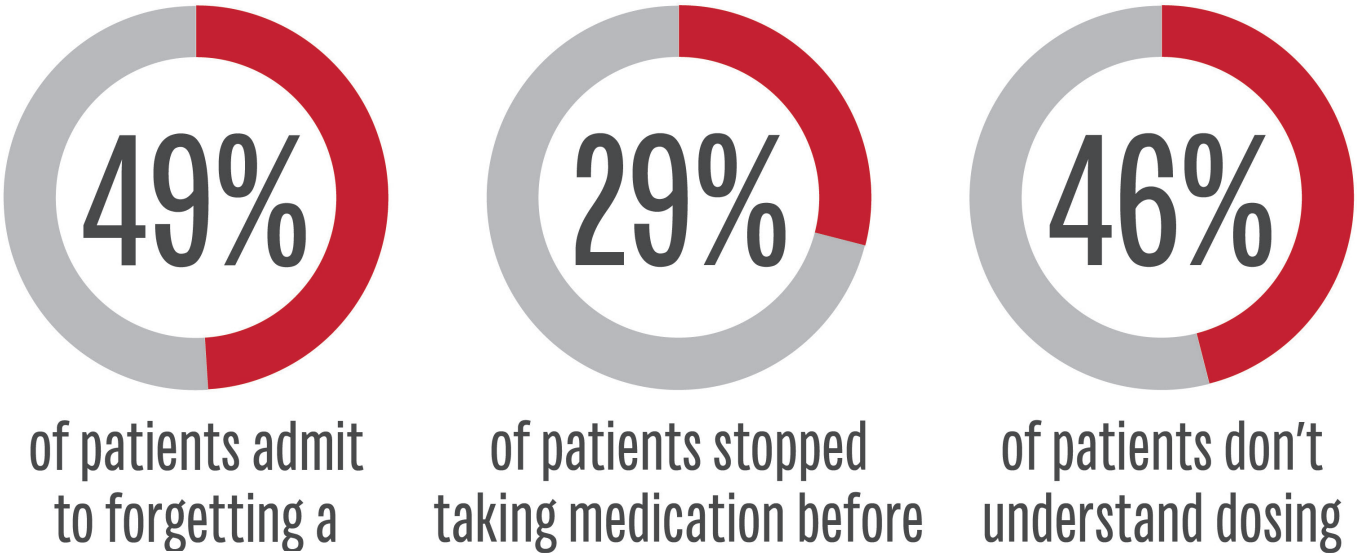

Figure 2: Overview of some the factors contributing to non-adherence.

SEVERAL FACTORS CONTRIBUTE TO NON-ADHERENCE

There are multiple patient-related factors involved in the problem of non-adherence.[2] Some of these are psychological in nature – ranging from simple patient forgetfulness,[3] to the fear of being stigmatised by a disease, to patients' misconceptions regarding the perceived benefit of their treatment. Other reasons patients may not stick with their prescribed course of medication are more practical in nature, such as an inability to pay for a prescription[3] or being unable to get the prescription filled, picked up or delivered.[3]

Apart from these factors, however, it has also been estimated that 46% of cases of non-adherence result from patients misunderstanding prescription dosing instructions.[4] This can result from an unsatisfactory relationship between the healthcare practitioner and the patient, including an inadequate amount of time spent training the patient, less-than-adequate quality of instruction received, an inability to properly understand the instructions for use, and an inadequate appreciation on the healthcare practitioner's part of the challenges of adherence following the period of initial instruction of the patient on their device (Figure 2).

A review article in The New England Journal of Medicine suggests that a rapid evolution in the time demands placed on healthcare providers is altering how they interact with patients. Specifically, the pressure on physicians to move quickly and accomplish multiple goals during a visit has intensified, and many patients in surveys have described their doctors as relatively hurried and unresponsive. The article suggests various factors have also led to a decrease in face-to-face interactions between doctors and patients. Even as there has been a narrowing in the scope of how doctors interface with patients, there has been a simultaneous growth in team-based instruction of the patient involving other professionals.[5] For those charged with training patients on the proper use of autoinjectors, accuracy and professional expertise are clearly vital.

> "According to a study conducted by the University of Texas Medical Branch in Galveston, most patients use their autoinjectors incorrectly."

This first 30–90 days after diagnosis – i.e. the onboarding period when the patient is originally introduced and trained on their autoinjector – is crucial for ensuring long-term adherence. However, some studies have shown that patients often have difficulty recalling the exact process of self-administering their medicine with an autoinjector following training. This reflects a study that concluded that 40–80% of all medical information supplied by a healthcare practitioner is forgotten immediately.[6] Supplementary to this finding, it has also been suggested that 19% of patients have a higher risk of non-adherence in the wake of poor physician/patient communication.[7] When patient training is incomplete or patients recall their training in a faulty manner, the results can include patient error, injury and adverse events – all of which, in turn, may influence patients to curtail use of their device.

AUTOINJECTOR USERS PRONE TO SPECIFIC ERRORS

Among the subset of patients who specifically use autoinjectors, a common set of errors is likely to play a role. According to a study conducted by the University of Texas Medical Branch in Galveston, most patients use their autoinjectors incorrectly. In the study, patients were asked to demonstrate the steps needed to correctly self-administer their autoinjectors, and it was found that more than half of patients missed three or more steps.[8]

The mistakes that patients were observed making included: failing to hold the autoinjector in place for the required amount of time; not pressing the device hard enough to trigger the release of the drug; and not choosing a suitable injection site on the body. Despite a redesign of the autoinjector for easier use, most patients continued to make at least one mistake with the device, the study found. In fact, most patients continued to make multiple mistakes.

The most common error, observed among 76% of patients, was a failure to hold the unit in place for at least 10 seconds after triggering. Additional errors involved improper safety cap removal, holding the device in the palm incorrectly, using a swinging motion to place the tip

> "AdhereIT can fit onto a trainer that closely mimics an autoinjector as well as onto a prescribed device itself."

of the autoinjector on the outer thigh and failure to apply sufficient pressure. The poor outcomes resulting from such errors can lead those using autoinjectors to respond negatively to their course of treatment, likely playing a role in inflating their rates of non-adherence.

THE ROLE OF CONNECTED DEVICES IN PROMOTING ADHERENCE

To address and alleviate these types of concerns, connected devices have been rising in popularity within the pharmaceutical industry over the past five years. At Noble, an interest in connected devices grew organically out of the company's role as an industry leader in developing patient-centric advanced drug delivery trainers – including autoinjectors, prefilled syringes, and wearable and respiratory devices. Having studied the errors that were commonly committed during autoinjector training for several years, the company saw an opportunity to help ensure patients could use their prescribed devices properly to sustain adherence.

From this vision, AdhereIT was born. This device offers various categories of features that can make it appealing for patients, healthcare providers and drug companies alike. The first of these features involves its flexible form factor – AdhereIT can fit onto a trainer that closely mimics an autoinjector (Figure 3) as well as onto a prescribed device itself. Drug companies may decide whether to adapt AdhereIT to one or both of these. AdhereIT can also easily fit onto a variety of autoinjectors created by different companies.

The second set of features involves the ability of AdhereIT to detect and monitor how users interact with the specific steps of drug delivery to ensure proper self-injection. For example, the device can detect the precise times at which a training session or an injection with the prescribed device begins and ends, as well as detect when the trainer/device makes contact with the injection site on the skin. It can also send injection scheduling reminders to the patient.

The third set of features involves connectivity. AdhereIT can wirelessly transmit the data it collects regarding the training session or actual injection – including any patient administration errors – to a smartphone or tablet. Its set of high-tech features, in effect, transforms trainers and autoinjectors into "smart" devices. This can provide helpful feedback to the patient in real time during the training period as well as during injection with the prescribed device. AdhereIT has also been configured to integrate with developers' wireless platforms for enabling the collection and customisation of usage data.

Late last year, Noble received a patent allowance for AdhereIT, and the product was launched into the market soon thereafter. Since then, Noble has continued to refine the platform's form factors and capabilities.

AdhereIT – and other connected devices like it – provide both short- and long-term benefits for patients, healthcare practitioners and pharmaceutical manufacturers. Most obviously, for patients, the use of these devices may provide the informative feedback that encourages them to adhere to their prescribed dosing regimens for longer periods.

For their part, healthcare practitioners can provide their new autoinjector patients with a tool that provides an added layer of assurance that self-injecting is being performed properly – both during the training phase as well as when the prescribed device is being used. Data collected by the connected device can be shared with the practitioner and reviewed for any irregularities that need to be discussed with the patient.

For drug pharmaceutical manufacturers, the decision to develop a connected device such as AdhereIT for use in tandem with a trainer and prescribed autoinjector can be prudent as well. Specifically, it allows the manufacturer to differentiate itself from competitors in a crowded marketplace and improve the experience and satisfaction of their patients. Noble's technical expertise and in-house engineering capabilities make the conception, design and manufacturing of the connected device a turnkey process for manufacturers.

Figure 3: An example of how the AdhereIT adherence device can be used with an autoinjector trainer. It can also fit onto a prescribed device.

Given their potential for enhancing rates of adherence, connected devices such as AdhereIT are likely to play an increasingly important role for patients, their healthcare practitioners and pharmaceutical companies as rates of self-administration rise steadily.

ABOUT THE COMPANY

Founded in 1994, Noble is a global leader in medical device training solutions, patient onboarding strategies and multisensory product development for the world's top pharmaceutical brands and biotechnology companies. Focused on driving innovation, Noble works closely with brand, device and commercialisation teams to develop turnkey solutions that improve onboarding and adherence, bringing value to clients and patients alike.

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Craig Baker is Executive Vice-President at Noble, a global leader in medical device training solutions, patient onboarding strategies and multisensory product development for the world's top pharmaceutical brands. He leads an award-winning, multidisciplinary team responsible for global business development, marketing, brand management, product strategy, market intelligence, client services, logistics and customer experience. With more than 20 years of management experience in the pharmaceutical product development field, Mr Baker's unique insights and extensive expertise have made him a respected thought leader throughout the industry. He also holds a bachelor's degree from the University of Iowa as well as a master's degree from the University of South Carolina.

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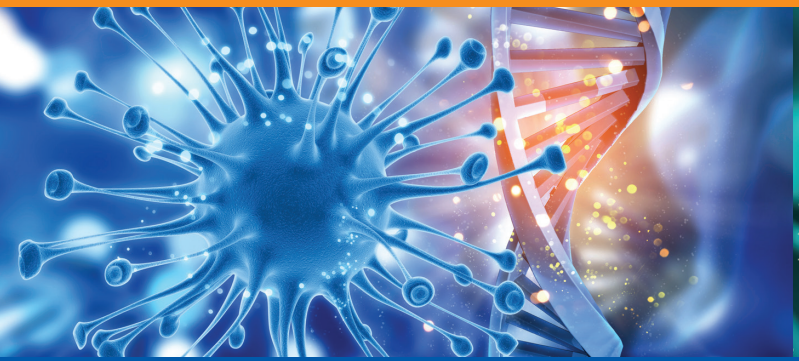

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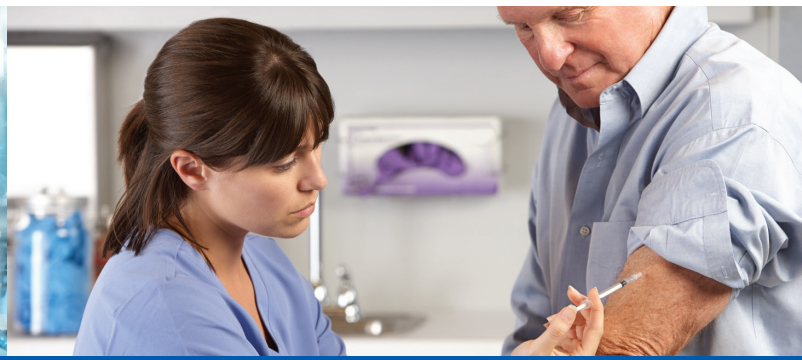

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LOW-COST CONNECTIVITY MEETS PATIENT & PHARMA MEDICATION MANAGEMENT NEEDS

Here, Neil Williams, Director of Front-End Innovation and Head of Connected Health, Phillips-Medisize, describes the potential connected drug delivery systems hold to address serious challenges in healthcare, including poor adherence, and also deliver substantial value, and outlines the company's highly scalable enterprise platform, the Connected Health Platform (CHP).

A digital revolution is transforming healthcare across the globe, and it's high time drug manufacturers got in on the action. This new landscape runs the gamut from continuous glucose monitoring (CGM) and remote patient surveillance, to point-of-care test results in the clinic and at home. Artificial intelligence (AI) is establishing virtual diagnosis and care pathway plans, while e-prescribing systems are informing clinicians about drug compatibility and formulary preferences. However, digital data related to medicine adherence is conspicuously lacking. Without accurate, detailed knowledge of when – or even if – patients take their prescribed medication, it is nearly impossible to gauge the effectiveness of drug therapies or to manage diseases.

Monitoring, measuring and supporting patient adherence to prescribed medications is vital, especially in today's value-based healthcare environment where outcomes are the new income for patients, providers, payers and pharma. Poor adherence rates take a toll in terms of reduced patient health and quality of life, as well as financially. An estimated US$290 billion (£229 billion) in avoidable US healthcare costs – approximately 13% of the total – has been attributed to poor medication adherence.[1]

Pharmaceutical companies also pay a high price for these low adherence rates, which account for approximately $188 billion in lost revenue.[2] With adherence rates of 31-66%, common auto-immune, diabetes and respiratory medications leave an estimated $1-10 billion dollars "on the table" annually.[2]

Yet our estimates show that a 3% increase in adherence has the potential to generate an additional $1-3 billion in revenue over five years, far offsetting the cost of investment in connectivity.

> "Our estimates show that a 3% increase in adherence has the potential to generate an additional $1-3 billion in revenue over five years, far offsetting the cost of investment in connectivity."

UNDERSTANDING THE CHALLENGES

Connected health solutions for medication management, patient support and analytics offer promising potential for addressing the unique medicine-related needs and challenges faced by key stakeholder groups in healthcare, including patients, clinical researchers/data scientists, pharmaceutical manufacturers, and families and friends.

Neil Williams
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Patients

The ability to track their medication dosage, frequency and health via a mobile app, to receive alerts and reminders, and to access helpful information about their condition, helps patients maximise their medication benefit and manage their disease or chronic condition more successfully. When patients use a connected drug delivery device such as an inhaler or injector with a regulated Mobile Medication Application (SaMD/MMA), they can easily and accurately capture data about when they take their medication and how much, right on their phone, tablet or other smart device.

The number of health apps is extensive, but they certainly don't all offer equal value. More than half of the apps on the market perform only a single function, such as inform, instruct or record data.[3] A mere 6% feature medication reminders.[3] Without the ability to remind, alert, communicate or share data, apps serve as little more than digital diaries. To engage patients effectively, apps should feature a human factors-tested, patient-centric design, and potentially include motivational tools that are cohort based to encourage adherence and lifestyle choices.

Connected health solutions built on Phillips-Medisize's Connected Health Platform (CHP), for example, can be integrated with a highly secure, regulated mobile app platform (Figure 1) that provides medication scheduling and reminders, adherence tracking and contextualised educational content tailored to individual patient needs. The app can also integrate patient-reported outcome measures (PROM), data from other monitoring devices the patient may use at home as well as external data such as hospital lab results, to provide a more holistic view of the patient's condition in real-time.

"Without the ability to remind, alert, communicate or share data, apps serve as little more than digital diaries. To engage patients effectively, apps should feature a human factors-tested, patient-centric design, and potentially include motivational tools that are cohort based to encourage adherence and lifestyle choices."

Figure 1: The Connected Health Platform can be integrated with a highly secure, regulated mobile app platform for patients.

Providers

Typically, healthcare specialists see patients with chronic conditions only once or twice a year, unless the patient's risk profile deteriorates. In those cases, it may be too late for the provider to have meaningful impact on the patient's health. However, the ability to monitor data from a connected drug delivery device, integrated with other patient data, provides an opportunity to work with observed rather than expected results and stratify patients by risk so that health professionals can swiftly identify patients at risk of significant deterioration and therefore intervene.

By using a connected health platform's analytics component to risk-stratify those patients, care providers can intervene on a timely basis in a number of ways, such as calling, messaging or requesting the patient schedule a clinic visit. In addition, AI and content management capabilities can be used to help patients better manage their health. For example, clinicians can send a message reminding the patient, "You've been missing your evening injection. Here's why it's important to have it." They can also include multimedia educational content targeted at the patient.

Phillips-Medisize's platform can create healthcare practitioner (HCP) dashboards (Figure 2) and alerting tools, and integrate patient data directly into a clinical portal and the healthcare system's electronic health record (EHR) system or to a regional health information exchange (HIE). The bidirectional capability allows patients to send their drug delivery data to the hospital but also to receive medical images, lab results, care continuity information from their providers and other data, so they can access and own their medical data.

Figure 2: Healthcare practitioner dashboards and alerting tools integrate patient data directly into a clinical portal and the healthcare system's electronic health record system or to a regional health information exchange.

Clinical researchers/data scientists

The Phillips-Medisize CHP allows data scientists to create new dashboards and conduct analytics that support their research on the effectiveness of various drug therapies, and all data within the platform is compliant with US FDA CFR 820 Part 11 standards. Data on adherence and effectiveness can also be shared with payers, if patients give permission and the pharmaceutical company is willing.

Pharma Manufacturers

Connected health solutions offer value to pharma companies both during the early-stage clinical trials of a new drug as well as in Phase IV studies once the drug is commercialised and on the market with Part 11 compliant data. By differentiating and improving the drug delivery and digital experience, and identifying patient cohorts, more prescriptions can be written, in turn improving patient engagement and generating additional revenue.

Access to connected health solution data also has the power to radically transform patient support programmes (PSPs), which play key roles in furthering adherence. Current PSPs run by pharma companies take a proactive approach to supporting patients in their homes or other remote care settings in order to promote better compliance and improved outcomes. These programmes often provide brochures, letters, phone calls, messages, targeted video content and emails. Many also have patient contact information and patient/condition guidelines. But until recently, they have not had accurate, timely information about patient health on a regular or on-demand basis.

A connected health solution allows physicians, nurses and other patient support professionals to view how patients are doing, enabling them to devote more time and energy to those who need greater support. They then can tailor patient care based on real-time feedback, with potentially significant impact.

Families & Friends

Connected health solutions provide an opportunity for families, friends and caregivers to monitor via a mobile app how their child, elderly parent or other family member is doing so they can offer help as needed. After all, sometimes mothers, fathers, sons, daughters or other relatives or friends who have a trusting relationship with patients are more effective persuaders about medication adherence and healthy behaviours.

> "After developing the first connected health combination product (including autoinjector, app and cloud platform), approved by the FDA for a specific drug four years ago, Phillips-Medisize has invested in creating a highly scalable enterprise platform for the evolving and expanding market."

In addition, it enables patients to connect with other patients via a closed or public social media platform. Sharing similar challenges, experiences and insights can be valuable in supporting adherence in an age when nearly one-quarter of consumers say they use social media to get information about health options.[4] Phillips-Medisize's CHP supports integration with social media platforms and also includes a discrete social community capability.

TAKING THE LEAP TO CONNECTED HEALTH

With the cost of new drug development pushing $2.6 billion,[5] many pharma manufacturers are understandably wary of investing significant additional funds in connectivity. As a result, only a few connected health solutions related to drug delivery are on the market to date. But the upside for unlocking the value in connected health and digital intervention is sure to drive initiatives.

Three primary components comprise the connected health ecosystem: connected devices, such as inhalers and injectors; digital interfaces, including patient apps and HCP dashboards; and a cloud platform that enables data integration with multiple sources to generate insightful analytics (Figure 3). The opportunity to build drug delivery devices and healthcare apps on an existing connected health platform helps pharmaceutical companies, drug delivery device developers and medtech manufacturers substantially reduce risk, cost and time to market.

Since developing the first connected health combination product (including autoinjector, app and cloud platform),

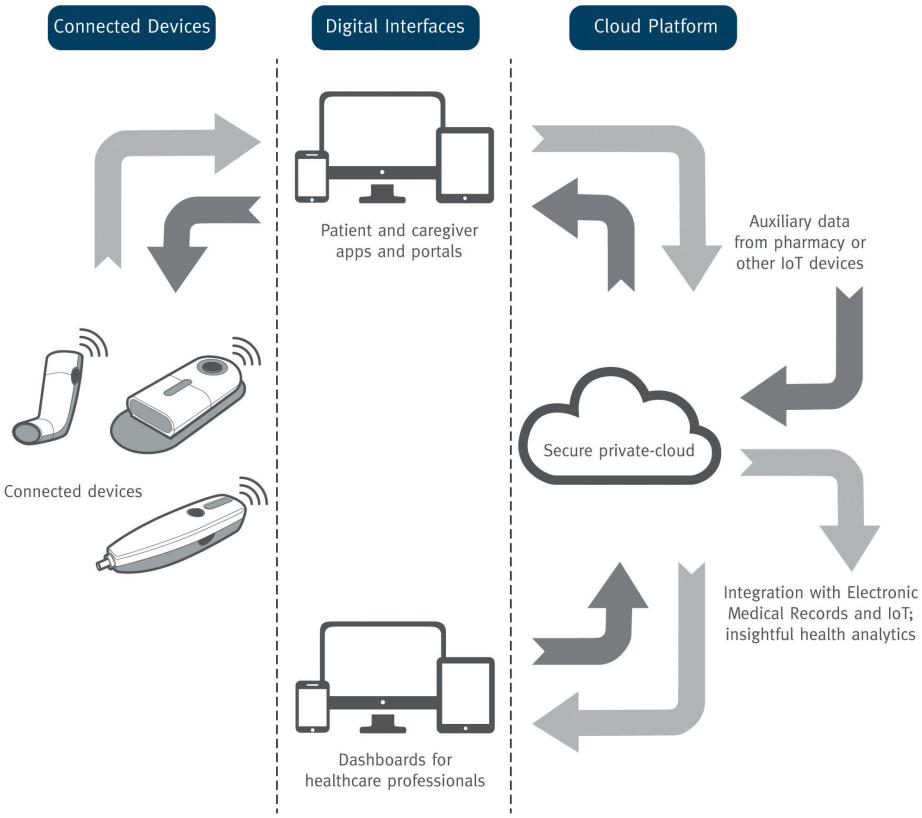

Figure 3: The three primary components of a connected health ecosystem.

"Three primary components drive the cost of connectivity: integrated circuits, sensors and batteries."

approved by the FDA for a specific drug four years ago, Phillips-Medisize has invested in creating a highly scalable enterprise platform for the evolving and expanding market.

The third-generation CHP offers several benefits including comprehensive information-sharing and analytics capabilities, robust cybersecurity, streamlined regulatory documentation, a modular approach, the capability to support global franchises with normalised clinical coding and post-market surveillance pharmacovigilance reporting within a per client "private cloud."

Listed as a Medical Device Data System (MDDS), the Phillips-Medisize platform can be configured "out of the box" to support multiple therapeutic areas affording patients with different diseases and medications a targeted experience including multiple apps and associated device(s), if applicable. The forthcoming Phillips-Medisize healthcare app framework can be quickly customised to link patients and devices to the platform. These capabilities, combined with the other advantages Phillips-Medisize offers as an end-to-end solution provider of medical products and connected health systems, create value from strategy setting through to on-market drug delivery and digital engagement for pharma, device and medtech manufacturers seeking to capitalise on connected health solutions.

During the strategy, feasibility and development phase, the Phillips-Medisize team works closely with the pharma company to create a patient-centered design that improves the drug delivery and digital intervention experience far more effectively – and efficiently – than an off-the-shelf solution where designs are already fixed. The existing regulatory documentation packs also mean a solution will be ready for a US Part 11 Compliant study, premarket submission for 510(k), Combination Product submission and EU CE mark filing sooner; helping to reduce project costs, regulatory approval documentation and, ultimately, time to commercialisation.

The ability of Phillips-Medisize to manufacture the electronics internally also makes connectivity much more affordable, both for re-usable and disposable drug delivery devices. Three primary components drive the cost of connectivity: integrated circuits, sensors and batteries. As a Molex company, Phillips-Medisize can take advantage of its vast global electronics design, manufacturing capability and purchasing power to keep connectivity and total manufacturing costs – including the moulding, automated assembly, circuit board assemblies and metal stamping – low. In addition, all solutions are designed and manufactured to meet environmental standards.

Finally, Phillips-Medisize offers supply-chain integration as part of its end-to-end service. The company's cold-chain storage facilities enable it to monitor and regulate the temperature of drugs delivered to load into the connected health solutions. These can then be shipped in climate-controlled containers directly to customers.

BUILDING VALUE THROUGH SMART DEVELOPMENT PRACTICES

Integrating connectivity into innovatively designed, patient-centric drug delivery devices provides promising potential for pharmaceutical companies and medtech manufacturers to better meet the needs of patients, healthcare providers, payers and clinical researchers. By improving the patient and provider experience, connected health solutions can help support increased adherence, potentially enabling greater compliance and persistence, as well as revenue opportunities from an engaged patient population.

ABOUT THE COMPANY

Phillips-Medisize is a provider of outsource design, development and technology-driven manufacturing, with a primary focus in the medical device and diagnostics, drug delivery, primary pharmaceutical packaging and commercial markets. Phillips-Medisize operates on a partnering business model, and works with pharmaceutical, biopharmaceutical, consumable diagnostic and medical device companies with the purpose of increasing speed to market. It was the first company to deliver a US FDA-approved connected health system to the market.

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ABOUT THE AUTHOR

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. 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.

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I SPY WITH MY LITTLE EYE: EYE TRACKING DRIVES PATIENT-CENTRED DEVELOPMENT OF CONNECTED SYSTEMS

The development of connected self-injection systems is driving industry to rethink its current approaches to patient-centred new product development. In this article, Andreas Schneider, PhD, Innovation & Business Development Manager at Ypsomed, summarises a recent field study that used eye tracking for the formative usability testing of SmartPilot for YpsoMate – a re-usable passive monitoring module that transforms the two-step autoinjector YpsoMate into a fully connected product.

Patient centricity has long been regarded as a guiding paradigm for the development of self-injection devices. Industry and academia alike have intensively studied how to capture the patient's voice optimally throughout the innovation process – either during early-stage formative usability testing or as part of late-stage summative design validation.

> "The development of connected self-injection systems is about to challenge the well-established methodological principles."

Interestingly, there has been little methodological advancement to date. For three decades or so, the industry has largely relied on patient self-reports, open-ended interviews or shadowing users during their daily drug administration routines as design inputs. Such insights led to innovative self-injection device concepts. In fact, these approaches have built a standard methods usability toolbox that – if adequately applied – permits patient-centred product development.

Entering the digital era, that is no longer true. The development of connected self-injection systems is about to challenge the well-established methodological principles.

Connected self-injection systems typically consist of multiple components and user interface elements that may advance patient adherence to the next level. However, the interplay between these elements – such as an autoinjector, a companion mobile application and a re-usable connected monitoring module (Figure 1) – must be carefully orchestrated. How to guide users step by step through the injection process? Where to locate visual, audible or tactile feedback elements? How to blend the mechanical with digital elements?

And yet, patients may not be able to appropriately verbalise their experiences when operating such a multi-element product system. Knowledge in general is hard to put into words. Verbalising experiences becomes particularly challenging when tied to emotions, intuition or physical experiences. New usability approaches are thus needed to inform the design development of connected self-injection device systems better.

A recent study investigated the application of eye-tracking in the development of connected self-injection systems.[1] Figure 1 illustrates the need to optimise the interplay between user interface elements of any

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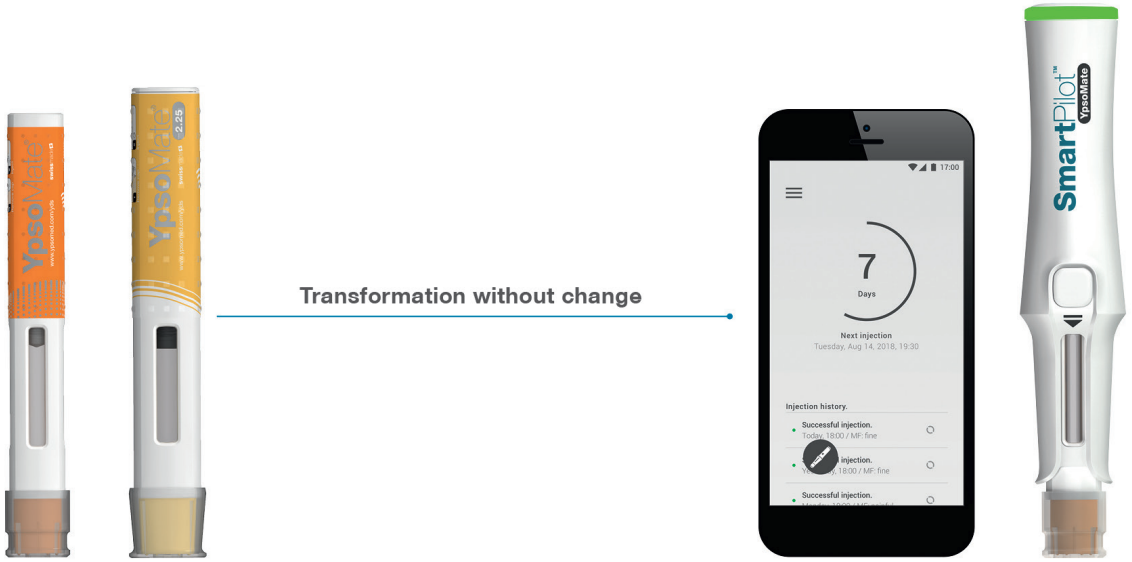

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Figure 1: The connected self-injection device system included in the study.

connected self-injection device system. It introduces the study device: SmartPilot for YpsoMate. SmartPilot is a re-usable smart monitoring module that flexibly transforms the marketed YpsoMate autoinjector into a cloud-connected product system. Advanced sensors track injection events and guide patients in real time through the injection process. Therapy-relevant injection data is encrypted on-chip and then made available to the broader healthcare ecosystem via wireless connectivity. Thus, YpsoMate comes with two sets of key functionalities. One monitors device usage and makes available the therapy-relevant injection data to providers, caregivers and healthcare stakeholders. The other guides patients step-by-step through the drug administration process including, for example, authentication of the self-injection device, or advice on holding time.

AN INTRODUCTION TO EYE TRACKING

Neurologists have long concluded it is through seeing that we construct meaning. Tracking patients' gaze patterns thus sheds light on their cognitive attention. Mobile eye tracking continually follows participants' eye movements as they engage with a connected self-injection system. The gaze patterns collected serve as input to evaluate the underlying cognitive processes during user engagement with a product system. The method thus permits the objective assessment of product usability without the need for participants to express their experiences while performing use steps.

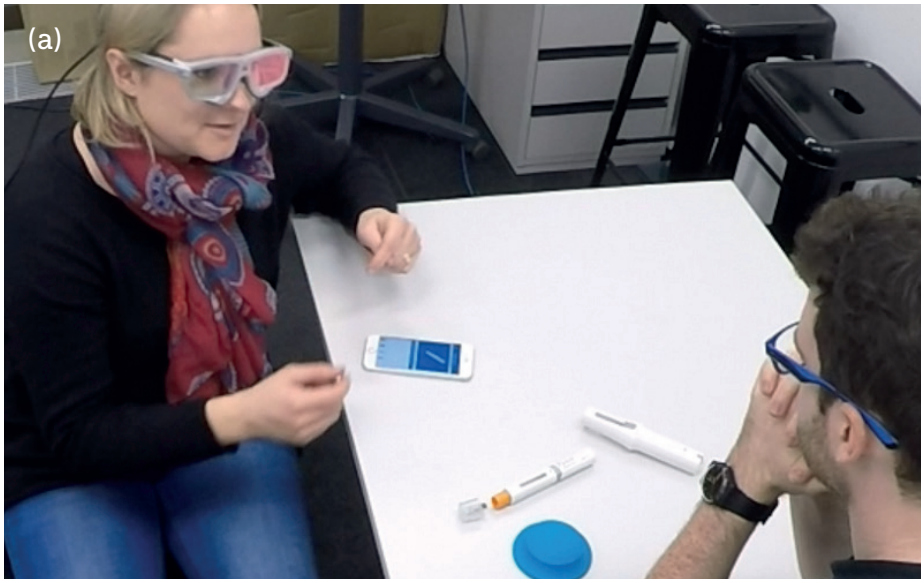

Figure 2: A snapshot of the experimental set-up – image A shows the use of eye-tracking glasses while image B illustrates the study participant's visual attention as an orange ring.

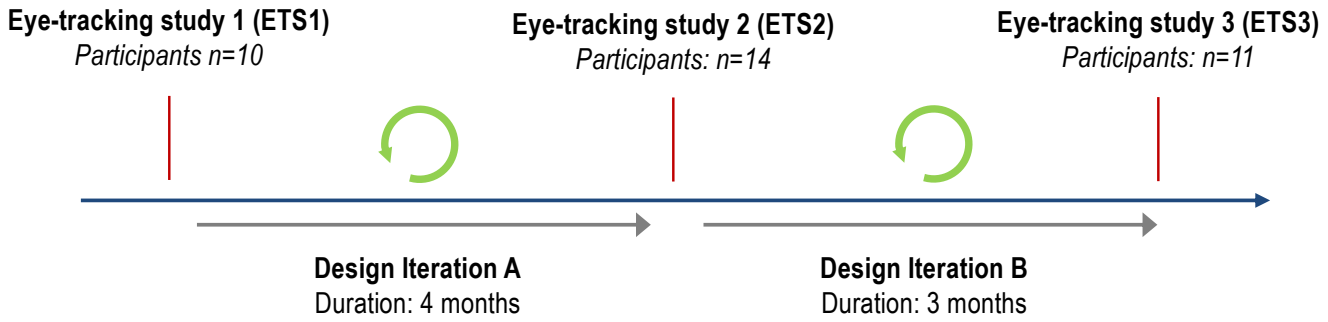

Figure 3: The longitudinal research design of the empirical study. Injection-naive users were recruited anew for each study.

Figure 2 illustrates the study's experimental set-up and the type of raw data obtained through mobile eye tracking. The evaluation required the use of eye-tracking glasses (Figure 2A), which must allow participants to move without restrictions while engaging with the product system. In this study, the SMI Eye-Tracking Glasses 2 Wireless system (SensoMotoric Instruments, Teltow, Germany) was used. Cameras integrated in the glasses capture the participant's field of view and construct the "scene video". The data are then converted into the viewing angle and the participant's continuous gaze point. Figure 2B shows the study participant's visual attention represented as an orange ring. The tracked gaze patterns served as a starting point for evaluation.

Figure 3 shows the research design of the simulated use study. Three eye-tracking studies were conducted, each informing a subsequent design iteration of the connected self-injection system's user interface. A total of 35 injection-naïve participants were newly recruited for the studies, during which participants simulated a self-injection into a foam cushion. The users were not exposed to the connected product system prior to the study. The companion mobile application installed on the smartphone provided real-time step-by-step instructions on how to operate SmartPilot for YpsoMate.

The insights gained from each eye-tracking study then informed the subsequent design iteration of the connected self-injection system. Three different design variants were evaluated, providing a longitudinal perspective on how product usability has evolved over time.

EYE TRACKING EVALUATED THREE USABILITY DIMENSIONS

The results of the empirical study concluded that eye tracking effectively guided the evolution of product usability along three dimensions – effectiveness, efficiency and ease of use. These usability indicators, as derived from eye tracking, improved as a result of the modifications and design adjustments made to the connected self-injection system. Figure 4 summarises the key findings of the empirical study.

> "User guidance was improved as a result of the design iterations guided by the eye-tracking studies."

The study provides empirical evidence that the overall product usability was step-wise improved over the course of the three eye-tracking experiments (ETS1, ETS2 and ETS3).

First, the data confirms that the product usability dimension, effectiveness, improved substantially over time. Effectiveness describes the user's ability to complete a certain use-step successfully. The extent to which a use-step was successfully completed was assessed using a four-point rating scale with the following items: (1) use error requiring moderator intervention; (2) close call/ temporary interruption; (3) user hesitation; and (4) uninterrupted completion.

Eye tracking provided rich contextual data from a unique first-person perspective

USABILITY DIMENSION	DEFINITION	VALUE OF EYE-TRACKING	RESULTS OF THE STUDY
A. Effectiveness	Extent to which patients successfully complete given use step	• Unique first-person perspective • Fine-grained insights into contextual engagement	Step-wise improvement of mean product effectiveness (4-point rating scale): – ETS1: 3.00 – ETS2: 3.43 – ETS3: 3.68
B. Efficiency	Duration per use step	• Precise assessment of transition points between use steps	Step-wise reduction of mean duration: – ETS1: 86.1 sec – ETS2: 81.4 sec – ETS3: 58.7 sec
C. Ease-of-use	Cognitive efforts (thus visual attention) required to complete given use step	Patterns in how participants gaze hits various user interface elements • Duration per user interface element • Guidance toward relevant elements	Visual attention spent on user interface elements relevant for given use step: – ETS1: 84.2% – ETS2: 93.5% – ETS3: 93.1%

Figure 4: Overview of the results of the empirical study (ETS = eye-tracking study).

to capture that first dimension. Detailed analysis of the video data recorded using the eye-tracking glasses shows that not only were use errors significantly reduced but also the overall robustness of the product increased. Initial usability challenges that resulted in process interruptions or use errors were completely eliminated over time.

Second, formative eye-tracking data also showed a step-wise improvement of the usability dimension efficiency, meaning a reduction in the duration needed to complete a specific use step. Shorter visual attention per user interface element corresponds with lower cognitive efforts to understand product usage. Eye-tracking data enabled the separation of overall product usage into distinct use steps and the precise definition of the transition points between them. The results confirmed a step-wise decrease in the duration required to complete the overall use process, thus providing empirical evidence that overall product efficiency was improved.

Third, eye-tracking-derived indicators also shed light on ease of use. Here, the product system is dissected into separate user interface elements. This shows how users directed their visual attention to those elements that were required for the completion of the given use step. The study advanced our understanding that eye-tracking data can be used to capture ease-of-use data objectively for each user-interface element. The results showed that user guidance was improved as a result of the design iterations guided by the eye-tracking studies: the more mature the connected self-injection system became, the less visual attention – and thus cognitive effort – was lost on irrelevant user interface elements.

PATIENT CENTRICITY – IN THE EYE OF THE BEHOLDER?

The study summarised here shows how eye tracking enables an in-depth analysis of patient engagement with a connected self-injection system, with a level of detail that would have gone unnoticed using traditional methodologies. Eye tracking confirmed that the design iterations targeting the usability of the connected self injection system SmartPilot for YpsoMate were highly effective. Specifically, the eye-tracking-derived indicators were of pivotal importance to assess the improvement of three usability dimensions over time: effectiveness, efficiency and ease of use. Empirical evidence tells us that the interplay between the distinct user interface elements was improved as the system's maturity increased.

The results furthermore suggest that eye tracking has great potential to guide new product development beyond connected self-injection systems. The digital transformation will radically change the way in which users interact with digital tools and connected technologies. In particular, the digital era drives the adoption of software-enhanced multi-element product systems – such as smart inhalers, sensor-augmented smart insulin pump systems or smartphone-based mobile electrocardiogram (ECG) devices – both at home and in the critical care environment. These systems all share a common trait: the digital and mechanical elements become integrated to realise advanced user feedback.

The relevance of eye tracking thus continues to grow. Formative and summative usability testing will increasingly study how to orchestrate the interplay between distinct user interface elements. Hence the drive to adopt novel methodological approaches to usability testing. New product development must result in the marketing of innovative healthcare tools and technologies that improve ease of use, rather than increasing patient cognitive burden.

ABOUT THE COMPANY

Ypsomed is an independent developer and manufacturer of both innovative mechanical and connected autoinjector and pen injector systems for self-administration. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pens, ready-to-use prefilled wearable bolus injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio.

With more than 30 years of experience and pioneering spirit in the development and manufacturing of innovative injection systems Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested into the development of a range of smart devices and therapy-agnostic digital device management services.

Anticipating the future needs of patients, pharmaceutical customers, payers, and healthcare professionals, Ypsomed moves beyond connected sensors: Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of diseases, and integrating these insights with third-party ecosystems. It leverages its unique in-house capabilities in electronics, software and connectivity for the development of new smart products and digital product systems.

Ypsomed's platform products and services are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by both pharma customers and regulatory agencies and supply devices for global markets including US, Europe, Japan, China and India.

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ABOUT THE AUTHOR

Andreas Schneider is Innovation & Business Development Manager with Ypsomed Delivery Systems. His responsibilities at Ypsomed include the definition and development of new platform devices with a particular emphasis on connected and smart device systems. As such, he has been actively involved in the design and development of SmartPilot for YpsoMate, a re-usable connected add-on that transforms the proven two-step autoinjector into a connected system. Dr Schneider has published various articles and held presentations in the areas of innovation management and drug delivery. He received his PhD in Innovation Management and Organisation Sciences from ETH Zurich, Switzerland.

COMPLETING ITS TRANSITION FROM GENESIS TO MATURITY, BIOCORP OPENS NEW HORIZONS

As Biocorp prepares for the market launch of its connected injector pen add-on, Mallya, Eric Dessertenne, Chief Operating Officer, and Arnaud Guillet, Business Development Director, share insights about key steps in the company's development and the opportunities that lie ahead. The article discusses the many partners Biocorp has entered into collaborations with, and includes a mini-interview with Sergio Monti, Plant Manager for one such partner, V.A.R.I.

It is well known that the world of the medical device moves at its own pace. Constrained by multiple standards to ensure the safety of patients, teams must comply with the necessary validations at each stage. Thus, after five years of hard work, Biocorp launches its first connected device this year. Many milestones have been achieved since 2014, thanks to foresight, agility and determination.

FROM GENESIS TO CE MARK AND DISTRIBUTION

Mallya is the add-on that turns any insulin pen into a smart device. The concept was born in 2014 when, based on the observation that some critical needs of patients with diabetes were not fulfilled, Biocorp challenged its team to find a way to achieve compliance for patients.

> "Mallya is indeed the first CE-marked class II-b medical device to be offered on the market."

The goal was to answer unmet needs in an immediate way and, considering that the timeline to develop an add-on is far shorter than for a whole connected product, an add-on approach was chosen. The idea was relevant, and the concept of Mallya was born, consisting of a connected smart cap compatible with any pen injector, recording and logging the exact dose dialled by the patient, along with the time and date, with the data being sent to a mobile app using Bluetooth technology.

Figure 1: Mallya is an add-on that turns any pen injector into a smart device.

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Since Mallya is an add-on, it can be used with existing products without any modification to their design (Figure 1), which saves a lot of time. Considering the market mainly offers disposable pens, adding connectivity becomes affordable thanks to Mallya, which is rechargeable (USB) and re-usable for up to two years. The diabetes field is widely adopting continuous glucose monitoring (CGM) and electronic blood glucose monitoring (e-BGM), so bringing the pen injector into the connected sphere is the last piece of the puzzle.

The device was first displayed at Pharmapack Europe 2016 (Paris, France, February 2016) where it won the Pharmapack Innovation Award. From the very beginning, the R&D team was committed to industrialisation capacity, designing Mallya from the outset to be produced on a large scale. Likewise, Biocorp has spent a lot of time ensuring that using the device is as seamless as possible for patients too, making it really easy to install Mallya on the pen and requiring no further steps to activate it and use the pen. All the formative and summative testing that Biocorp has been performing shows a high degree of acceptance of the system by patients of different age groups.

Mallya was originally developed for Eli Lilly's Kwikpen®, for the delivery of Humalog® (insulin lispro), and the CE marking file being finalised will be applicable for these pens. Mallya is also ready for SoloSTAR®, Sanofi's pen for the delivery of Lantus® (insulin gargine), and it will be finalised for Novo Nordisk pens by the end of 2019. Mallya is indeed the first CE-marked class II-b medical device to be offered on the market.

"We participated in the 2017 E-health awards at the E-health Summer University in Castres (France) and won First Prize for best connected Healthcare object, from a judging panel composed of pharmaceutical companies, HCPs, regulatory authorities and payers."

Figure 2: Inspair, a smart cap for inhalers that not only tracks medication use but also provides feedback on inhalation technique.

In 2016, Biocorp expanded its add-on approach to the respiratory field with Inspair (Figure 2), a smart cap for inhalers that not only tracks medication use but also provides feedback on inhalation technique. The development of this solution was based on the observation that many patients are unable to use their inhalers effectively, and critical errors are frequently observed, specifically for patients using pressurised metered-dose inhalers (pMDIs). These errors lead to lower drug deposition to the lungs, waste of medication and thus poor disease control, reduced quality of life, increased emergency hospital admissions and higher treatment costs.

"The Inspair platform showed a high degree of flexibility, in terms of integration, shape, functionalities, and adaptation to different device formats and technical constrains."

Based on preliminary technical specifications, an initial functional prototype of the solution was released at Pharmapack Europe 2017 (Paris, France, February 2017). Our first move was to seek the endorsement of various healthcare stakeholders. In that context, we participated in the 2017 E-health awards at the E-health Summer University in Castres (France) and won First Prize for best connected Healthcare object, from a judging panel composed of pharmaceutical companies, HCPs, regulatory authorities and payers.

Following this initial validation, we improved the device and moved its development forward through feasibility studies and customised programmes with pharmaceutical companies, on standard pMDIs and other types of respiratory device, either for clinical trials or commercial applications. Through these programmes, the Inspair platform showed a high degree of flexibility, in terms of integration, shape, functionalities, and adaptation to different device formats and technical constraints.

In parallel with these specific initiatives, Biocorp initiated the development of a standard off-the-shelf version of Inspair, with a defined set of unique functionalities. This version is now close to the verified prototype stage and will be industrialised in the coming months, at Biocorp's own facility in Issoire, France).

"Inspair guides patients to all steps necessary for correct use of the medication, from shaking the MDI to improving co-ordination between firing and inhaling the product. This gives a strong advantage versus all other smart devices currently on the market which only record when patients fire the drug."

Biocorp's strategy for Inspair will be the same as for Mallya, to obtain medical-grade classifications in Europe, the US and other markets, and follow the same development standards and requirements to guarantee the highest level of accuracy, repeatability, and robustness.

REACHING MATURITY

In parallel with exciting technical developments, Biocorp has built connections and signed partnerships with the most influential actors in the diabetes and respiratory markets, not only from a commercial perspective, but also to establish our solutions and guarantee high patient adoption and sustainable usage.

In the diabetes field, Biocorp has initiated collaboration strategies on many levels. Following the conclusions of leading diabetes experts, healthcare professionals and patients that combining glucose readings and insulin delivery data in a single platform could significantly improve diabetes management and control, Biocorp built connections with major glucose monitoring players (BGM and CGM) and insulin dose titration platforms, to provide comprehensive e-monitoring solutions.

In February 2019, we signed a distribution agreement with AgaMatrix (Dillingen, Germany), a major BGM player, and a collaboration agreement with DreaMed Diabetes (Petah Tikva, Israel), for its US FDA-approved insulin dose advisor software, DreaMed.

Mallya will feed our partners' platforms with exhaustive, reliable and 100% accurate insulin use data. Beyond these initial agreements, several technical evaluations and pilot studies are ongoing with other major diabetes players including pharmaceutical companies, CGM players and disease-management platforms, and further announcements are anticipated in the upcoming weeks.

On the scientific side, through collaborations with renowned hospital networks, institutions and key opinion leaders, clinical studies will begin soon in Europe, the US and the Middle East, to assess the impact of Mallya on adherence, diabetes control and treatment outcomes (specifically HbA1c levels). The outputs of these studies and evidence gathered will support our reimbursement strategy and our initiatives towards health plans and payers.

On the Inspair front, Biocorp has signed a global distribution agreement with Lindal Group company V.A.R.I., a leading player in the respiratory field. This deal will accelerate the technical development of the platform, in particular the "off the shelf" version of Inspair mentioned previously.

The agreement features exclusive distribution rights in some specific geographies (Asia, South America), merging the expertise of Lindal in the areas of valves and canisters with Biocorp's expertise in connectivity and sensing technologies. We recently talked with Sergio Monti, Plant Manager at V.A.R.I., about the benefits of this partnership and expectations over this collaboration, and this mini-interview appears in Box 1.

PROVEN EXPERTISE OPENING NEW HORIZONS

The success of Mallya and Inspair positions Biocorp as the reference player to develop add-on devices and bring connectivity to any type of drug delivery device, whenever there is a need to boost treatment adherence, monitor device use, or support patients in the management of their disease.

First, we can leverage our current add-on platforms. Our Mallya solution can be replicated to any pen injector in many therapeutic areas, specifically for self-managed and self-titrated diseases (e.g. fertility, multiple sclerosis, Parkinson's disease, psoriasis, and conditions requiring growth hormone). We have a reliable technology that was designed from the outset to be able to be readily adapted to the specific constraints and form factors of each pen. A similar approach could be considered for autoinjectors, to track compliance with device use-steps, and timely delivery by patients. Not to mention prefilled syringes, where key healthcare industry players are looking for solutions that are user friendly, easy to implement from an industrial standpoint, and economically viable.

In the respiratory field, Biocorp has already adapted its Inspair platform to various types of inhalers through feasibility studies and customised developments for clinical trial applications and, beyond MDIs, has been solicited for projects involving soft-mist inhalers, nebulisers and nasal delivery devices.

Beyond our traditional parenteral and respiratory fields, Biocorp has launched feasibility studies and development programmes in the ophthalmic, animal health and derma-cosmetic fields.

Through these initiatives, Biocorp has proven its ability to answer both the technical challenges (adapting to different form factors, sizes, and user requirement specifications) and the economic constraints specific to each project (design solutions from below €1 up to €100 in some cases).

Based on its experience and expertise in the field, all Biocorp's add-on developments follow five key principles:

- Seamless integration for maximum user convenience
- No interference with the existing drug delivery device user process or the formulation
- Minimal impact on existing drug delivery device industrial process
- Solutions with the highest level of accuracy, repeatability and robustness
- Compliance with economic criteria.

[Continued on Page 52...]

"Biocorp has launched an internal programme to develop a highly price competitive add-on solution for the injectable field which we believe will revolutionise monitoring of medication delivery in various therapeutic areas. Details will be disclosed this autumn."

BOX 1: INTERVIEW WITH...

SERGIO MONTI, PLANT MANAGER, V.A.R.I

Sergio Monti holds a Mechanical Engineering degree from Politecnico di Milano (Italy), an MBA from Northumbria University (Newcastle-upon-Tyne, UK) and Executives Education courses at London Business School. He began his pharma career in the Technical Service Team of ACS Dobfar, a major antibiotics manufacturer, heading all new projects and investments. Mr Monti joined Lindal Group in 2008 as Sales Director, contributing to the growth of its V.A.R.I. respiratory division. In 2017, he was promoted to Plant Manager of Lindal's Italian pharmaceutical facility.

Q **Mr Monti, could you briefly remind us what are the activities of Lindal Group?**

A Lindal Group is specialised in the design, development, manufacture and supply of aerosol dispensing packaging solutions tailored to meet a broad spectrum of customer needs and market applications. Our product offering includes a comprehensive range of valves, actuators, barrier packs and associated accessories that address the technical and aesthetic dispensing requirements.

V.A.R.I. is Lindal's wholly owned subsidiary focusing on respiratory applications. V.A.R.I. has been supplying valves and actuators for MDIs for more than 30 years and today we are one of the world's leading manufacturers in this field. Our main markets are the EMEA regions, Central and Latin American countries and Russia. We are growing significantly in Asia.

Q **Please describe the partnership you have in place with Biocorp?**

A Our partnership with Biocorp enables V.A.R.I. to commercialise Inspair to all our inhalation market customers we are supplying today and in all countries where we have strong market presence. Together, Biocorp and V.A.R.I. additionally offer a comprehensive service taking care of all technical aspects relating to the MDI devices.

Q **What are the benefits of this partnership for Lindal?**

A This partnership with Biocorp enhances Lindal's product portfolio with a highly innovative offering in a context where connected health is becoming more and more popular. Patients are very keen on collecting their health data to actively manage their therapy by sharing it with their doctor. This technology is particularly interesting for people with chronic diseases, like asthma or COPD, helping them to adjust their treatment easily and accurately.

Q **Do you see a strong demand for connected solutions among your key customers?**

A Yes, pharma companies are well aware of issues with adherence and device use, which is one of the historical weaknesses for MDIs. Our customers are looking for innovative solutions to help patients during their self-care. Inspair will help patients to get the dose at the right time and in the right way, with the ultimate objective of improving their quality of life.

Q **In your opinion, what are the key differentiators of Inspair versus competitive solutions?**

A Beyond tracking medication use and sending reminders, Inspair assess the quality of administration and the proper use of the device. Inspair guides patients to all steps necessary for correct use of the medication, from shaking the MDI to improving co-ordination between firing and inhaling the product. This gives a strong advantage versus all other smart devices currently on the market which only record when patients fire the drug.

Being an add-on is another important advantage of Inspair. This can significantly reduce the cost of smart devices. Inspair has a shelf life of two years and it can be used for several inhalers during this period.

Q **What made you choose Biocorp as your preferred partner to launch a connected offering?**

A Biocorp is well known for its innovations. As a pioneer in the field of connected solutions for drug delivery devices and with in-depth experience of the diabetes market, Biocorp was the best partner for Lindal to explore these new smart technologies. Right from the first contact, Biocorp impressed us with their knowledge of respiratory applications. Their flexibility and reactivity made all communications very easy. It has been a pleasure to start this collaboration and I really look forward to the first projects together.

[...Continued from Page 50]

Underpinning this, Biocorp has the ability to aim for any medical-grade classification the project demands, and meet the highest development and regulatory standards.

In parallel with numerous initiatives based on specific client requests, in anticipation of emerging market demand, Biocorp has launched an internal programme to develop a highly price competitive add-on solution for the injectable field which we believe will revolutionise monitoring of medication delivery in various therapeutic areas. Details will be disclosed this autumn at the PDA Universe of Prefilled Syringes and Injection Devices, October 22-23, 2019, Gothenburg, Sweden.

ABOUT THE COMPANY

For 25 years, Biocorp has been designing, developing and manufacturing medical devices for the pharmaceutical industry, enhancing drug reconstitution, safety, packaging and delivery. Today, Biocorp continues to innovate in medical plastics, bringing new solutions to the market such as the Newguard™, an integrated passive safety system for PFS compatible with nest, and Biopass™, a reconstitution system with an integrated needle ready to inject.

Recognised for its expertise in device R&D, Biocorp has incorporated software development capacities to develop connected drug delivery systems, including the Datapen™, a reusable smart pen injector that automatically transmits data to a treatment mobile app, helping patients to manage their treatment, and a range of add-ons, smart sensors for existing drug delivery devices (pen injectors, MDIs).

In addition to its R&D activities, Biocorp also provides manufacturing services for plastic injection, process assembly and blister packaging.

ABOUT THE AUTHORS

Eric Dessertenne has worked for the pharmaceutical and medical devices industries for many years. He holds a pharmaceutical degree from the University of Clermont-Ferrand (France), an MBA from ESSEC Business School (Paris, France) and is a graduate of the Therapeutic Chair of Innovation at ESSEC Business School. He began his career in the pharmaceutical industry working for Servier in France in the Corporate Strategy department and then moved to the Chinese subsidiary in Beijing, where he handled positions in the marketing and sales force department. Mr Dessertenne then joined LEK Consulting where he worked as a consultant in the Life Sciences and Private Equity practices. In 2014, he brought his experience and insights on market opportunities to Biocorp as Head of Business Development & Commercial Operations.

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

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MALLYA
DATAPEN
INSPAIR
ONEJET

USER-CENTERED DEVICE CONNECTIVITY

In this article, Mark Tunkel, Partner and Head of Business Development, and Carolyn Rose, Director of Research and Strategy, both of Insight Product Development, discuss the benefits of taking a user-needs approach, and mapping the patient journey, in a connectivity strategy.

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

In addition to these measures, virtually every developer in the branded and generic space is formulating some variation of a digital health strategy that features device connectivity for parenteral and inhalation devices. Initially, these strategies focus on the development of add-ons or accessories that are compatible with a commercially available device and provide users with device performance feedback – like when an autoinjector is ready to inject or when an injection is complete. They can also provide error correction and other means of feedback to help eliminate use errors. The Smart Pilot accessory from Ypsomed (Burgdorf, Switzerland) is an example of a device providing this level of functionality.

> "There has been convergence within the drug delivery ecosystem, where all aspects of managing a disease state are integrated through connectivity."

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

There has also been convergence within the drug delivery ecosystem, where all aspects of managing a disease state are integrated through connectivity. A good example of this is the Bigfoot Biomedical connected diabetes management ecosystem, which is a comprehensive solution that integrates the Abbott Diabetes Freestyle Libre sensor-based glucose management technology into Bigfoot insulin pens and pumps. Abbott has also partnered with Novo Nordisk in a similar arrangement. All these ecosystems are reliant upon sensor technology and mobile applications that act as the primary interface for all the component pieces. Similar to the add-ons scenario, these ecosystems are addressing known workflows and device component constraints.

In the future, it is reasonable to expect that novel and platform device ecosystems will begin to integrate connected technology into the device architecture itself. While there are regulatory issues to address, patient experiences that include connectivity and analytics supported by Amazon Web Services or Google cloud platforms hold immense promise to deliver better outcomes and experiences for patients and health systems.

Achieving success will require the use of a robust digital health strategy. A critical tool in helping developers formulate a user-driven strategy is a thorough mapping of the patient journey – to develop an intimate understanding of foundational user needs so that the entire journey is considered at the earliest stages of development.

A comprehensive understanding of the user enables the team to determine how these needs can be most effectively

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addressed, whether through the device, a software capability or with an interplay between the two augmented by other assets. This approach helps ensure developed technologies are not only meeting actual market needs; they're doing so in an optimal way – eliminating potential redundancies and conflicts that are inevitable when developing device and software in isolation.

Understanding, characterising and prioritising user needs is best achieved through applied ethnography (Figure 1) which consists of a combination of interviews and observation within the context of use. This method can yield a deep, longitudinal understanding of the patient journey (Figure 2) – from diagnosis to treatment selection, onboarding and ongoing use. With an emphasis on system touchpoints like education/training materials, secondary packaging and device interaction, the patient journey can then be leveraged as a critical early-stage decision-making tool.

Figure 1: Applied ethnography helps developers learn about the context of use and the patient journey in self-administration as the foundation for a connected device strategy.

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

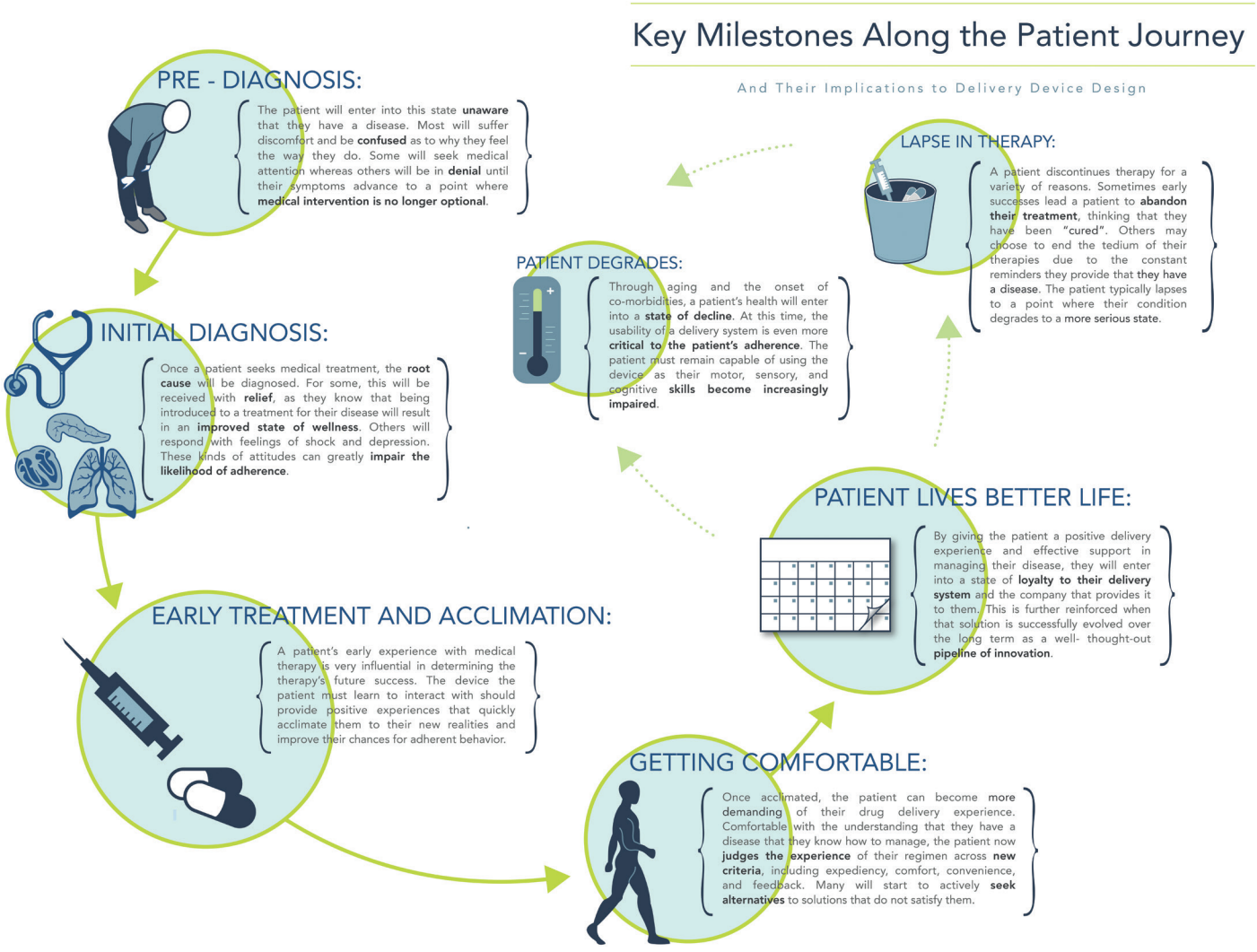

Figure 2: The output from ethnography is a patient journey map that identifies opportunities for improving user experience or mitigating risk, including by using connected solutions.

> "User needs should be characterised as soon as there is a known target patient population."

While usability testing activities are well understood when it comes to device selection and are critical at this stage, discovery research is a fundamentally different type of activity that seeks to define and understand user needs rather than help ensure they are met. User needs should be characterised as soon as there is a known target patient population – to most effectively drive the development of solutions covering the device, connectivity, mobile applications, data analytics and enhanced training that address the whole of the patient journey.

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

This is particularly important when determining where the integration of connectivity and data analytics can meaningfully support the experience. The road map also becomes the foundation for later requirements definition for the device, the mobile application and any other clinical interface required, ensuring that requirements stem from user needs, rather than known technical capabilities and limitations.

The benefits of taking a user-needs approach in a connectivity strategy include:

- Helps developers ensure that all elements of a device strategy for a new drug product effectively address user needs optimally and holistically
- Provides early guidance on device selection (for platform devices) or organic device development requirements as well as gaps that need to be addressed by packaging, instructions for use, training and areas where connectivity can be impactful
- Identifies potential areas of user-based risk that may be present in clinical trials and in market so they can be mitigated as early as possible in development
- Works as the basis for developing a data analytics strategy that harnesses the insight into what elements of disease state management are most meaningful and worth of measurement for a particular application.

Ultimately, this approach drives efficiency in development as both commercial and research and development teams can address key portions of the strategy proactively to ensure all meaningful aspects of the patient journey or healthcare provider experience are enabled to support the ideal envisioned care model – and not used as a mitigation to a substandard experience or risk.

This will also benefit either novel or platform devices with connectivity features as a means of commercial differentiation, particularly in biosimilar or generic applications where multiple entrants may be using similar (or identical) devices.

ABOUT THE COMPANY

Insight Product Development is a design innovation consultancy focused on the medical device and drug delivery sectors since 1988. Capabilities include human factors engineering, design research, industrial design, engineering and prototyping. Insight supports its clients' device strategy across novel and platform devices. The company has expertise in contextual research and human factors driven understanding of the patient journey as well as design and development of autoinjectors, wearable injectors and inhalation devices across multiple chronic disease states.

ABOUT THE AUTHORS

Mark Tunkel is a Partner and Director of Business Development at Insight Product Development. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharmaceutical industry, Mr Tunkel has advised many of the world's leading companies on their product development and innovation strategies with an emphasis on driving realisation and the most favourable business outcomes.

Carolyn Rose is the Director of Research and Strategy at Insight Product Development. With 18 years as a design researcher, she has consulted with hundreds of clients generating meaningful research insights and defining actionable strategic opportunities. Over the last 10 years at Insight, Ms Rose has led the research team to better understand the behaviours, expectations and motivations of patients and clinicians, as well as the environments, attitudes and trends that shape them.

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CONNECTED DEVICES – MEDICATION DELIVERY JUST GOT PERSONAL

Thierry Decock, Device Development Leader, and Hadrien Gremillet, Senior Marketing Analyst, both of Nemera, explore how the obstacles to the adoption of connectivity can be overcome and how connected devices can deliver truly patient-centric care that will clearly improve adherence rates, whilst demonstrating a clear cost benefit to the pharmaceutical partner.

Personalisation has become an essential component in people's everyday lives and technology is a key enabler of the ability of drug delivery device and pharma companies to deliver that level of personalisation. From wellbeing apps to connected homes, people are demanding technology that serves them personally. It could be argued that for people with chronic conditions there is no more important area of their lives where personalisation can make a difference than their medication.

It is no secret that low patient adherence has been identified as a substantial problem, causing significant yet avoidable healthcare costs to payers and healthcare systems and, most urgently, impacting quality of life for affected patients failing to control their conditions.

Whilst the concept of connected devices is widely accepted, barriers to the implementation of such technology remain, in particular regarding the demonstration of cost versus benefit, and the transference of technology across different therapy areas.

It's impossible to deny that poor patient adherence is a problem. Yet there is a significant issue in defining its true economic impact because differences in the methods adopted by various studies make understanding the true picture difficult. For example, one source estimates the annual costs of medication non-adherence range from US$100-290 billion (£79-229 billion) in the US[1] whereas another estimates the equivalent figure for Europe to be just €1.25 billion (£1.11 billion).[2] It is highly unlikely that the cost of non-adherence in Europe is really 100-fold smaller than in the US, but differing analytical methods have led to wildly different estimates. All the time there is no universally agreed measure, the argument for defined investment in a solution such as connectivity can always be challenged.

Nevertheless, even though the figures for cost vary, the abundant data on the scale of non-adherence are consistent in that they paint a picture of a significant problem. For example, worldwide, nearly half of all adults and approximately 8% of

> "All companies surveyed reported investing in device connectivity, with 73% expecting R&D spending on software development to be more than 10% of budgets by 2020."

> "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments."

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children aged 5–17 years have a chronic condition[3] and it is estimated that non-adherence can be as much as 50% in long-term therapies for chronic illnesses.[4] 10% of hospitalisations in older adults are attributed to medication non-adherence[5,6] resulting in three extra medical visits per year and an increased annual treatment cost of US$2,000.[7] In diabetes, the estimated cost savings associated with improving adherence range from $661 million to $1.16 billion.[8] And these data don't count the personal cost to patients who, for any number of reasons, fail to take their medication properly.

DIGITAL MEDTECH DELIVERS ANSWERS

It is interesting to note that connected drug delivery devices themselves are likely by far the best, cheapest, most reliable means available to us for gathering the very data that would demonstrate most reliably, accurately and in the most detail, the true extent, nature and cost of non-adherence. This situation could be seen to represent a frustrating "Catch 22" – the best way of gathering the data that provides the evidence supporting the adoption of connectivity is to adopt connectivity.

At first glance it is almost impossible to quantify because the market is so immature – all of the device manufacturing companies have invested heavily in concept creation, but there are still relatively few connected drug delivery devices on the market. That said, as connected technology is gradually being adopted in the drug delivery sector, the body of knowledge about non-adherence is beginning to grow accordingly. And we can learn from other innovations, such as visual reminders, and the impact they have had on adherence and cost benefit to the healthcare community.

For example, data from electronic monitoring systems has revealed that there are six patterns of patient adherence – resulting in "the rule of one sixth". Approximately one sixth of patients come close to perfect adherence; one sixth take nearly all doses, but with irregular timing; one sixth miss an occasional single daily dose and have some timing irregularity; one sixth take drug breaks every three to four months, with occasional omissions of doses; one sixth have one or more drug breaks monthly, with frequent omissions of doses; and one sixth take few or no doses, but may report that they are compliant.[9]

> "There is a clear consensus that traditional considerations such as ergonomics and handling continue to be important, but putting novel technology in front of users provides new insights and reveals different wants and needs."

A literature review, which examined the effect of reminder systems on patient adherence to treatment, 11 published randomised controlled trials were found between 1999 and 2009 which measured adherence to a daily medication. Analysis showed a statistically significant increase in adherence in groups receiving a reminder intervention compared with controls (66.61% versus 54.71%). Eight of the 11 studies showed a statistically significant increase in adherence for at least one of the reminder group arms compared with the control groups receiving no reminder intervention.[10]

Chronic management of asthma is typically associated with adherence rates of less than 50%, with increased risk of mortality, meaning that both the scope for improving adherence in this area, and the benefits of doing so, are clear. Charles *et al* investigated whether an audio-visual reminder could improve adherence to inhaled corticosteroid therapy in asthma. In the study, 110 adults and adolescents with asthma were randomised to receive 24 weeks of inhaler therapy via a metered-dose inhaler with or without an audio-visual reminder function.

The study demonstrated a positive benefit of the reminder system. The absolute difference in median percentage adherence between the two groups was 18% (95% CI, 10-26%; P <.0001). Furthermore, the proportion of subjects taking >50% of their medication was 95.5% in the intervention group compared with 71.7% in the control group. The proportion of subjects taking >80% of their medication was 88.6% in the intervention group, compared with 39.1% in the control group. Finally, the proportion of subjects taking more than 90% of their medication was 63.6% in the intervention group compared with 19.6% in the control group, an approximately three-fold improvement.[11]

INDUSTRY ADOPTION IS UNDERWAY

In 2018, The Deloitte Center for Health Solutions and the US Advanced Medical Technologies Association (AdvaMed) surveyed 22 medtech companies to understand how R&D leaders are responding to key trends such as the need to improve efficiency and reduce costs as health systems, patients, and payers require evidence to justify product value and reimbursement. All companies surveyed reported investing in device connectivity, with 73% expecting R&D spending on software development to be more than 10% of budgets by 2020.[12]

Companies are investing more than ever in connectivity as evidence detailing the economic consequences of non-adherence continue to grow. Haynes *et al* went as far as to suggest that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments."[13]

Some drug delivery device companies, such as Nemera, are already ahead of the curve. Renowned for delivering patient-centric device designs, Nemera has already developed proof-of-principle connected devices for nasal and ophthalmic drug delivery as well as injection. The company has invested in connected and smart devices based on the strong belief that the technology directly benefits patients by improving adherence.

Value Through Application Across Different Therapy Areas

Referring back to the Deloitte study, it is anticipated that, by 2020, companies will be devoting a significant portion of R&D budgets (>10%) to software development.[12] Nemera believes that investment can be maximised by efficiently delivering common technological "building bricks" that can serve multiple device categories, themselves each serving a still larger number of therapy areas.

Nemera has an established global reputation in, and a first-class device portfolio spanning, the parenteral, nasal, pulmonary and ophthalmic delivery device categories, amongst others. The company manufactures hundreds of millions of devices and components each year, for numerous therapeutic markets worldwide.

In the same way that Nemera uses its expertise and know-how built up in one drug delivery device category to inform developments in others, the technical and functional knowledge developed around connectivity as applied to one device can be leveraged for others. The e-Novelia® connected add-on for ophthalmic delivery, for example, delivers adherence monitoring, dosage history, digital tutorials and medication reminders – designed to improve the personal experience and increase adherence. This knowledge and experience has been, and is being, applied in the development of connected nasal (e-Advancia®) and injection devices, amongst others. The ability to transfer the technology wherever it's needed to additional device categories and additional therapy areas increases efficiency, drives down costs, and maximises the return on R&D investment (Figure 1).

Figure 1: Electronic features are transferable across multiple device platforms such as nasal, ophthalmic and parenteral

Users Contribute to Device Aesthetics and Functionality

The best way to deliver connected devices that can truly personalise the treatment experience is to ask the people who are going to use it what they want. This is a key characteristic of Nemera's approach – consulting both clinicians and patients in the early phases of development. There is a clear consensus that traditional considerations such as ergonomics and handling continue to be important, but putting smart novel technology in front of users provides new insights and reveals different wants and needs. Examples include the desire to replace paper prescriptions with automated electronic ones, and ideas such as step-by-step video instructions on use, rather than complicated guidance notes, are also frequently mentioned. Overall the message from users is clear – enable us to take control of our own care.

New Payment Models Influence a Wave of Innovation

In addition to personalising the device user experience, connectivity is already beginning to influence industry commercial practices and processes. For example, connectivity facilitates the adoption of novel payment / reimbursement models, enabling them to be personalised in that they can be tailored to individual patient behaviours (including adherence and compliance) and even treatment outcomes.

The Deloitte study revealed some interesting perspectives. 68% of surveyed companies are shifting their focus on innovation because of reforms to payment models and care delivery. These payment models can positively impact both caregivers and patients. For hospitals and clinicians, incentives to deliver better quality care while also delivering better value are being explored with metrics such as improved outcomes, reduced costs, decreased post-treatment complications and increased procedural efficiency cited as motivations for this move. 64% of surveyed companies also reported discussing, piloting or implementing value-based contracts with payers or providers, all tied closely to device performance and patient outcomes where patients are rewarded for greater adherence.

CONCLUSION

Whilst barriers to their adoption exist, not least around the justification of the cost versus benefit, connected drug delivery devices undoubtedly present opportunities to tackle the vast problem of medication non-adherence, to facilitate novel payment models, and to take the personalisation of medication to a new level not previously imaginable in the pre-connectivity era.

As an early adopter, with the ability to leverage know-how and capabilities across a broad technology portfolio spanning most drug delivery categories, and transfer technological advances across numerous therapy areas, Nemera is perfectly positioned to overcome the barriers that remain, maximising the return on investment in R&D, driving the development of connected drug delivery devices, and their subsequent adoption by industry. The potential for improving patient quality of life and health outcomes, and equally the impact on healthcare costs, is compelling.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of leading-edge delivery devices. Its vision is to be the most patient-centric drug delivery device company. Working with the world's leading pharmaceutical, biotechnology and generics companies, Nemera's portfolio of services and products is comprehensive, including ophthalmic, nasal, inhalation, dermal and transdermal, and parenteral categories. Committed, creative and patient focused, Nemera's Innovation Centre drives its development, delivering commercialised systems, customised design and development, and customer IP manufacturing.

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ABOUT THE AUTHORS

Thierry Decock graduated as a Mechanical Engineer from INSA in Strasbourg, France. After gaining experience in the telecoms and automotive industries, he joined Nemera in 2009 where he started to work in Development and Innovation. Today, Mr Decock is Device Development Leader, heading up design activities. He participated in the development of Nemera own-IP products such as Novelia and the connected e-Novelia® and e-Advancia® electronic medical devices. He also works on customer inhalation and injectable product development projects.

Hadrien Gremillet works in the strategic department of Nemera as a Senior Marketing Analyst. He is responsible for Nemera's electronic strategic projects. Prior to Nemera, Mr Gremillet spent three years as an entrepreneur in the mobile internet sector and three years as a consultant at McKinsey & Company. He graduated from Ecole des Mines de Saint Etienne (France) and ESSEC Business School (Paris, France).

Elcam
Drug Delivery Devices

ADDING CONNECTIVITY TO DRUG DELIVERY DEVICES

Connectivity in drug delivery devices may be changing from being the exception to the rule. In this article, Tsachi Shaked, Managing Director and Chief Business Officer of E3D, explores how – as the trend towards moving healthcare from the hospital to the home continues – more healthcare providers are assessing the viability of connected drug delivery devices.

The trend towards home-based care is being driven by healthcare providers as well as patients. For providers, it makes better economic sense to enable patients to be treated at home as it cuts down on costs and frees up both beds and the valuable time of healthcare professionals. For patients, it eliminates the inconvenience of having to make frequent trips to hospital or a clinic, saving time and money, whilst allowing treatments to be carried out in a more comfortable and familiar environment. Many patients with chronic conditions have indicated that they would prefer this option – a June 2017 industry insight report from Ericsson ConsumerLab showed that 39% of chronic condition patients prefer online consultations to face-to-face meetings.[1]

> "39% of chronic condition patients prefer online consultations to face-to-face meetings.[1]"

Progress in using connected drug delivery devices can currently be seen with inhalers and autoinjectors. In these use cases, responsibility for drug administration has fallen primarily on the patient, their family members or caregivers. But while this development has freed patients from visits to their healthcare professional or hospital, it has also reduced the opportunity for clinicians to monitor whether patients are administering drugs on schedule and in the right amount. Encouraging and supporting patient adherence continues to be a challenge and provides a further compelling case for adding connectivity to drug delivery devices.

> "Whilst failure to take medication has obvious implications for a patient's health, it also impacts on healthcare payers."

PATIENT ADHERENCE

A variety of factors contribute to non-adherence with a prescribed treatment regimen. Patients sometimes simply forget to take their medication at the right time, while others may not correctly understand the dosing instructions. Patients may fail to complete the full course of a treatment, which can greatly impact its efficacy. While training can go a long way towards helping patients understand how to successfully self-administer and address possible fears and concerns, the problem of forgetting to take medication is less easily addressed and it often falls to family members or other caregivers to ensure medication has been taken on time.

Whilst failure to take medication has obvious implications for a patient's health, it also impacts on healthcare payers who have a clear interest in finding ways to improve the cost-effectiveness of healthcare. About half of patients suffering chronic

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illness do not take their medication as prescribed, costing US$100-300 billion (£77-236 billion) annually in avoidable direct healthcare costs in the US alone, according to Springboard.[2]

CONNECTING DRUG DELIVERY DEVICES

Connected consumer devices have been around for some time, enabling consumers to control everything from their home security system to their garden irrigation system by remote control. While convenient, these systems are often vulnerable to hackers and represent a very real security concern.

As DCA Design pointed out, when it comes to medical and pharmaceutical devices, connected devices are a very different proposition. To make it to market, new products need to be demonstrably safe and effective – and regulators demand extensive evidence of this. Likewise, it's also imperative that medical devices are secure, to ensure both safety and confidentiality. However, DCA noted that the benefits of being able to pass information to or from a drug delivery service open up a number of interesting possibilities. Beyond dose reminders, the addition of sensors enables the monitoring of a patient's condition for side effects or to evaluate the effect of regimen changes.[3]

PRESERVING PATIENT PRIVACY

It would be understandable for pharmaceutical companies to welcome an opportunity to make use of injection data from a connected device to enhance the design of future products. But while connecting drug delivery devices to the internet represents a technically viable solution, it also opens up valid privacy concerns. Recent scandals in the social media sphere have made consumers very wary of who is collecting their data and what it's being used for. As healthcare digital strategist Tom Lawrie-Fussey of Cambridge Design Partnership pointed out, context is key when it comes to creating patient-friendly drug delivery devices. It would be a mistake to assume that patients want to have an interaction with your organisation each time they self-administer.[4]

> "There's no doubt that connecting devices to smartphones offers a world of possibilities."

Figure 1: Flexi-Q eMU-P electromechanic re-usable autoinjector and disposable PFS-based cassette.

This ultimately becomes a consideration of what data is being collected and presented – as well as who is to be granted access to that information. The onus falls on pharmaceutical company suppliers to ensure they have consent before collecting or using patient data. This means asking some key questions, such as: Who will have access to the patient's data? How will the data be used? How will it be stored? Has the patient given consent for the data to be recorded and shared? These issues must be addressed by pharmaceutical companies to ensure that patient information is only provided to those authorised to receive it and to ensure that patient confidentiality is maintained.

There's no doubt that connecting devices to smartphones offers a world of possibilities, since all the features of the phone and its related apps can be used – encouraging better adherence, improved patient outcomes and enhanced usability as well as reducing healthcare costs. The benefits are great and growing, as new applications for connected drug delivery devices are brought to market.

STRATEGIES FOR IMPLEMENTING CONNECTIVITY IN DRUG DELIVERY DEVICES

Springboard identified three main strategies for implementing connectivity in a drug delivery device – the first being an add-on, typically to an existing design. The second strategy was upgrading an existing device, which is integrated but does not change the core functionality or use case. The third strategy identified was built-in connectivity, which can change the core functionality and use case. However, Springboard noted that devices with built-in connectivity could be more difficult to make re-usable, which adds inherent cost and environmental impact.[2]

NEXT-GENERATION ELECTRONIC MULTI-USE AUTOINJECTORS

Various solutions are under development to meet the need for connected drug delivery devices. One such device – the Flexi-Q eMU-P electronic autoinjector designed by E3D – was developed following extensive usability tests involving patients from various groups (gender, age, illness, disability, etc.) All aspects of the Flexi-Q eMU-P autoinjector, including shape, convenience and ease of use, location of buttons, size of display and ideal ratio between injector width and display size were extensively tested and optimised (Figure 1).

The result is a compact, user-friendly and easy-to-use device, designed to solve one of the key reported reasons for

non-adherence – failure to understand how the device works. The large-display LCD screen shows each stage of the injection process, providing the patient with clear instructions in real time (Figure 2.)

Since one of the major problems with adherence is patients simply forgetting to administer the dosage (or failing to remember whether they have done so), the Flexi-Q eMU-P device also provides reminders and injection history (Figure 3). This data greatly assists with compliance, verifying that doses have been administered and giving patients peace of mind.

Specialised mobile apps (Figure 4) enable data regarding injection habits and patient compliance with the prescribed treatment programme to be enhanced. Reminders, logs and injection data can be automatically sent to patients, family members and carers as well as healthcare professionals. Data such as the time, quantity, drug type and whether a full or partial injection was delivered can all be recorded and sent from the Flexi-Q eMU-P via a wireless connection to remote data storage.

Sending data collected from a drug delivery device to a smartphone not only provides patients with a larger screen size on which to view information, if needed – it also offers the ability to provide explicit usage instructions in audio or visual format.

Figure 2: Injection stages and instructions on screen.

IMPROVED PATIENT SAFETY

Once the patient lifts the Flexi-Q eMU-P autoinjector from the body, the injection process is automatically stopped (even if injection has not been completed) and the cassette in which the drug-filled syringe is contained becomes void. This prevents the patient re-injecting with a previously used syringe and cassette at a later stage. To further ensure patient safety, the disposable cassette includes an RFID component, on which the pharmaceutical company can encode the drug name and dosage, expiry date and anti-fraud barcode, as well as various permissions and definitions. If the drug has expired or is a counterfeit, the Flexi-Q eMU-P will issue a warning and will not allow the injection to proceed.

Additional features include the ability to measure drug temperature before injection is permitted, and the ability for patients to control injection speed in the interests of comfort and reduced injection pain. Drugs with a wide range of viscosities can all be injected using the same device platform.

PERSONALISING PATIENT CARE

E3D autoinjectors are designed to provide each patient with effective care according to their own specific treatment programme. By making the product safe and easy to use, reducing needle phobia, ensuring delivery of the full dosage and enabling better therapy follow-up, the quality of care, patient safety and adherence to therapy can all be improved.

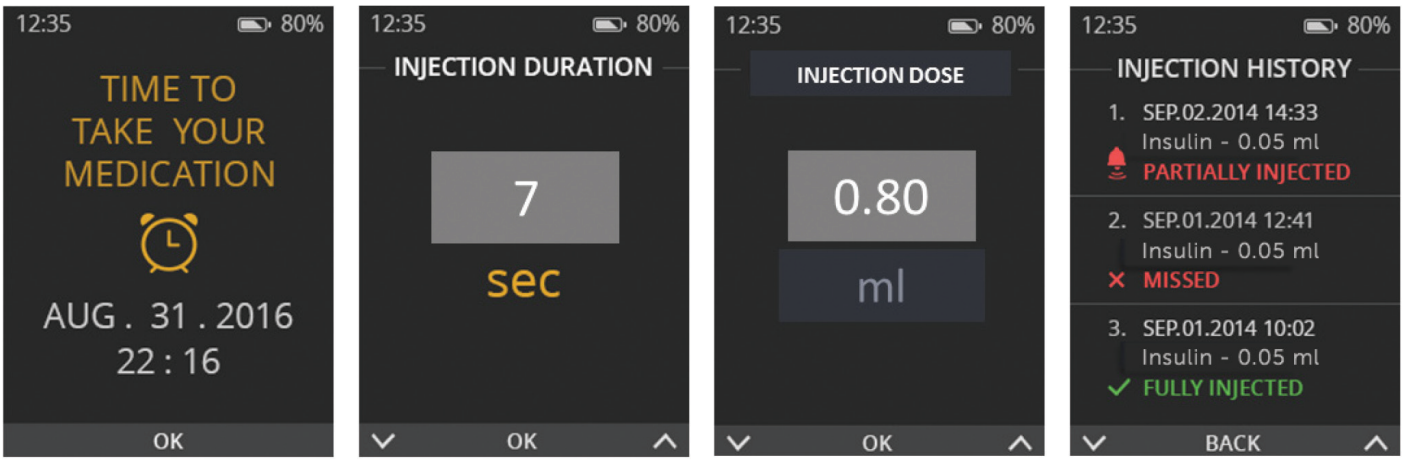

Figure 3: Reminders, data and history display.

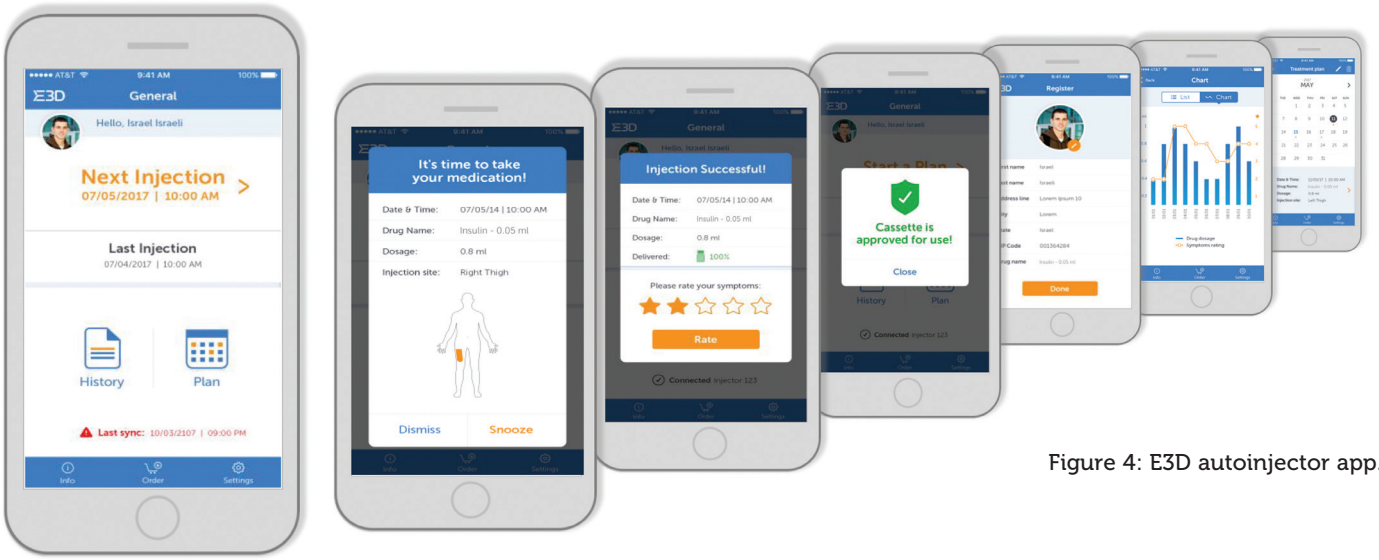

Figure 4: E3D autoinjector app.

By enabling full supervision of the amounts of drug used, injection logs, reminders to patients, and reports to family members and physicians, every participant in the entire healthcare system can become more involved (even at a distance), thus providing enhanced and effective care. The software enables control of dosage and other therapeutic factors, customising them to individual patient needs after a specific follow-up of injection logs and analysing the therapeutic results attained. This is, in effect, one step closer to so-called precision (or personalised) medicine. Adjustments can be made by patients and/or doctors, depending on parameters predefined by the drug company, allowing high-quality treatment to be administered from a distance.

ADDRESSING ENVIRONMENTAL CONCERNS

E3D's autoinjectors reduce the storage and waste footprint for both drug manufacturers and patients, thereby reducing any negative environmental impact. As the demand for improved patient compliance and quality of care grows, there's increasing awareness of production costs. E3D's re-usable autoinjectors provide an effective solution to the costs associated with self-injection. Disposing of only the single-use cassette element (rather than the entire injector device) after an injection reduces the cost per injection significantly, creating considerable economic advantages.

VERSATILE PRODUCTS TO MEET PHARMA COMPANY NEEDS

The selection of drug delivery devices depends on numerous factors, including formulation, primary package, dosing — and the ability to ensure safe and effective usage. E3D provides re-usable autoinjector units, single-use cassette components, automatic final assembly equipment (for loading drug-filled syringes or cartridges into the cassette) and software for electronic labelling (i.e. RFID chip on cassette) in accordance with each company's requirements.

> "The ability to provide home-based self-injection has many benefits."

The ability to provide home-based self-injection has many benefits: it helps the healthcare industry save costs otherwise associated with clinic-based treatment and offers patients enhanced independence via self-treatment. Appropriate use of smart, connected delivery devices enables remote monitoring to ensure treatments are being administered on time as well as delivering the desired therapeutic results.

Connected drug delivery devices are already here: it remains to be seen to what extent they are embraced by healthcare providers and pharmaceutical companies as well as how they are accepted by the patients they serve.

ABOUT THE COMPANY

E3D is a sister company of Elcam Medical ACAL, developing and manufacturing autoinjectors and patch pumps for biologic and biosimilar drugs using moulding injection and assembly know-how, engineering and technologies of Elcam Medical as well as its well-established quality assurance and quality control. E3D believes in a growing need for customised autoinjectors that enhance the therapeutic and commercial value of drugs and their lifecycles. Customisation and flexibility are at the core of its product development.

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Elcam Drug Delivery Devices

Adding connectivity to drug delivery devices

Flexi-Q eMU-P

Electromechanical multi-use Auto-Injector for drugs in prefilled syringes

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Where everything connects

PUSHING THE BOUNDARIES OF INFUSION PUMP INTEROPERABILITY

Interoperability is not a new concept for infusion pumps. But in many cases hospitals have been slow to embrace the full potential of connectivity. When is this likely to change? What will hospitals need when it does? And where should infusion pump manufacturers focus innovation efforts in the meantime? These questions are difficult to answer but important to ask. In this article, Tim Frearson, Senior Consultant at Sagentia, considers the options.

It's more than 15 years since smart infusion pumps were first introduced. Wireless connectivity offered exciting new opportunities to improve the management of pump populations and integrate them with the wider healthcare system. Instead of operating in isolation, multiple pumps could be joined up with a single server, enabling software revisions to be uploaded remotely. And monitoring several patients' infusion status from a single station without having to visit the bedside was a tantalising prospect.

> "Unfortunately, parachuting new technology into healthcare environments rarely delivers tangible improvements unless the workflow around it also changes."

These were just some of the promised benefits, and it was expected that they would quickly translate into better efficiency and treatment. Yet just because the technical capabilities exist, it doesn't necessarily mean they are embraced. Unfortunately, parachuting new technology into healthcare environments rarely delivers tangible improvements unless the workflow around it also changes. So a modern infusion pump with a digital maintenance log might be returned to the technical team with a handwritten label that simply says "broken". And, most of the time, nurses still dash to the bedside to differentiate between critical, non-critical and false alarms when infusion pumps need attention.

AN ONGOING JOURNEY

In 2014, Tim Vanderveen (now retired but then Vice-President of the CareFusion Center for Safety and Clinical Excellence in San Diego, CA, US, since acquired by BD), described a future vision for infusing patients safely:[1]

- All infusion pumps will be connected to a hospital wireless network
- All infusion pumps will be associated with a specific patient and clinician
- Image recognition (barcode, radio frequency identification) will be used to identify the intravenous (IV) drug/concentration being infused
- Infusion pumps will be automatically programmed from the pharmacist-reviewed physician's order
- Smart pump safety software will protect against programming errors during titrations, bolus dosing and STAT (i.e. urgent) infusions, and in operating room procedure areas
- All IV infusion data will be automatically recorded in each patient's electronic medical record in near-real time
- Infusion status of all infusions will be available to pharmacy to facilitate IV compounding
- Discrepancies between in-process infusions and computerised prescriber-order-entry orders will be identified for resolution
- Critical lab values and missing lab values that impact IV infusions will be immediately communicated to the appropriate caregiver
- All patients receiving high-alert IV medications will be continuously monitored with appropriate vital sign monitoring, even outside the ICU
- Infusion pump alarms and alerts will be sent directly to the appropriate caregiver(s)
- Infusion pump performance issues will be automatically communicated to biomedical staff.

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Five years later, many of these points are still futuristic for most hospitals.

Vanderveen's paper is quick to point out that interoperability is a journey, not a destination. This is true of all transformative developments in the digital economy, and the sheer scale of healthcare organisations – coupled with the importance of patient safety – makes it difficult to introduce changes at pace.

However, demands to deliver better patient outcomes whilst improving healthcare efficiency continue to escalate. This means at some point the journey will accelerate. As healthcare systems become more digitally enabled, infusion pumps could represent an effective starting point for more sophisticated and integrated closed-loop systems.

As Vanderveen said: "Several factors make infusion pumps an ideal starting point for interoperability: the very large number of devices in a typical hospital, the critical importance of the drugs being infused, the growing base of wirelessly connected pumps already installed and their uniquely bidirectional information transfer, both to and from the pump."[1]

He added that development could manifest itself in various ways, depending on individual hospitals' priorities. One might choose to focus initially on the ability to send alarms directly to the clinical team. Another might consider interfacing smart pumps with barcode medication administration systems. The ultimate goal would be a fully integrated, closed-loop medication system – but this would most likely be achieved gradually over time, with small advancements driving cumulative benefits.

WHEN WILL INTEROPERABILITY TAKE OFF?

There are signs that the healthcare sector could be about to reach a tipping point in terms of digital transformation. Deloitte estimates that the Internet of Medical Things market will be worth more than US$158 billion (£121 billion) in 2022.[2] Infusion pumps will certainly form part of this. According to MarketsandMarkets, the global infusion pump market is expected to reach almost $16 billion by 2023, up from $12 billion in 2018.[3]

> "There are signs that the healthcare sector could be about to reach a tipping point in terms of digital transformation."

In this environment, infusion pump manufacturers have many opportunities to develop their product offering. But the million-dollar question is how and where to focus innovation. Is it possible to take device capabilities to a higher level, so they play a more sophisticated role in connected drug delivery? Or would it be better to evolve technologies for easier integration with existing systems? Could closed-loop systems offer new ways to overcome enduring infusion pump challenges, like those associated with air-in-line false alarms? What about addressing variations between different markets and different healthcare segments? After all, infusion pump challenges and demands in an intensive care unit (ICU) setting are quite different from those on a general ward. And there is stark variation in requirements between developing countries and the most developed nations.

It's difficult to know where to start, but you must start somewhere and, when you consider how long it takes for an infusion pump to transition from concept to active operation, time is of the essence. Many businesses and entrepreneurs will be looking to earn a slice of this potentially lucrative market. Unless action is taken, well-established infusion pump manufacturers could suddenly find themselves at a disadvantage, with disruptive new entrants cornering emerging opportunities.

BARRIERS TO INTEROPERABILITY

Various practical and cultural challenges hinder existing smart infusion pumps from achieving more. Finding ways to overcome these could help trigger widespread uptake of interoperability more quickly.

> "Well-established infusion pump manufacturers could suddenly find themselves at a disadvantage, with disruptive new entrants cornering emerging opportunities."

Regional variations

At present, US hospital systems tend to be more progressive than the rest of the world. They have the advantage of large-scale institutions and installations underpinned by multi-million-dollar investments. Other regions, including Europe, are less advanced. The UK's NHS is a case in point. Limited funding, combined with an ageing hospital infrastructure and a diverse mix of devices connecting to hospital systems, means the environment is fraught with problems. Interoperable devices sometimes require *ad hoc* interfaces to support their integration with the wider system and ensure they deliver value. In less developed countries such as Romania and Hungary, caregivers are well-educated and keen to benefit from the improved performance, accuracy and safety associated with the latest devices. However, they lack the infrastructure to exploit capabilities fully.

Practical matters

Interoperable infusion pumps can face conflicting demands, depending on the department where they're deployed. On a general ward, patients are typically connected to one or two infusion pumps. But in an ICU, an individual patient might receive drugs and nutrients from 20 or more devices, so space around the patient bedside becomes a significant consideration.

In some regions, infusion pumps need to be compatible with docking stations. These enable multiple devices to be located efficiently around the bedside, so they don't get in the way of the clinical care team. However, an individual pump may also have to work as a standalone device and operate independently from the docking station – for example, if the patient is to be transferred to a general ward. Furthermore, when multiple smart pumps try to connect to Wi-Fi simultaneously, it poses software architecture challenges. Overcoming technical issues like these could improve usability and act as a stepping stone for infusion pumps to unlock fully interoperable healthcare.

Outside the US, there is still an extensive need for standalone infusion pumps. They may have Wi-Fi capability installed but it's not necessarily used to begin with. Since the typical life of a service pump is seven years, the rationale behind this

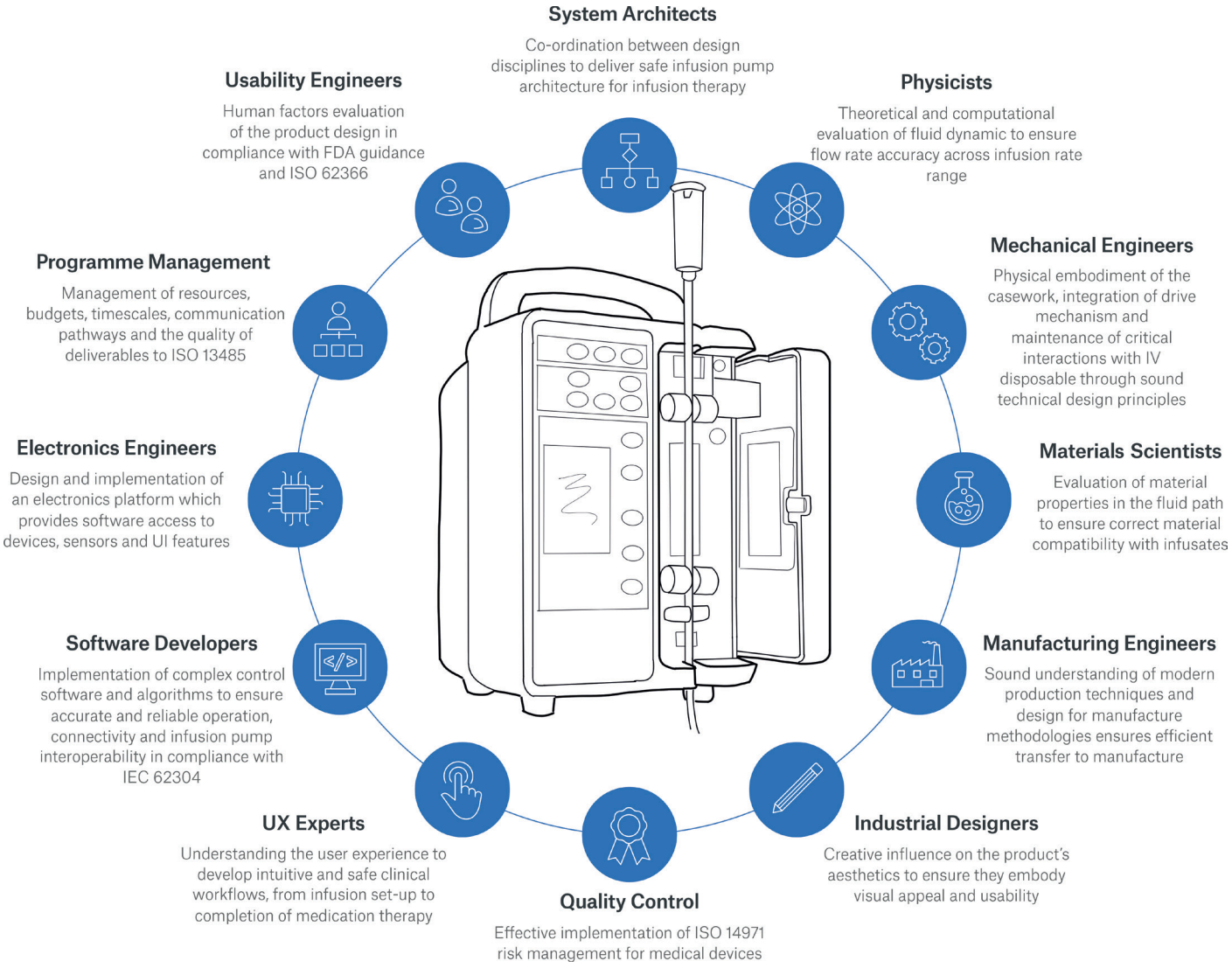

Figure 1: The multidisciplinary skills involved in innovative infusion pump design and development.

approach is sound. Within that timeframe, infrastructures may evolve, meaning devices need to be futureproofed so connectivity can be leveraged later. We explored device connectivity trends in detail in a 2018 article for *ONdrugDelivery*.[4] Developing infusion pumps with scalable capabilities – so they can easily adapt to healthcare environments as they change – could be a prudent move for manufacturers.

Cybersecurity

Cybersecurity issues are a vital consideration for all smart medical devices. The US National Cybersecurity Center of Excellence (NCCoE) and National Institute of Standards and Technology (NIST) have flagged specific risk factors related to connected infusion pump ecosystems: "With an increasing number of infusion pumps connecting to networks, the vulnerabilities and risk factors become more critical, as they can expose the pump ecosystem to external attacks, compromises, or interference."[5]

This has led the NCCoE to develop an "example implementation". It demonstrates how healthcare delivery organisations can use standards-based, commercially available cybersecurity technologies to protect the infusion pump ecosystem, including patient information and drug library dosing limits.[5] Infusion pump manufacturers must address both patient safety and security when developing smart products. Software architecture decisions made early in the process have a significant bearing on this.

MULTIDISCIPLINARY INNOVATION

Overcoming challenges and maximising opportunities for infusion pumps in the digital age demands a wide range of specialist expertise. Figure 1 shows the extent of multidisciplinary input required, and the role each element plays.

Historically, infusion pumps have had long development lifecycles led by mechanical, electrical and software engineering disciplines. But to achieve the closed-loop interoperability vision, further emphasis on the wider system is required. This means systems architects, software developers and human factors experts have an increasingly important role to play. Developing architectures that can cope with multiple devices competing for Wi-Fi bandwidth is a complex challenge which has the potential to directly impact patient safety. Cybersecurity is also a serious concern. Manufacturers need to draw on the skills of experienced systems engineers and architects who can make effective and informed decisions in this rapidly evolving environment.

Input from physicists, materials scientists, and simulation and analysis experts is also required at an early stage in the innovation process. Their expertise in

> "Drawing on a wide range of skills can reveal new opportunities for innovation that might otherwise be overlooked."

matters such as fluid dynamics (to ensure efficient mechanism characteristics across wide flow-rate ranges, whilst maintaining fluid-flow accuracy) and material properties (to ensure compatibility with infusion medication) plays a critical role. Having all this expertise available under one roof ultimately accelerates the product development process and timescales.

Drawing on a wide range of skills can reveal new opportunities for innovation that might otherwise be overlooked. Take the air-in-line issue. It's vital that infusion pumps alert medical staff if there is a risk of a large air bubble entering a patient's bloodstream. However, sensors can be triggered unnecessarily on a frequent basis, which creates the potential for nuisance alarms and can be disturbing for patients.

The combined knowledge of materials scientists, chemists and physicists could identify which aspects of pumps, their consumables and infusion medication exacerbate the false-alarm problem. For example, the fluidic properties of some drugs mean they are prone to forming harmless microbubbles on the inside surface of the IV line that may "bounce" in the location of the air-in-line sensor due to the action of the pump mechanism. Also, some IV tube materials suffer from the "cold weld" phenomenon where the tube takes on a permanent set after being in use for a period of time. This can result in the IV tube geometry decoupling from the air-in-line sensor so that air pockets form between the outside of the tube and the sensor.

Both the above scenarios can result in the detection of air and subsequent false alarms – but collaborative multidisciplinary innovation might eradicate such problems. Overlaying developments like this with elements of Vanderveen's future vision for infusing patients safely in a closed-loop system could truly revolutionise healthcare outcomes and efficiency, one step at a time.

Co-ordinating this depth and breadth of technical input in a cohesive way is no mean feat, but setting robust design controls at the outset of an innovation project helps. It ensures complex needs and requirements are addressed properly and in a timely fashion. When barriers and potential problems are identified at the outset, their avoidance or elimination becomes central to the strategy. However, if they emerge towards the end of the process, they can stall a project in its final stages. This can lead to significant financial repercussions, or even prevent FDA market approval.

CONCLUSION

It's fair to say that the needle hasn't moved significantly since Vanderveen set out his future vision for infusion pumps in 2014. But, to quote Bill Gates: "We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten. Don't let yourself be lulled into inaction."[6] The Internet of Medical Things is gathering momentum, and healthcare systems will transform – albeit at a slower pace than other sectors. To remain relevant as this unfolds, infusion pump manufacturers need to develop a multidisciplinary mindset that supports and accelerates innovation.

ABOUT THE COMPANY

Sagentia is a global science, product and technology development consulting company that helps its clients maximise the value of their investments in R&D. Sagentia partners with clients in the medical, consumer and industrial sectors to help them understand the technology and market landscape, decide future strategy, solve complex science and technology challenges, and deliver commercially successful products. Sagentia employs over 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has 16 European and North American offices, two UK-based, dedicated R&D innovation centres and more than 400 employees. Other Science Group companies include Leatherhead Food Research, TSG Consulting, Oakland Innovation and OTM Consulting.

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ABOUT THE AUTHOR

Tim Frearson is a Senior Consultant at Sagentia. He has over 17 years of experience in medical device development. During his career he has been responsible for the design of electromechanical systems for intravenous drug delivery devices, has led Operational Excellence Lean Six Sigma process improvement projects focused within R&D and manufacturing, and project managed the next-generation platform for a major infusion pump manufacturer in the US. Today, he works as a programme manager with a focus on delivering complex medical device development programmes for Sagentia's clients.

CUSTOMISED INFUSION PUMPS: THE FUTURE OF SELF-ADMINISTRATION?

In this article, Shaul Eitan, Chief Executive Officer, Avoset Health, explores the challenges of home infusion and examines how customisation and connectivity could help provide a solution.

Infusion self-administration at home has emerged as an important option for improving patient satisfaction and reducing the strain on overcrowded hospitals. However, our current approach has also missed opportunities to achieve significant improvement in the level of home care that the medical industry can provide. If we expand our mindset regarding home infusion to include other trends in the industry – such as patient engagement, connectivity and big data – patients, clinicians and the pharmaceutical industry could all stand to benefit.

PROBLEM: COMPATIBILITY AND COMPLIANCE

There are two essential challenges when it comes to home infusion solutions – compatibility and compliance. The issue of drug compatibility is the burden of pharma companies that are developing new specialised drugs for advanced treatments. Some of these drugs face major hurdles to be infused in hospital, let alone at home, due to a drug's make-up and its reaction to environmental conditions. As such, pharma companies developing these speciality drugs with specific compatibility requirements must find customised infusion solutions that can protect and deliver the drug without harming its integrity.

The other challenge – compliance – is the burden of the patient. We know that, for a number of reasons, patients struggle to administer medicine correctly, creating risks during home infusion therapies.[1] Even when a patient is doing their best to follow the doctor's orders, they may still encounter issues such as line complications and adverse reactions to medication. The urgency of this problem increases when considering that doctors rely on patient self-reporting to track infusion compliance and to know whether to continue treatment. It should be concerning to anyone working in the field that around 20% of home infusion patients end up back in hospital at least in part due to misuse of their infusion device.[2]

> "There are two essential challenges when it comes to home infusion solutions."

Existing home infusion devices only partially address these two issues. While they ensure that many different drugs are compatible, they fail to meet the needs of more specialised medicines, which are becoming more common. As such, the number of drugs deliverable through home infusion is limited.

Furthermore, in device manufacturers' pursuit of widespread compatibility, infusion devices include many options that are irrelevant for a given patient. Patients are forced to either receive help from a healthcare professional or to navigate the adjustments themselves. Each complicating factor increases the chances of a patient not complying with infusion instructions.

Compliance, for the reasons mentioned above, is also a major challenge for the home infusion industry. Devices have no method of providing information about compliance and are therefore creating a gap in which patients can be harmed by home infusion treatments.

Despite great advances, the current approach to home infusion is lacking.

With two steps we can significantly improve home infusion and, in doing so, create value for doctors, patients and pharma companies.

SOLUTION 1: CUSTOMISATION

Firstly, more infusion pumps should be customised for specific drugs. Customised pumps would create efficient solutions for more complex drugs with high rates of usage or complex make-ups – and for the specific needs of different patient populations.

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"A customised pump can help extend the lifecycle of a drug and provide differentiation in crowded markets."

Customised pumps would be simpler, allowing a patient to receive the drug and device, hook it up and begin, without having to sift through the many options that come with general infusion pumps. Likely, this would reduce adverse drug events caused by patient confusion related to a doctor's orders or device set-up. And the healthcare industry could save on the labour costs involved in sending medical professionals to patients' homes repeatedly to set up and troubleshoot the pumps.

Additionally, orphan drugs – which may not be considered in the design of a general pump – would also be able to more easily enter the infusion market with an available customised pump. Currently, 500 orphan drugs exist in the US where the FDA has increased the drug approval rate in recent years – with almost 50% of approved drugs from 2000–2017 having been approved after 2013.[3] Infusion options should be readily available for these treatments just as they are for more common treatments.

A customised pump can also help extend the lifecycle of a drug and provide differentiation in crowded markets. Assuming the price point is the same, there is little doubt that patients and medical professionals would prefer a drug that comes with a plug-and-play pump as opposed to one that involves a general infusion approach.

SOLUTION 2: CONNECTIVITY

Beyond customisation, infusion pumps should be connected to the cloud – allowing for data analysis and integration with platforms. Connected pumps would provide massive benefits for the pharma industry, doctors and patients. At the most basic level, connected pumps would allow the industry to get clear data on infusion for the first time. We need these numbers to accurately approach infusion treatments away from hospitals.

Connected devices would also provide pharma companies with a simple way of conducting post-market surveillance to discover new indications and side effects. It would allow for HIPAA-compliant tracking of each individual's basic data and the side effects, indications and other important data points that the patient is experiencing. That data can then be used to enhance the lifecycle management of a given drug significantly.

Pharma companies could also use connected devices to enter into outcome-based payment contracts more easily by confirming patient engagement. Currently, many US states allow for deals with companies in which they promise reimbursement if the drug fails to work for a patient. However, there is no way to know if the patient used the drug correctly. We do know that some drugs, such as antibiotics, are often thought to be ineffective when, in fact, they are inappropriately administered. Outcomes-based payment contracts would increase revenue from any truly effective drug and improve the standard of care for patients.

In addition to the benefits to pharma companies, connected devices would allow for the integration of apps into home infusion care. An app on a patient's device could remind them of their next scheduled infusion, provide them with ways to record their recovery, and give them the ability to receive feedback and support from their doctors or even the manufacturer of the drug. Loved ones could track the treatment as well and assist in the therapy to ensure it goes as planned.

NEW HORIZONS IN INFUSION CARE

Perhaps the greatest advantage of creating customised and connected pumps would be the expansion of the range of drugs that is safe for home care. An exciting example of this would be more patients undergoing chemotherapy from the comfort of their home. As chemo is already a stressful and uncomfortable process, allowing patients to be in a more relaxed environment could greatly improve their treatment. However, this can only be made possible by a

"The greatest advantage of creating customised and connected pumps would be the expansion of the range of drugs that is safe for home care. An exciting example of this would be more patients undergoing chemotherapy from the comfort of their home."

device that is simple to use and which can communicate with the patient's doctor to ensure safe and comfortable use of the drug.

We have seen early examples of simple customised wearable infusion devices that help patients leave hospital earlier after a chemo treatment to continue at home. With connectivity, this model could be significantly expanded.

Home infusion is an important advancement in healthcare but it must be customised and connected in order to be fully leveraged to support the various players in the system. Patients would receive simple-to-use pumps that integrate with their smartphones to improve user experience and compliance. Doctors would be able to send more patients home – reducing the burden on hospitals. Pharma companies would be able to increase the number of drugs offered for home infusion and use post-market surveillance to improve those drugs after release. Home infusion is another segment of the healthcare industry that is set to be improved by the integration of customisation and connectivity.

ABOUT THE COMPANY

Avoset Health is a medical device company focused on providing solutions across the spectrum of home infusion including the development and manufacturing of connected home infusion devices, fleet tracking, caregiver-patient interactions and streamlining pharmacy workflow. One of three privately held companies operating under the Eitan Group, Avoset leverages core capabilities and expertise in drug delivery technology development, manufacturing and regulatory experience to offer a robust platform solution meeting the needs of the home infusion industry. By developing a connected and easy-to-use platform Avoset is reducing hospital readmissions, encouraging accurate data collection, easing workflows and bringing infusion care home.

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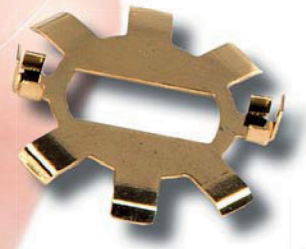

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