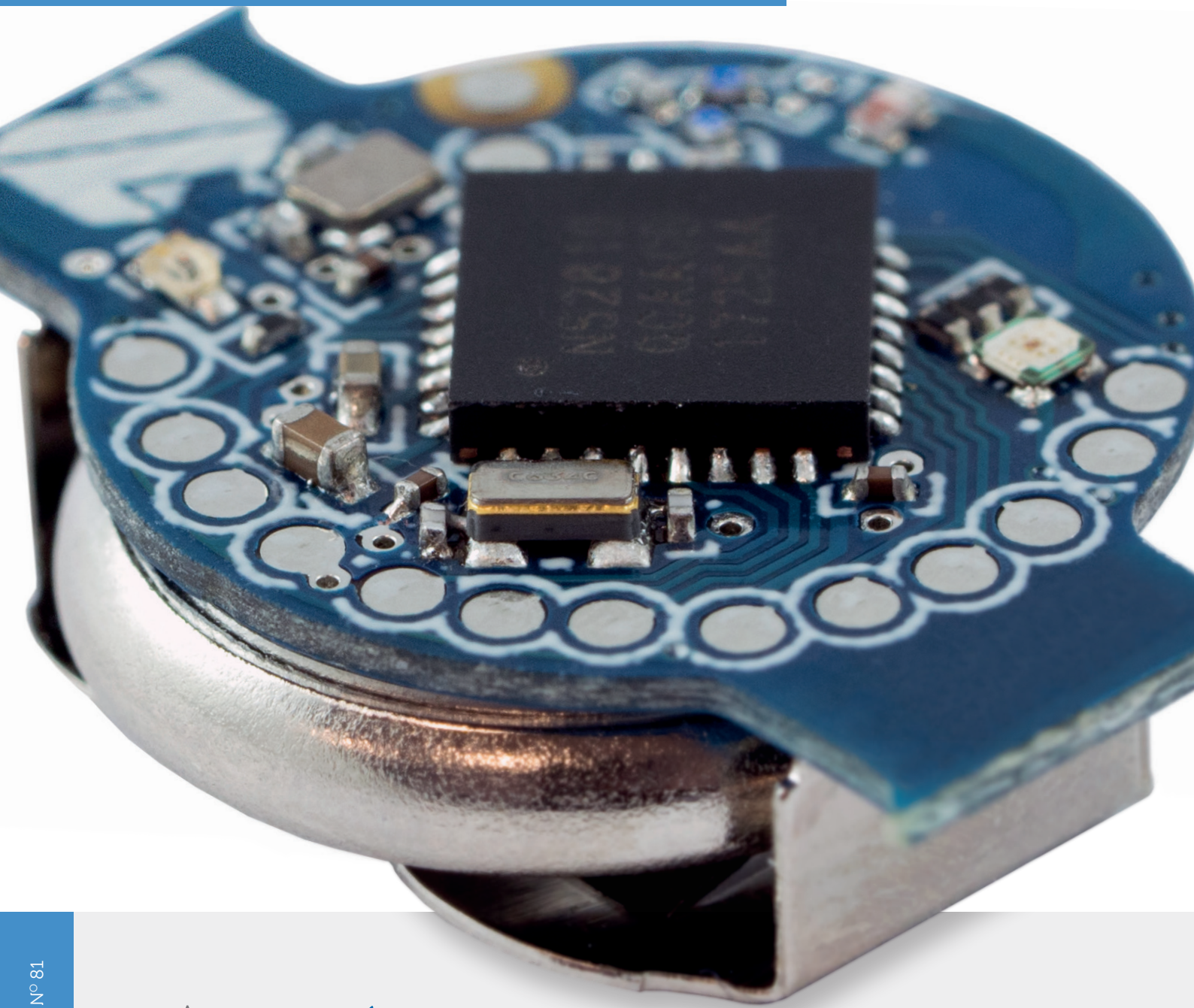
CONNECTING DRUG DELIVERY

ON drugDELIVERY



DECEMBER 11TH 2017 • ISSUE Nº 81

Aptar pharma

BIOCORP

Medicom Innovation Partner a Phillips-Medisize Company

Nemera

NORDIC SEMICONDUCTOR

QuiO

YPSOMED SELFCARE SOLUTIONS

ONdrugDelivery Issue N° 81, December 11TH, 2017

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.

2018 EDITORIAL CALENDAR

Jan	Ophthalmic Delivery
Feb	Prefilled Syringes & Injection Devices
Mar	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Delivery
May	Injectable Delivery: Devices Focus
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery Systems
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Delivery
Dec	Connecting Drug Delivery

EDITORIAL:
Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

James Arnold, Editorial Assistant
T: +44 1273 47 28 28
E: james.arnold@ondrugdelivery.com

SUBSCRIPTIONS:
Audrey Furness, Subscriptions Manager
E: subscriptions@ondrugdelivery.com
10-11 issues of ONdrugDelivery Magazine published per year, in PRINT & PDF.
PDF subscription is always completely **free**.
PRINT subscription costs **£99/year + postage**.
Print subscription includes delivery of a printed copy of each issue to one address anywhere in the world.

ADVERTISING:
Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:
Frederick Furness Publishing Ltd
The Candlemakers, West Street, Lewes,
East Sussex, BN7 2NZ, United Kingdom

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

ONdrugDELIVERY

Front cover image, "A proof-of-concept printed circuit board developed by Nordic Semiconductor, which accelerates the development of BLE-connected medical products", supplied by Nordic Semiconductor. Reproduced with kind permission.

What is the link between a smartphone and a drug delivery device?

Discover how to improve nasal and ophthalmic compliance with e-Advancia® and e-Novelia®

Nemera

Drug Delivery & Packaging
Pharmapack

Booth D30

Paris, 7-8 February 2018

we put patients first

HOW CONNECTIVITY WILL REMODEL HEALTHCARE

In this article, Marjorie Villien, PhD, and Jerôme Mouly, both Technology & Market Analysts at Yole Développement, provide a forecast of the place of connectivity in the healthcare market and the significant changes it is likely to bring to both devices and the market itself.

Healthcare is facing one of its most significant turning points in decades. After penetrating the consumer market, the digital revolution and the IoT (Internet of Things) concept are rapidly changing health models.

A confluence of factors is driving these changes. First of all, the prevalence of chronic diseases in modern societies; as an example more than 400 million people are suffering from diabetes (types 1 and 2). In addition to genetic factors, some diabetics' risk factors derive from behavioural causes, such as obesity, lack of exercise and bad eating habits. The incidence of respiratory diseases, asthma for example, is strongly increasing due to environmental issues in highly industrialised cities. The estimated cost of chronic diseases could soon reach US$1.5 trillion (£1.1 trillion) per year for global health organisations, therefore reducing the impact cost of these conditions is a matter of urgency.

> "Development of connected solutions will not only help patients to better estimate the dose of medication to deliver, but will also alert them should they forget medication and record their data, leading to better adherence and avoiding errors that may led to emergencies and hospitalisations."

The second factor is a shift in the attitudes and expectations of patients, who are willing to manage their health in a manner similar to how they now monitor steps and calories via worn fitness bands connected to their smartphones. More than two billion people are using internet-connected smartphones around the world today, fostering the rapid adoption of connected medical devices. Such devices have already generated $9 billion to date, estimated to grow to $23 billion by 2022.[1]

THE CONNECTED DRUG DELIVERY DEVICE MARKET IS GROWING

The global connected drug delivery device market, including implanted drug delivery pumps, inhalers, insulin pens and insulin pumps, has already reached two million units, including over 45 million with the capacity for Internet of Medical Things (IoMT) connectivity (Figure 1). Diabetes and respiratory diseases are two major chronic medical conditions, patients of which require regular and accurate medication. Development of connected solutions will not only help patients to better estimate the appropriate dose of medication, but will also alert them should they forget medication and record their data, leading to better adherence and avoiding errors that may led to emergencies and hospitalisations.

Connected inhalers for asthma are changing patients' lifestyles. Built as a fully integrated solution or as an add-on to standard inhalers, patients record all their inhalations via a Bluetooth connection to their smartphone or tablet. As an example, 3M is developing its Intelligent Control Inhaler, expected in 2018. The inhaler will help patients with respiratory diseases to control flow rate and record data. Using an app, patients and physicians can remotely visualise records and patients are able to access feedback. 3M is currently looking for a pharmaceutical partner to gain access to the market. A strong increase is anticipated in the inhaler market, with a 75% annual growth rate forecast for inhalers from 2016 to 2022.

In the area of diabetes, connected insulin pens are also changing the lives

Dr Marjorie Villien
Technology & Market Analyst
E: villien@yole.fr

Jerôme Mouly
Technology & Market Analyst
E: mouly@yole.fr

Yole Développement
Le Quartz
75 cours Emile Zola
69100 Lyon-Villeurbanne
France

www.yole.fr

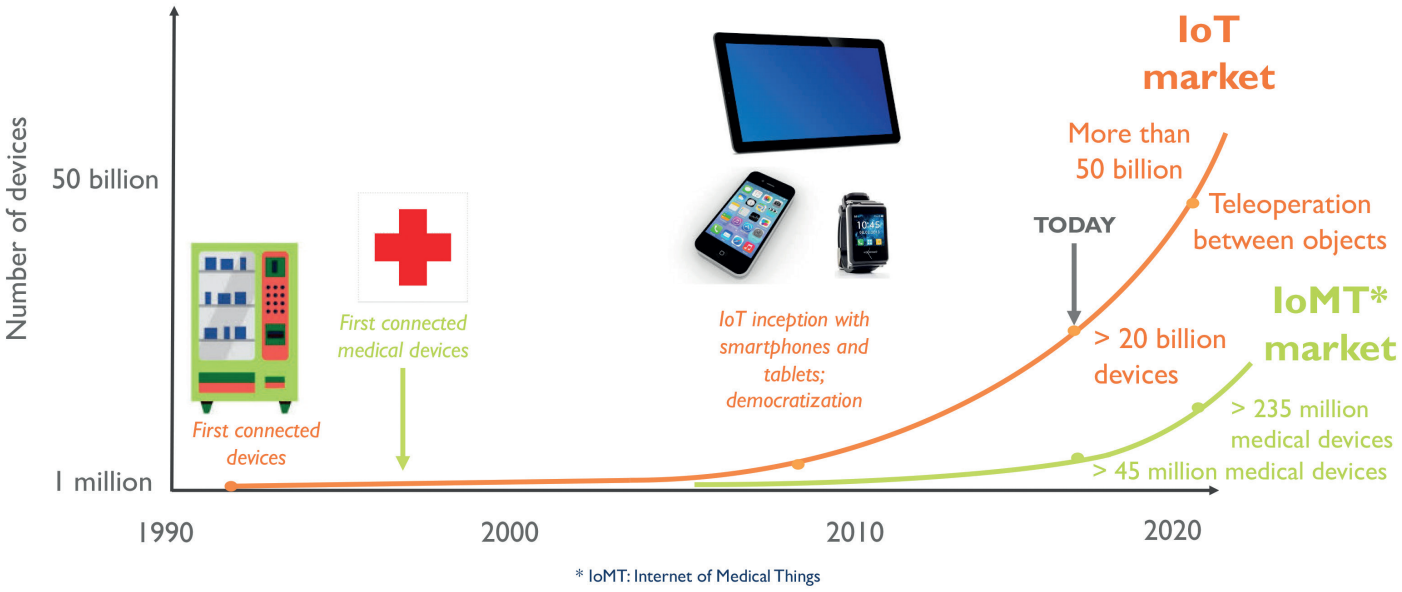


Figure 1: The number of devices capable of connecting Internet of Medical Things is increasing at a rapid, accelerating rate.[1]

of patients with diabetes types 1 and 2. Precise dosage measurements avoid under- and overdosing of insulin and patients could receive information from their smartphone to anticipate their needs more accurately, thanks to machine learning. Interest shown by pharmaceutical companies will likely boost adoption by patients. Novo Nordisk, the inventor of the insulin pen, has teamed up with Glooko, a developer of remote monitoring software, and is expected to launch the new generation of Echo-Pen imminently. Moreover, the development of the artificial pancreas, a (hybrid) closed loop system that communicates to automatically deliver the right dose of insulin, promises a less constrained life for type 1 diabetes patients.

ARTIFICIAL PANCREAS

An artificial organ is a device that is implanted or integrated into a human – interfacing with living tissue and/or fluid – to replace the functions of a faulty or missing vital organ. Hence, by this definition, the artificial organ has to be either wearable or implantable and replace an entire organ or function. Sometimes the use of an artificial organ is a temporary measure, a step in treating the disease process, acting as a bridge to a solution, while other times the artificial organ is a permanent solution. Moreover, some artificial organs are mechanical, such as an artificial heart or lung; based on biology, such as a bioartificial pancreas or liver; or delivering drugs, such as the artificial pancreas.

Presently, the only artificial organ operating as a drug delivery device is the artificial pancreas. The diabetes epidemic is truly global, affecting more than 8% of the world's population. Better management of diabetic patients is crucial, and this is where the artificial pancreas is playing a major role. The name "artificial pancreas" is something of a misnomer, however, as rather than mimicking an organic pancreas an artificial pancreas is simply a smart insulin delivery device. A more appropriate term is "closed loop system". Indeed, a closed loop system combines real-time continuous glucose measurement (CGM) with an insulin pump by using a control algorithm to direct insulin delivery. The aim of this system is to improve diabetes self-care by improving glucose control to mitigate the risk of hypoglycaemia. The systems coming to the market today are hybrid closed loop systems, since they employ a closed loop at all times but need manual-assist dosing at mealtimes and during exercise. The next generation will be fully automated insulin closed loop systems, (manual mealtime and exercise boluses will be eliminated) and the third generation will be fully automated multi-hormone closed loop systems.

It is worth considering that the performance of a closed loop system is limited by the speed of insulin absorption and glucose-sensing inaccuracies, and that the software has to take these limitations into account. In the near future, the next generation of artificial pancreas will have both myriad embedded sensors to monitor the status of the patient and greater intelligence to take changes in physiology into account (e.g. meals, exercise, sleep etc).

The software piloting an artificial pancreas using such technology must parallel engineering developments. A plethora of different algorithms exist, each with their own intrinsic advantages and disadvantages, but all with an internal control law. These span from very simple binary answers to fast, complex algorithms which take into account complicated combinations of multiple data from various sensors, physical laws and precise output calculations. Next generation algorithms are currently in development and major improvements are anticipated. New, fashionable methods like machine learning (and deep learning when the data is available) are entering research through fuzzy logic algorithms. These methods seem promising and will permit fully automated control of the artificial organ.

> "After decades of development, artificial organ products are now ready to enter the medical device market. For that reason, the artificial pancreas segment will experience massive growth, with a $CAGR_{2017-2022}$ of 49%."

Yole Développement expects the uptake of the artificial pancreas to be both high and rapid throughout the type 1 diabetic population, since the solution has been desired for years. As of 2017, only Medtronic has an artificial pancreas system approved by the US FDA and none have been granted a European CE mark. However, many companies' products are ready for approval and commercialisation. There are two collaborations of particular note: one between Diabeloop, Dexcom and Cellnovo and one involving TypeZero, Dexcom and Tandem. After decades of development, artificial organ products are now ready to enter the medical device market. For that reason, the artificial pancreas segment will experience massive growth, with a $CAGR_{2017\text{-}2022}$ of 49%.[2]

Historical artificial organs were made of mechanical parts, today they are based on electronics and tomorrow they will be smart. Sensors and software are playing major roles in the growth of the artificial organ market. If bioartificial pancreases and artificial livers are based on biology, most other devices are full of electronics, sensors, emitters and software. The part such technologies play can only increase as the healthcare industry moves towards more intelligent devices.

THE TECHNOLOGY IS READY

The dual challenges for medical device producers are to integrate sensors, electronics and connectivity into approximately the same footprint as equivalent, non-smart devices and to facilitate patient adoption. Most of the sensors integrated to connected medical devices are already available from other markets, such as consumer or automotive, and are already miniaturised, low cost, offering low power consumption, etc, but are not specific to the medical market.

After stabilisation and large scale adoption of connected medical devices, a second wave of innovation is expected. This wave will see the development of sensor solutions specifically dedicated to medical grade requirements in terms of reliability and accuracy, as well as new criteria, such as low invasive sensors, taking advantage of microelectromechanical systems (MEMS) technologies (Figure 2).

Connected inhalers benefit from the miniaturisation of flow sensors to evaluate the volume of medication inhaled. Sensirion, a Switzerland-based company, has developed a 5x8x5 mm differential pressure sensor, called SDP3x, that could be integrated in smart inhalers. Miniaturisation also enables the progression of systems from portable to wearable, making them ever more user-friendly.

NEW PLAYERS ENTER THE HEALTHCARE MARKET

The IoMT is at the crossroads of medical devices, telecommunications and information technology (IT). As such, an entirely new infrastructure needs to be set up, involving these new players in the medical area. Medical device companies like Medtronic and Johnson & Johnson have a great interest in this field. Naturally, pharmaceutical companies have an inherent interest in giving more value to medical devices associated with the medications that they are selling to patients.

Numerous companies are developing smart inhalers and insulin pens and are licensing their products to pharma companies (Figure 3). An example being the recent announcement of a development agreement between Dexcom, a manufacturer of continuous glucose monitoring devices, and Eli Lilly; the aim of this partnership being to combine knowledge and tools to simultaneously reduce complexity and improve disease management for patients with diabetes.

The IoMT also represents a huge opportunity for new players such as IBM's Watson augmented intelligence system to enter the healthcare market and to bring computing power to predictive medicine, as well as relevant infrastructure to interoperate connected devices from home, hospitals or anywhere data needs to be shared. Companies like Qualcomm Life, with its solutions 2net and Capsule, are dedicated to IoMT applications.

It is worth noting that security and data privacy are at the forefront of healthcare administration, to avoid

"After stabilisation and large scale adoption of connected medical devices, a second wave of innovation is expected."

Figure 2: The adoption of connectivity in the healthcare market will spur further, more creative innovation.[1]

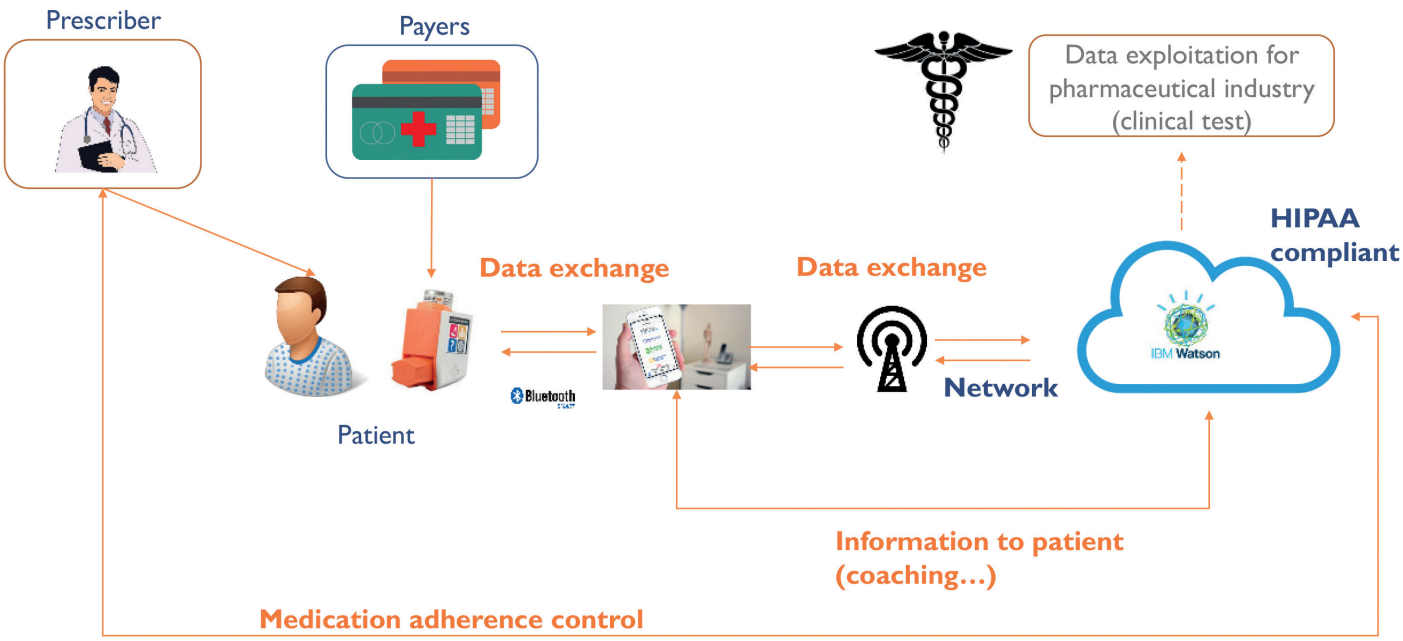


Figure 3: Example of a business model for a connected inhaler.[1]

unregulated use of information generated and also to guarantee the safety of patients (e.g. preventing hacking of implanted connected medical devices).

WHO PAYS AND WHO BENEFITS?

Current changes in healthcare require innovative business models to be realised. It is a fundamental change of paradigm for health administration, and the co-existence of two reimbursement models. From evidence-based medicine, connected medical devices enable the "P4" medicine concept: Preventive, Predictive, Personalised and Participatory. Innovative business models may well be being set up, but who will pay for prevention?

Health insurance companies are working with employers and telemedicine service companies to promote services to share the cost of connected medical devices (including architecture). Health insurance incentives or rebates are proposed for patients, should they participate in a programme increasing their adherence to medication by using a connected device that sends data to the patient, their physician and the insurance company.

This new shift in the healthcare landscape will require an evaluation of the performance of this new approach: will P4 medicine cost less than the evidence-based medicine concept? Ultimately, it is only long term analysis that will show the true impact. It is not only insurance companies which will benefit from connected drug delivery systems. Data generated could have great value, and pharmaceutical companies are looking to this precious information to analyse the impact of medication on patients more rigorously and accurately, enhance a personalised medicine approach, and accelerate clinical tests.

Monetisation of data is the next step after data storage in the cloud. Machine learning and artificial intelligence should help to process and analyse a large amount of data. What about Google, Apple and the other giants of the big data and analytics world? For several years the medical device market was far from their field of interest, with low volumes, strict regulations and long development times. The limits of healthcare devices as data generators are also a consideration; consumer well-being devices have fewer regulations on data privacy and data

> "From evidence-based medicine, connected medical devices enable the "P4" medicine concept: Preventive, Predictive, Personalised and Participatory. Innovative business models may well be being set up, but who will pay for prevention?"

ABOUT THE AUTHORS

Marjorie Villien, PhD, is a Technology & Market Analyst and member of the Microfluidic & Medical Technologies (MedTech) business unit at Yole Développement. She is a daily contributor to the development of MedTech activities with a dedicated collection of market & technology reports as well as custom consulting projects. After spending two years at Harvard, Dr Villien served as a research scientist at INSERM in the field of medical imaging. She has spoken at numerous international conferences and has authored or co-authored 11 papers and one patent. Marjorie Villien graduated from Grenoble INP (France) and holds a PhD in Physics & Medical Imaging.

Jerôme Mouly serves as a Technology & Market Analyst, specialised in microtechnologies for biomedical & medical imaging applications, at Yole Développement. Since 2000, Jérôme has participated in more than 100 marketing and technological analyses for industrial groups, start-ups and institutes related to the semiconductor & medical technologies industries. Jérôme holds a Master of Physics from the University of Lyon, France.

transfer architectures, which provides more comfortable territory and generates much more data. The monetisation of data is key for these giants and regulations surrounding medical data are more constraining compared with those that apply to the regular consumer data they are more used to.

THE ERA OF CONNECTED DRUG DELIVERY IS TAKING OFF

The market share of connected drug delivery devices is expected to increase at a rapid pace, with a more than 75% CAGR over the next five years for systems used in the context of chronic diseases. A feedback of accurate information will help patients to better monitor their health with fewer constraints, reducing hospitalisations or unnecessary visits to the doctor's office. The impact on society should be significant, with lower costs for healthcare organisations as well as better therapeutic outcomes for patients, thanks to a participative approach to sharing health data. The challenges of data privacy and patient safety will be key, involving new players in the healthcare ecosystem. Consolidation of the market and the supply chain will occur later, with a series of mergers and acquisitions aiming to gather the most innovative products and regroup solutions with high synergies.

ABOUT THE COMPANY

Founded in 1998, Yole Développement is a market research & strategy consulting company that has grown to become a group of companies providing marketing, technology and strategy consulting and media in addition to corporate finance services.

Yole has a global vision and customer base. Yole, and its partners, System Plus Consulting, Blumorpho, Piseo and KnowMade, support industrial companies, investors and R&D organisations worldwide to help them understand markets and follow technology trends to develop their businesses.

REFERENCES

1. *"Connected Medical Devices and Business Models report". Yole Développement, September 2017.*
2. *"Artificial Organ Technology & Market Analysis report". Yole Développement, September 2017.*

Drug Delivery Partnerships

January 22-24, 2018
PGA National Resort & Spa
Palm Beach Gardens, FL

The business development event bringing you visionary ideas, disruptive technology, and partneringONE® to maximize your product lifecycle and generate new revenue streams

REGISTER WITH CODE ODD18 AND
SAVE 10% OFF CURRENT RATES

Even more partneringONE® hours than ever before!

For 2018, we have **doubled** the number of networking hours with partneringONE® for a total of **20+ hours** to allow you even more time to meet with potential partners.

Visit www.DDPevent.com for More Info

SOFTWARE AND SERVICES – THE MISSING LINK FOR CONNECTED THERAPEUTICS

Here, Alexander Dahmani, Co-Founder & Chief Executive Officer, QuiO, explains how the rise of smart devices and connectivity has enabled QuiO to develop ConnectedRx™, the first cloud platform designed for connected therapeutics, and discusses how ConnectedRx™ programmes can be a step towards solving the ongoing problem of adherence.

ADDRESSING THE PROBLEM OF MEDICATION ADHERENCE

Across therapeutic categories and chronic conditions, adherence rates have remained low for decades. This leads to avoidable medical costs, lost pharmaceutical revenue and failed clinical trials.[1] Even with all the attention over time, sustainable and scalable solutions for improving adherence have remained elusive.[2] An analogy for solving the problem of adherence is the search for a cure for cancer. In point of fact, cancer is actually a collection of hundreds of different diseases rather than a singular condition and, in a similar vein, poor adherence is a multitude of different problematic behaviours.[3] In order to actually solve either of these problems, we need to start with detection and characterisation of the specific case at hand.

MISSING LINK: DOSE-LEVEL DETECTION

In order to treat a case of cancer effectively, it must first be detected and characterised. Based on the diagnosis, the correct treatment can then be selected, whether it's surgery, radiation, pharmaceuticals or a combination of the above. We're getting ever better at detecting, characterising and treating cancer, and a feedback loop exists to continuously improve the treatment selection process based on past outcomes. This system has been lacking for adherence however, because there was no reliable means to detect and characterise poor adherence.

Patient self-reporting and pharmacy refill data are insufficient to support such a system. It's no surprise that people misrepresent their adherence level when self-reporting. It's also a burden for patients to constantly enter in data manually. While pharmacy refill data has been valuable for proving that there is an adherence problem in large observational studies, it doesn't represent a viable option for solving the problem. Picking up a refill on time does not mean the patient took each dose on time, if at all. It is also a lagging indicator of patient behaviour. By the time the pharmacy data

> "Healthcare providers also don't have the incentives or resources to become adherence and patient behaviour experts across medications, conditions and patient profiles. That level of expertise and service demands a dedicated, specialised third party."

Mr Alexander Dahmani
Co-Founder & CEO
T: +1 646 600 9979
E: alex@quio.com

QuiO
79 Madison Ave
New York
NY 10016
United States

www.quio.com

becomes available for use in calculating an adherence level, the patient has been non-adherent for weeks, if not months.

The optimal means for detecting adherence is at the point of consumption. This is made possible by connected therapeutics. Connected therapeutics refer to pharmaceuticals paired with technologies that enable remote detection of dosing events using sensors and connectivity (Table 1). The most common types are smart devices, including medication containers and drug delivery devices. Figure 1 shows the introduction of smart medication devices over time. It started 10 years ago with medication containers for oral therapies, such as pill bottle caps. The inhaler add-ons were introduced in 2010, and have been deployed at scale across clinical trials and patient support programmes. The most nascent vertical is injectable therapies, with the first devices just now becoming available. You can see in Figure 1 that the rise of connected therapeutic devices closely mirrors the rise of smartphones. This is largely due to the development of low-cost sensors and wireless technology for smartphones, which then becomes available for use in other devices.

The addition of wireless technology to a smart medication device is key, because it allows the device to share its dosing data with remote systems and stakeholders. This means the data can now be used to detect non-adherence in near real-time, and subsequently deliver targeted and personalised interventions. This data also represents an endpoint for measuring the effect of each intervention on adherence, creating a feedback loop that enables continuous improvement of interventions over time.

Container	Add-On	Delivery Device	Other
• Pill bottle • Pill bottle cap • Pill tray • Pill dispenser • Blister packaging • Medication storage case • Sharps disposable bin	• Inhaler sensor • Pen injector sensor • Pen needle sensor • Auto-injector sensor	• Inhaler • Pen injector • Auto-injector • Wearable injector	• Ingestible smart pill with wearable patch sensor • Ingestible smart pill with breath sensor • Mobile app with computer vision for confirming pill consumption

Table 1: Types of connected therapeutic solutions currently available.

MISSING LINK: DATA-ENABLED SOLUTIONS

Connected devices and dose-level data are just the first step. Once we can reliably detect adherence, it's still going to require software and clinical services to deliver, track and continuously improve adherence interventions. But who is going to provide such software and services? Many people believe getting the data into the electronic medical record (EMR) and in front of a healthcare professional is the solution. Based on our primary research, physicians are neither willing nor able to take responsibility for the patient outside of the clinic. Rather, they want access to adherence data when the patient is in the clinic in order to make better treatment decisions. Their time is already stretched with diagnosing and prescribing, they don't have any spare time to take on the additional role of remote care services. Healthcare providers also don't have the incentives or resources to become adherence and patient behaviour experts across medications, conditions and patient profiles. That level of expertise and service demands a dedicated, specialised third party.

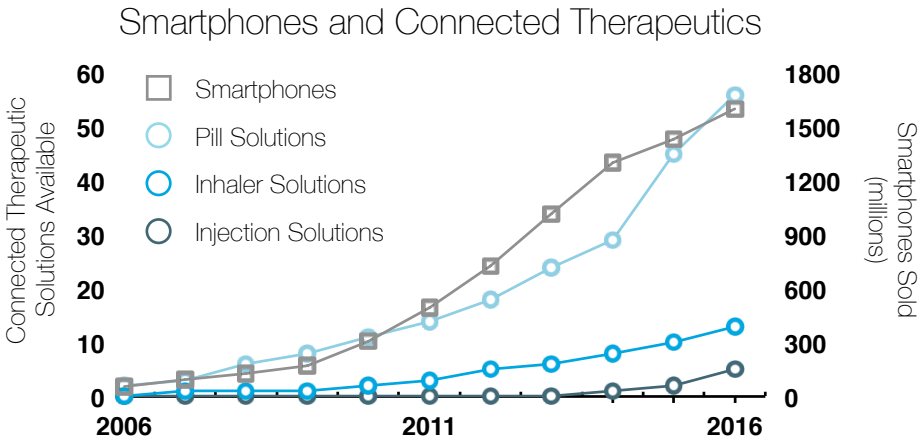


Figure 1: The adoption of smartphones and introduction of connected therapeutic solutions over the past 10 years.

> "An opportunity exists for a new kind of solution that leverages patient-generated health data and is focused on continuous monitoring and support outside of the clinic. This opportunity is only made possible by the arrival of connected therapeutics."

Additionally, traditional clinical software is ill-equipped for this task. EMRs represent a static view of patients based on data collected within the clinic. Standard EMR functionality is heavily focused on coding, payments and reimbursement. Care management platforms are basically customer relationship management (CRM) tools for health insurers to communicate with members. This is exemplified by the rise of Salesforce in the care management space. Population health platforms are analytical tools designed for combining EMR and claims data to identify gaps in care and patient segments that represent outliers with regards to utilisation, costs or outcomes.

None of these solutions are designed for, or capable of, continuously collecting data outside the clinic, let alone using that data to remotely monitor and support patients. An opportunity exists for a new kind of solution, one that leverages patient-generated health data and is focused on continuous monitoring and support outside of the clinic. This opportunity is only made possible by the arrival of connected therapeutics.

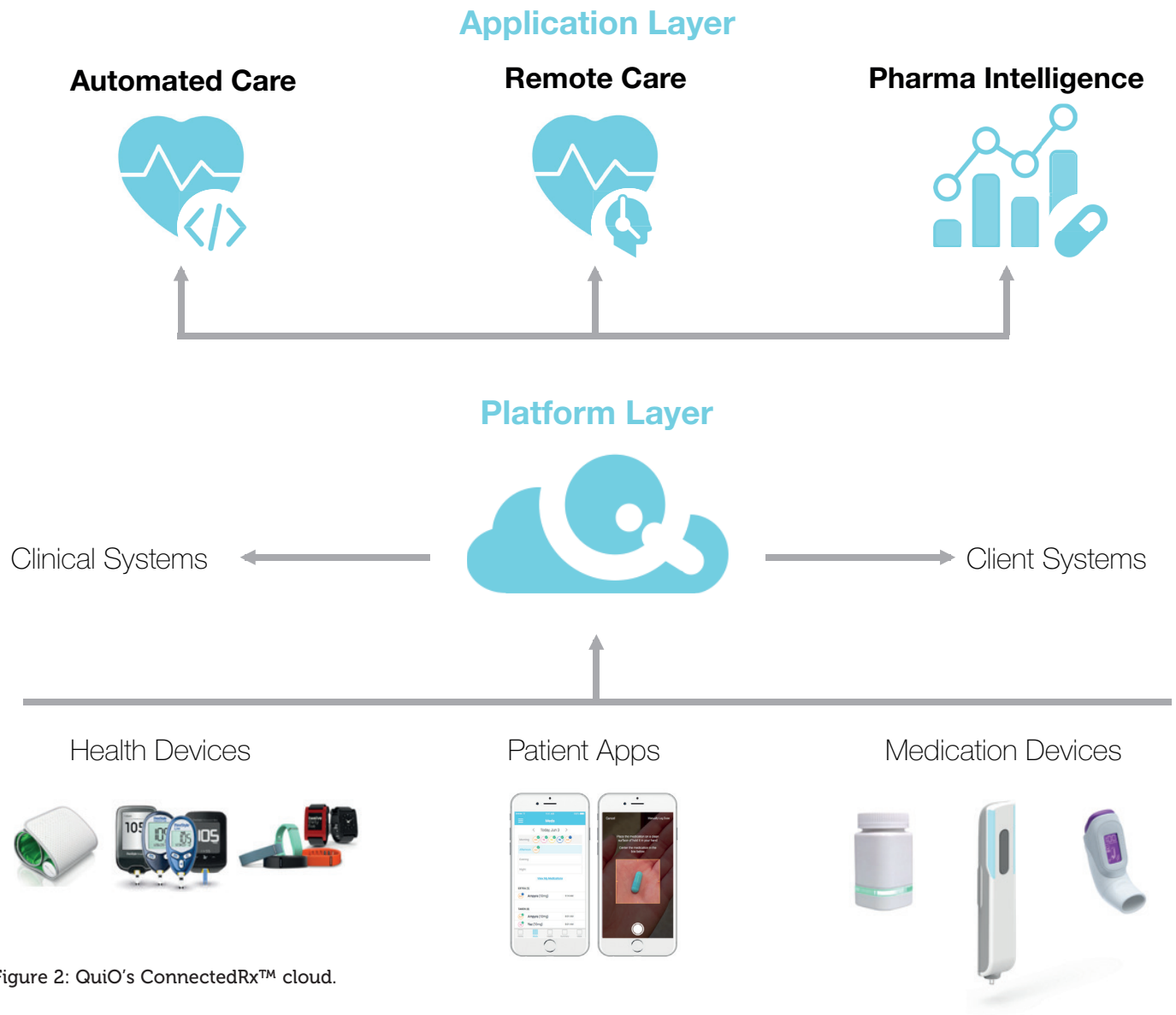


Figure 2: QuiO's ConnectedRx™ cloud.

CONNECTEDRX™: A CLOUD SOLUTION FOR CONNECTED THERAPEUTICS

The ConnectedRx™ cloud (Figure 2) is a fully managed solution for medical device and pharma companies looking to adopt connectivity. It includes a HIPAA-compliant cloud infrastructure with purpose-built software and services, enabled by patient-level and dose-level data.

Platform Layer

The platform is built from the ground up specifically for secure connected device and patient data management. All the device integrations and software functionality are developed under QuiO's ISO-13485 quality management system. The platform supports companion software use cases ranging from unregulated Medical Device Data Systems (MDDS) up to Class III medical devices. New devices can quickly be connected to the platform, whether they operate on Bluetooth, WiFi or cellular communication protocols. Over 300 patient monitoring devices have already been integrated, representing a robust ecosystem of connected devices ready for deployment.

The platform is able to structure and securely manage all the data collected from these devices, representing over 40 unique medication and health data points. In addition to connected devices and apps, the platform is compatible with electronic medical record (EMR) data structures, enabling bi-directional communication with clinical systems. Patient data is encrypted within the platform during storage, as well as during transit to and from other clinical or client systems. Most importantly, the platform is designed to meet current and future security and privacy requirements, including HIPAA and GDPR.

Application Layer

The ConnectedRx™ application suite provides the tools and analytics for stakeholders to properly utilise the data collected, including patients, healthcare providers and pharma clients (Figure 3):

a) **Automated Care**
- Automated patient communications (app, text, or call) based on medication alerts, with response capture for contextual data.
- Mobile and web app with features for tracking symptoms, health metrics and multiple medication regimens.

b) **Remote Care**
- Stratified patient panel based on device, app and patient response data.
- Alerts for identifying patients in need of attention.
- Multi-channel support delivered directly from the web application (in-app chat, SMS or VoIP calls).

c) **Pharma Intelligence**

- Anonymised data measuring patient experience, adherence, persistence and health outcomes.
- HIPPA-compliant patient matching with data integrated from EMRs, claims, disease registries and clinical trials.

Pharma clients can choose to offer our own mobile and web app to patients, or we can integrate with the pre-existing patient app of their choice. Our patient app can be transformed into a regulated companion app with therapy specific features by simply entering a unique code supplied to the patient. The code can be distributed with the connected device or prescribed by their physician. Less tech-savvy patients can also choose to receive alerts and information via automated texts and calls instead.

Our automated care service leverages natural language processing (NLP) and interactive voice response (IVR) to accomplish much of the same functionality as the patient app, a feat achieved by capturing patient data through text and voice, respectively. A key benefit of a managed solution like ConnectedRx™ is the continuous improvement in features and functionality. For example, the voice capabilities of our automated care service are being extended into home assistants such as the Amazon Echo. The mobile app experience is also being extended into wearable devices such as the Apple Watch.

Caregivers and clinicians can use the Care Dashboard to monitor and support patients remotely, based on data collected from devices, apps and automated communications. This data enables them to target support to the right patient at the right time. Caregivers can communicate with patients directly from the dashboard, enabling them to review patient data and enter in new data while in contact with them.

Pharma clients can use the Program Dashboard to view the data collected from each patient enrolled in the programme. Data is aggregated, anonymised and summarised for the client to leverage in a HIPAA-compliant fashion. The Dashboard provides complete transparency into the programme, including how many patients have been enrolled, how many patients are active and the products and services each patient is utilising. Clients are provided valuable, actionable insights they can use to track the real-world performance of their therapeutic product, including adherence rates, persistence rates and patient satisfaction. We can also perform HIPAA-compliant, patient-level matching with third party data sets, including patient registry, EMR and claims data. This enables clients to understand clinical outcomes in the context of dose-level adherence patterns.

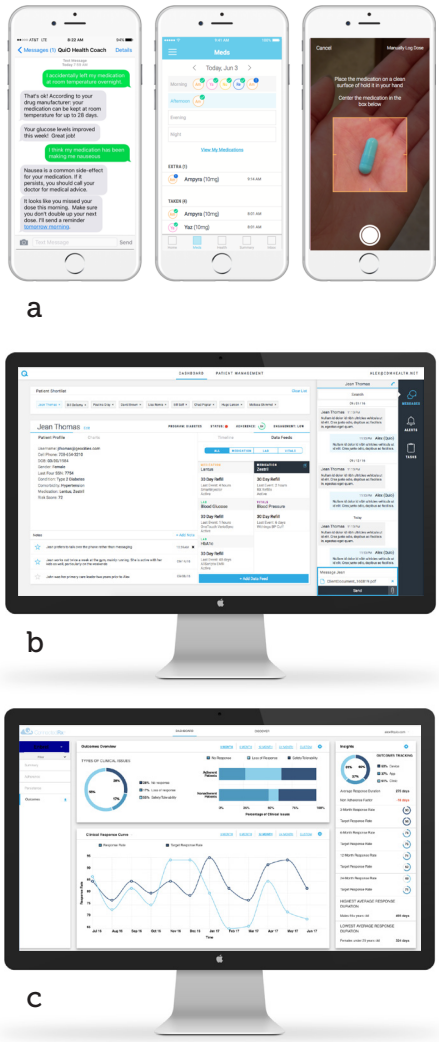


Figure 3: The ConnectedRx™ application suite enables patients to self-manage their health and medications (a), healthcare providers to monitor and support their patients remotely (b), and pharma and device companies to access real-world data and metrics on their therapies (c).

"Over 300 patient monitoring devices have already been integrated, representing a robust ecosystem of connected devices ready for deployment."

Dose-Level Adherence

MedScore™ is our proprietary adherence metric, designed and validated for dose-level data. With the introduction of connected devices capable of collecting dosing data, there needs to be a standard way to measure adherence, just like prescription refill adherence is measured using "proportion of days covered" (PDC) and "medication possession ratio" (MPR). The conventional adherence metrics currently used for dose-level data, such as "percentage of doses taken" (PDT), don't properly account for the impact dose timing and amount have on therapeutic efficacy.

Figure 4 compares these conventional metrics with our MedScore™, using a twelve dose data set for two patients on a weekly therapy. Both patients received their 90 day supply on time and are considered adherent based on prescription refill data. With dose-level data, you can reveal much more information beyond just the refill date. Conventional metrics don't calculate adherence level in a clinically meaningful way because they treat late doses, partial doses and missed doses equally, whereas MedScore™ treats dosing mistakes differently by providing distinct weights to these events. It can even be customised for each medication, for example, taking into account its therapeutic index.

As Figure 4 (next page) shows, Patient One missed 25% of the scheduled doses. That significantly diminishes the likely drug efficacy compared with Patient Two, who was more sporadic, but successfully consumed every dose. That's why Patient One has a much lower MedScore™ than Patient Two. When analysing health outcomes in the context of adherence, Patient One should not be considered more adherent than Patient Two. When limited support resources are a reality, Patient One should receive more time and attention from caregivers. This clinically meaningful metric enables more targeted patient support efforts and more accurate tracking of real-world drug performance, both of which are key for the healthcare system to achieve a return on investment from connected devices.

CONNECTEDRX™ PROGRAMMES: EASY TO ADOPT AND IMPLEMENT

Pharmaceutical Clients

We offer a fully managed solution for pharmaceutical clients interested in

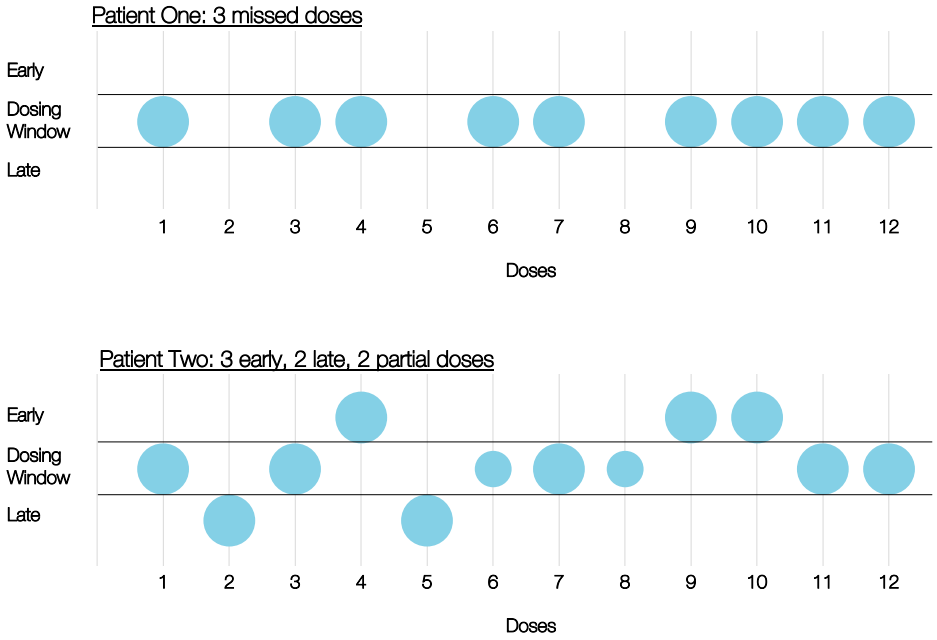


Figure 4: QuiO's MedScore™ compared with conventional adherence metrics. Each blue circle represents a dose taken. Circle size indicates dose size. Circle position indicates dose time.

adopting connected devices. They simply select one or more devices they want to pair with their therapy and we handle the rest. A typical programme starts with customising the patient experience based on the specific therapy and indication(s). The patient experience comprises a mobile app, automated interventions (via app, SMS or phone call), educational content and self-management tools. We also provide our coaching service for enrolment, patient onboarding and high-touch support. Alternatively, we can work with third party service providers, such as speciality pharmacies or support hubs.

Throughout the programme, we provide pharma clients with full transparency into the number of active patients enrolled in the programme, along with their anonymised adherence, persistence and outcomes data. We even provide tools for them to identify and target their support resources to patient subgroups with lower adherence or worse outcomes.

Connected Device Partners

When connected device developers integrate their data into the ConnectedRx™ ecosystem they get the benefits of a fully managed, secure and compliant software stack, designed specifically for connected therapeutics. An example of this is our recently announced partnership with SHL Group. We are integrating their devices into our cloud platform, enabling interested pharma clients to start piloting their connected devices today, including the ENYA add-on for pen injectors and the Molly® C Recording Unit for auto-injectors.

We enable pharma clients to adopt connected devices easily, without having to build their own software stack or adopt multiple point solutions that don't work well together and require individual maintenance. With ConnectedRx™, device makers can focus on making the best devices possible, pharma clients can focus on getting their innovative therapies into patients' hands and we handle the connected therapeutic experience.

ABOUT THE COMPANY

QuiO is a connected therapeutics company that provides software and services enabled by smart medication devices. The company's solution helps chronic disease patients succeed on long term therapies, and helps stakeholders track the real-world performance of these therapies.

REFERENCES

1. *Moore T, Chawla S, Firlik K, "Estimated Annual Pharmaceutical Revenue Loss Due to Medication Non-Adherence". CapGemini/ HealthPrize Technologies Report, November 2016.*
2. *Choudhry N, Krumme AA, Ercole PM, "Effect of Reminder Devices on Medication Adherence The REMIND Randomized Clinical Trial". JAMA Intern Med, 2017, Vol 177(5), pp 624-631.*
3. *Neiheisel M, Wheeler K, Roberts ME, "Medication adherence part one: Understanding and assessing the problem". J Am Assoc Nurse Pract, 2014, Vol 26(1), pp 49-55.*

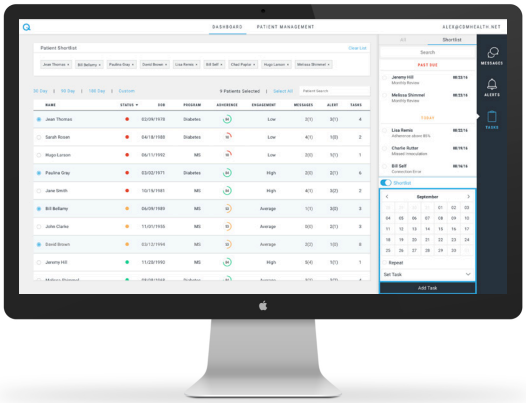
ABOUT THE AUTHOR

Alexander Dahmani, Chief Executive Officer of QuiO, founded the company in 2014 while pursuing a PhD in Microbiology and Immunology at Columbia University (New York, NY, US). At Columbia, his research focused on human T cell activity using an advanced humanised mouse model. During his PhD he also worked for Columbia Technology Ventures, where he helped review and commercialise new technologies invented on campus, including algorithms, sensors, medical devices and therapeutic molecules. Prior to Columbia, he worked for Heat Biologics (Nasdaq: HTBX), a biotech startup commercialising a novel cellular immunotherapy for multiple cancer indications. Mr Dahmani earned a BS in Genetics with a minor in Business from the University of Wisconsin (Madison, WI, US).

ConnectedRx™

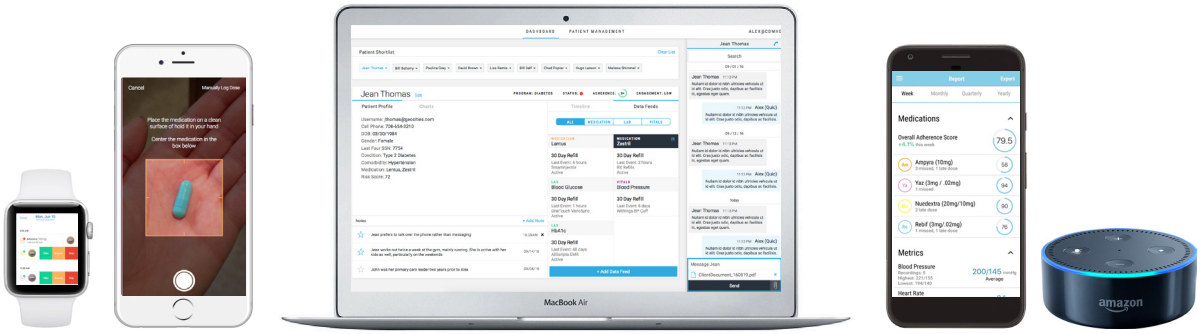
The first cloud solution designed for connected therapeutics

Clinical software for remotely monitoring and supporting patients



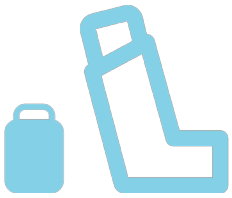
Client software for tracking real-world drug performance

Patient software, services and content for medication and disease management

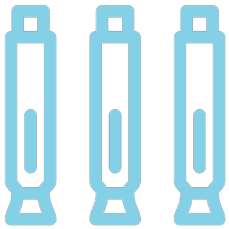


The secure, compliant software stack for all connected therapeutic devices:

Medication Containers



Add-On Sensors



Drug Delivery Devices

QuiO

For more information contact:

info@quio.com
www.quio.com

PARTNERING FOR BLUETOOTH: THE SMART ROAD TO CONNECTIVITY

Wireless communication can be used to improve the effectiveness of smart devices in several ways, such as offering better data sharing, helping users find lost devices or sending reminders to take treatments. Director of Business Development at Nordic Semiconductor, Thomas Soederholm explains how advances in wireless technology, such as new Bluetooth Low Energy chips and design tools, are now being used in wireless medical product development and how incorporating them can be made much easier by partnering with a specialist vendor.

Wireless communication, using the globally licence-free 2.4 GHz Industrial, Scientific and Medical (ISM) radio frequency (RF) spectrum, offers many advantages for monitoring and analysing data captured from medical devices. A medical product equipped with a bidirectional RF link can join the Internet of Things (IoT) via a bridge or hub. IoT connectivity transforms the product into a smart device ensuring, for example, that the user can locate a misplaced device or be reminded when to administer medication. In addition, a smart medical device can share data on drug dosage and timing remotely with physicians.

Bluetooth Low Energy (LE) is a low-power form of Bluetooth wireless – the popular consumer-oriented 2.4 GHz RF technology. It is a leading option for adding wireless connectivity to medical products as it has low power consumption, proven RF interference immunity, strong security, good data throughput and satisfactory range. Moreover, its key advantage over competing technologies is smartphone interoperability; medical products employing Bluetooth LE can wirelessly communicate with virtually all modern mobile devices (and PCs) with little user input beyond initial pairing of the devices. This connectivity allows data from the medical device to be wirelessly transmitted to a smartphone for analysis, then being forwarded to the IoT via an app hosted on the handset.

> "Nordic Semiconductor has introduced a proof-of-concept printed circuit board that simplifies drug delivery device development."

INCORPORATING BLUETOOTH TECHNOLOGY IN DRUG DELIVERY PRODUCTS

Drug delivery products employing Bluetooth LE wireless technology are in development, some having already achieved US FDA approval. For example, Aterica Health Inc. (Waterloo, Canada) has developed Veta Smart Case, a Bluetooth LE-connected carrier for EpiPen auto-injectors, as well as authorised generic auto-injectors made by Mylan (Morgantown, USA). Also, Dexcom (San Diego, USA) has received FDA approval for its G5 Platinum mobile continuous glucose monitoring (CGM) system which includes a Bluetooth LE component to transmit glucose levels from a monitor mounted on the patient's skin to a hand-held receiver.[1]

However, RF engineering is a challenging discipline requiring skilled practitioners who are in short supply, potentially restricting

Thomas Soederholm
Director of Business Development
T: +47 930 11878
E: thomas.soederholm@nordicsemi.no

Nordic Semiconductor ASA
Karenslystalle 5
0278 Oslo
Norway

www.nordicsemi.com

Figure 1: Nordic's nRF52810 is a flexible, mature and reliable Bluetooth 5-certified solution optimised for low power and high performance wireless connectivity.

Figure 2: The FDA-approved Dexcom G5 Mobile CGM transmits blood glucose readings to a smartphone using Bluetooth Low Energy wireless technology.

the use of Bluetooth LE wireless technology.

But now, Nordic Semiconductor ("Nordic"), a semiconductor company based in Trondheim, Norway, has introduced a proof-of-concept (PoC) printed circuit board (PCB) that simplifies wireless drug delivery device development. The PoC PCB uses the company's nRF52810 Bluetooth LE solution for hardware and

> "Drug delivery products employing Bluetooth LE wireless technology are already in development and some have already achieved US FDA approval."

S112 SoftDevice (Bluetooth LE RF protocol "stack") for its software. The product is an extremely flexible, mature and reliable Bluetooth 5-certified solution optimised for low power and high performance in a tiny footprint (Figure 1).

Bluetooth LE is based in part on Nordic's proven proprietary ultra-low power wireless technology, and the company's engineers played a key role in writing the specification upon which the standard is based. In 2016, the company's integrated circuit (IC) Systems-on-Chip (SoCs) were used in 45% of registered Bluetooth LE-equipped products.

ENHANCING MEDICAL PRODUCTS WITH WIRELESS CONNECTIVITY

Several studies suggest the efficacy of drug treatment programmes is undermined because patients fail to administer the correct dose of medication, mistime delivery or fail to take the medication at all.[2] A smart medical product could assist the patient in rectifying these problems whilst additionally recording useful data about medication delivery. In addition, wirelessly connecting the product to the IoT establishes a bidirectional link along which not only can data be transmitted but also information returned in the form of guidance for the patient, or software enhancements and security patches for the product.

Wireless connectivity not only helps patients improve their quality of life, but the technology also brings huge economic benefits. For example, through assisting patients with adherence to a medication regime, money is saved through a reduction in the complications that could occur without proper treatment of the primary illness.

Another significant benefit is that data are available from the Cloud to help medical equipment manufacturers understand how, when and where devices and medication are being used – leading to better products.

The FDA-approved Dexcom G5 Mobile CGM, for example, takes a blood glucose measurement every five minutes and transmits the information to the user's smartphone (and up to five additional phones via the cellular network). The device provides hyper- and hypo-glucose alerts, rate of change values and alerts, and calibration. The Bluetooth profile also allows for configurable high and low alerts to be set at levels specified by the user. The information enables the patient to control blood glucose levels by either administering insulin or ingesting carbohydrates to boost glucose levels (Figure 2).

Bluetooth LE Builds on Interoperability

Provided output power is restricted to below specified levels (and local regulatory instructions are complied with), the ISM portion of the RF spectrum centred on 2.45 GHz (the "2.4 GHz band") can be used without the requirement for a licence. Additionally, unlike several other licence-free bands, the 2.4 GHz band is recognised globally, enabling manufacturers to produce a single version of a product for worldwide distribution. Such advantages have encouraged the development of a range of wireless technologies using the 2.4 GHz band, for example, open standard-based Wi-Fi, Bluetooth, Bluetooth LE and Zigbee, plus a slew of proprietary technologies.

Wi-Fi and Bluetooth wireless technology claim the largest market share, their popularity having resulted in both

technologies being incorporated into PCs, smartphones and portable computers across global consumer electronics makers[3], which is not so for competing technologies. Interoperability with such devices is a key advantage because it enables drug delivery product makers to connect their products wirelessly to a wide range of established computing and communication infrastructure.

Wi-Fi was designed for high throughput wireless transmission, such as accessing the Internet or transferring large files. Such high throughput typically demands rechargeable Li-ion batteries that are too large and expensive for most drug delivery products. Bluetooth LE features lower throughput (but nonetheless ample for medical applications) and, crucially, the technology can be powered for long periods (up to several years, depending on the application) from primary batteries as small as 3V/220 mAh CR2032 coin cells.

A second key advantage of Bluetooth LE is the wireless standard's rapid evolution to meet the demands of new use cases. In 2017, for example, a revised version of the Bluetooth LE standard, Bluetooth 5, was introduced. Bluetooth 5 promises up to four times increased range or doubled throughput, together with improved interference immunity, enhanced security and lower power consumption. With the release of Bluetooth 5, a given amount of data can be transmitted twice as fast, halving the time the radio spends in a relatively high power state and thus extending battery life.

CASE STUDY: THE VETA SMART CASE

EpiPen auto-injectors are used to mitigate the effects of anaphylaxis. Because the reaction can occur at any time, users must continuously carry the auto-injector. Also, because the adrenaline injection only provides short-term relief, patients need to visit hospital soon after a reaction to check if further treatment is needed.

Aterica Health Inc, formed in 2012, is addressing both these challenges with the Veta Bluetooth LE-connected EpiPen smart case. The auto-injector is inserted into the smart case, which employs Nordic wireless technology, and is wirelessly paired with the patient's iOS or Android smartphone. The Veta App on the smartphone notifies the user (and their invited support network) should he or she become separated from the smart case by, for example, leaving the auto-injector at home (Figure 3). In addition, the smart case notifies the support network if the auto-injector is removed (indicating that it is being used) so that they can offer quick assistance. Other notifications trigger if the auto-injector is subject to high or low temperatures or if it is approaching expiry.

Figure 3: Aterica's Veta EpiPen smart case employs low-power wireless connectivity to notify the user in the event they become separated from the device.

SIMPLIFYING WIRELESS DESIGN

Single-Chip Solutions

Early Bluetooth LE solutions demanded a "connectivity chip" – in essence, just the Bluetooth LE radio – teamed with a separate microcontroller to supervise operation. While there are some situations where a separate microcontroller is an advantage, so-called "two-chip" solutions complicate design and development, increase power consumption and require more space in the end-product.

Today's Bluetooth LE solutions are typically supplied in the form of the aforementioned System-on-Chip (SoC) – a device that incorporates the radio, microprocessor, memory and power management onto a single chip measuring 6x6 mm or less. The SoC approach was pioneered by Nordic with the launch of its nRF51822 in 2012, the company having since enhanced the concept with its nRF52 Series products. SoCs overcome the drawbacks of two-chip designs and additionally offer a common software development environment for both the Bluetooth LE RF protocol and the product's application software.

For example, Nordic's nRF52810 Bluetooth LE SoC – the baseline device in the nRF52 Series, offering an excellent cost/performance ratio and Bluetooth 5 capability – features:

- A 100 dBm link budget 2.4 GHz multiprotocol radio
- 64 MHz, 32 bit ARM Cortex M4 MCU
- 196 kB Flash
- 24 kB RAM.

Notably, the memory allocation is ample enough to run the application code typical of high volume, low cost applications required for medical applications. Like all Nordic's nRF51 and nRF52 Series SoCs,

the nRF52810 supports Over-the-Air Device Firmware Updates (OTA-DFUs), allowing the software of devices in the field to be upgraded using just the radio link. The nRF52810 SoC is supplied with the latest version of Nordic's S112 SoftDevice – a Bluetooth 5 certified stack.

The nRF52 Series also brings other features crucial to medical product development, notably "out-of-band" (OOB) pairing via Near Field Communication (NFC). This enables Bluetooth LE pairing to be established by simply touching an NFC-equipped smartphone to the medical device with no other interaction required from the user. Second, once the medical device is paired with the smartphone, data is secured by protecting the Bluetooth LE link with 128 bit AES encryption – a widely accepted and proven security protocol.

Bluetooth LE Modules

While Nordic's nRF52810 SoC incorporates all the hardware and software for a Bluetooth LE solution, further development effort is required to construct a working solution. Wireless (RF) products demand the addition of passive components that form matching circuits, antenna and crystal(s) to function correctly. Such additional circuitry can be difficult to design, particularly for those with limited RF expertise. Further, no Bluetooth LE-based product can be commercially offered without certification and testing from the Bluetooth Special Interest Group (the custodians of the Bluetooth standard) as well as meeting regional RF regulations, for example those of the Federal Communications Commission (FCC) in the US. Such testing can be both time consuming and expensive.

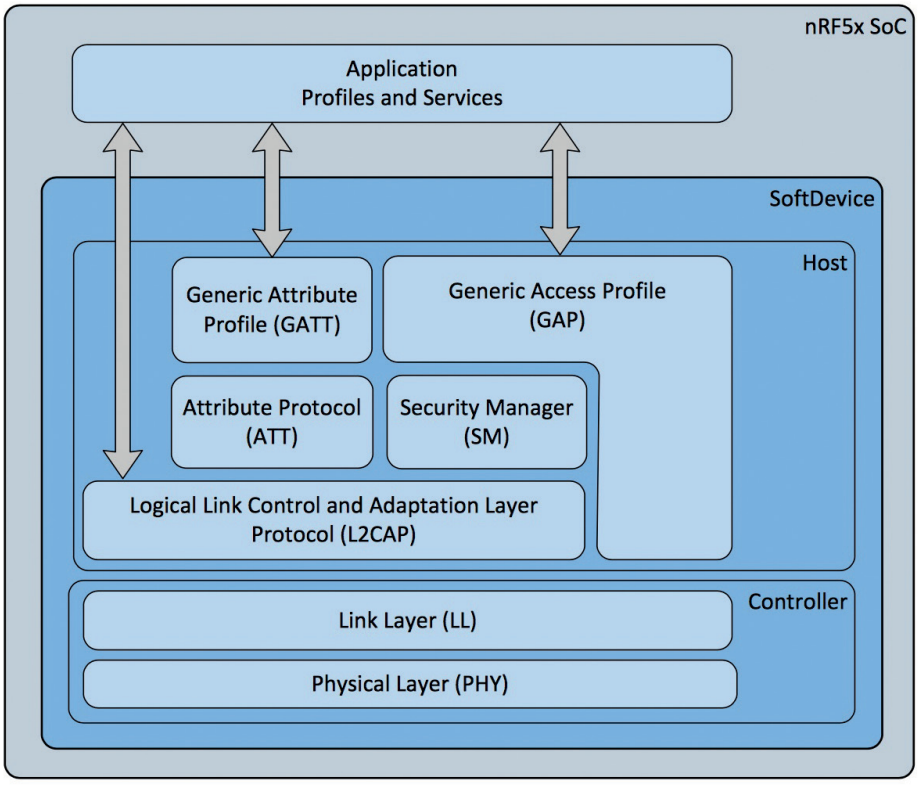


Figure 4: Nordic's software architecture separates the application code from the SoftDevice (the Bluetooth LE stack).

Reference designs from the Bluetooth LE SoC makers like Nordic significantly ease the design process. Adhering to a reference design ensures reasonable performance from a first prototype, which is then much easier to optimise for the specific application and shepherd through the certification process.

The design process can be further eased by adopting a module from the Bluetooth LE vendor or an approved third party. These modules are based on the same Bluetooth LE SoCs as discrete designs but also include pre-optimised external circuitry and antennas. A further key advantage is that the module will (in most cases) already be certified to Bluetooth Special Interest Group and regional RF regulations.[4]

Software Development

In addition to the hardware, some software development will be required for medical products. The factory supplied Bluetooth LE RF protocol looks after the communication link, but some application code is typically required to optimise the software for the target product. If the target application is, for example, an asthma inhaler, some coding will be required to monitor how often and when the device is used.

Among Bluetooth LE vendors, Nordic has a unique advantage during application code development. The company's software architecture separates the SoftDevice (the Bluetooth LE stack) from the application code, thereby removing the complexity of integrating the application software with the RF stack (Figure 4). Without this separation, it can be all too easy for the RF stack to be corrupted during software compilation – extending the development and debugging process. Nordic's SoftDevices are delivered as tested and verified binary files that always remain separated from the developer's application code. The company's development tools look after interfacing the application code to the SoftDevice during compilation.

Nordic also supplies a development kit (DK) and software development kit (SDK), which ease the design process. The DK includes the target nRF51 or nRF52 Series SoC and the SDK makes it simple to interface the SoC to the developer's preferred ARM integrated development environment (IDE). Notably, the SDK also includes simple application code examples which developers can use to accelerate the coding of their own application.

ABOUT THE AUTHOR

Thomas Soederholm is currently Director of Business Development at Nordic Semiconductor ASA in Oslo, Norway. He has a background in digital microelectronics design and has been in the microelectronics business for 18 years. Building on experience as a Regional Sales Manager in Europe, he now holds worldwide responsibility as Business Development Manager for sport, wearable and medical applications. Thomas has helped to establish 2.4 GHz connectivity (proprietary, ANT+ and Bluetooth LE) in the sport and fitness market. Today his focus is centred on applications in the medical and drug delivery space.

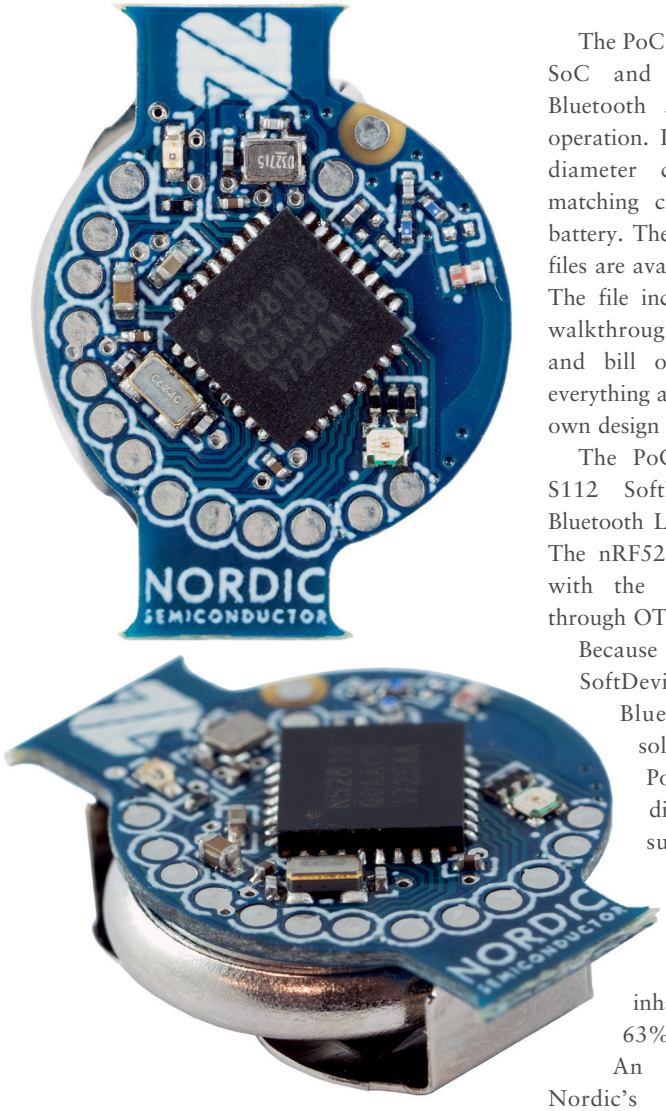


Figure 5: The proof-of-concept printed circuit board accelerates the development of Bluetooth LE-connected medical products.

Proof-of-Concept Development Tool

Nordic has brought together the key advantages of its nRF52 Series SoCs, Bluetooth LE SoftDevices, unique software architecture, reference designs and application code development environment in a PoC PCB designed to ease the process of adding wireless connectivity to medical products (Figure 5).

> "Adding Bluetooth LE wireless connectivity to a medical product promises to improve the effectiveness of drug delivery programmes dramatically..."

The PoC PCB is based on the nRF52810 SoC and S112 SoftDevice, enabling Bluetooth 5 certified peripheral device operation. It is assembled on a 13.5 mm diameter circuit board and includes matching circuits, antenna and coin-cell battery. The PoC and the necessary design files are available from Nordic on demand. The file includes a short description and walkthrough, circuit board schematics and bill of materials (BOM). This is everything a designer needs to develop their own design based on the PoC.

The PoC comes preloaded with the S112 SoftDevice and an Eddystone Bluetooth LE beacon application example. The nRF52810 SoC can be programmed with the developer's own application through OTA-DFU.

Because the nRF52810 with S112 SoftDevice forms a cost-effective Bluetooth 5/Bluetooth LE solution, the Nordic medical PoC PCB is suitable for targeting disposable drug delivery products such as asthma inhalers. According to a recent report from analyst Allied Market Research, the market for smart (wireless) asthma inhalers is set to grow at over 63% $CAGR_{2016\text{-}2022}$.[5]

An inhaler equipped with Nordic's Bluetooth LE technology can enable medication management by providing:

- An automatic medication diary, recording the amount and type of medication and when it was administered
- Notifications to remote family members and healthcare staff
- Usage statistics.

With the permission of the patient, the data could also be automatically sent to the manufacturer via the internet to allow for improvements to the performance of future products.

CONCLUSION

Adding Bluetooth LE wireless connectivity to a medical product promises to improve the effectiveness of drug delivery programmes dramatically by assisting patients with the management of medication while additionally recording useful data about drug usage for family members and healthcare professionals.

Designing wireless products can be daunting and many medical product companies may not have the necessary in-house RF skills to take advantage of the technology. The lack of such knowledge could prevent the company entering a market that not only promises to enhance patient care but is also likely to prove to be a rapidly expanding sector.

However, entry to the wireless medical product market can be considerably eased by partnering with a Bluetooth LE vendor such as Nordic. Such a partnership provides access to proven hardware, protocol firmware, reference designs, development tools and technical expertise which ease the path to prototypes, and then volume production, for companies lacking RF experience.

ABOUT THE COMPANY

Nordic Semiconductor is a fabless semiconductor company specialising in ultra-low and low power wireless communication in the license-free 2.4 GHz and sub 1 GHz Industrial, Scientific and Medical bands, and commercial LTE telecommunications bands targeting the Internet of Things and other wireless applications. Nordic is a Norwegian public company listed on the Oslo stock exchange (OSE: NOD).

REFERENCES

1. *"Dexcom G5 Mobile Continuous Glucose Monitoring System – P120005/S041", US FDA, December 20, 2016.*
2. *Brown MT, Bussell JK, "Medication Adherence: WHO Cares?". Mayo Clin Proc, 2011, Vol 86(4), pp 304-314.*
3. *Kastrenakes J, "Wi-Fi and Bluetooth are coming for the smart home". The Verge, 2016.*
4. *"Bluetooth 4.1, 4.2 and 5 Compatible Bluetooth Low Energy SoCs and Tools Meet IoT Challenges (Part 2)". Digi-Key Electronic, 2017. (www.digikey.com/en/articles/techzone/2017/apr/bluetooth-41-42-5-low-energy-socs-meet-iot-challenges-part-2)*
5. *Cision, "Smart Inhalers Market is Expected to Reach $191 Million by 2022, Globally – Allied Market Research". PR Newswire, 2016.*


CONNECTING YOUR DRUG DELIVERY DEVICES
Nordic Semiconductor delivers the most flexible, mature and reliable connectivity solution on the market, while maintaining low power and high performance in a tiny footprint. All running the latest Bluetooth 5 implementation. Easy-to-use development tools and samples are available through a worldwide distribution network.
COME DESIGN WITH US!
nordicsemi.com
nRF52810
nRF52832
nRF52840
NORDIC
SEMICONDUCTOR

NEIL WILLIAMS, MEDICOM INNOVATION PARTNER

Neil Williams is Director of Front-End Innovation and Head of Connected Health at Medicom Innovation Partner, which he joined in 2015 and where 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.

In this interview with ONdrugDelivery Magazine, Williams discusses the crucial role connectivity is taking in the drug delivery device industry, describes some of the challenges associated with patient privacy and how Medicom understands and overcomes these, and also explains how, as part of the Phillips-Medisize / Molex businesses, Medicom is well positioned to deliver connected delivery systems to clients, for small scale manufacture right up to very high volumes. He also introduces the third-generation connect health cloud platform that Medicom will be releasing in 2018.

Q Thinking of all the stakeholders – patients, clinicians, pharma industry, etc – what do you see as the most significant trends and most pressing demands driving the connectivity of drug delivery systems at present?

A For more than ten years the digital health world has been talking about the cost of care doubling, due in part to pressures on the healthcare system. There is pressure on the provider and care networks due to an ageing population: the diseases that occur as people age, the comorbidities and the cost of managing those conditions. Then we see a very significant increase in the payment-by-results agenda which puts a lot of pressure on the pharma industry to really demonstrate that they are getting the results they claim. That needs to be answered if pharma companies want to maintain price points.

There is, definitely, a big directional change in the biopharma world to realise this. I think, ultimately, the pressure is coming from the payers who are saying that if a treatment really meets its claimed p-value then they will pay, but if it doesn't meet that then the stipend that the payers arrange at the end-of-year contract isn't awarded.

I think, in almost every other aspect of our lives, technology has improved things for us. It could be argued perhaps that too many emails, for example, make life more complex, but overall things have improved thanks to connectivity. You can now turn your lights, heating and oven at home on and off from anywhere in the world using your smartphone, you can set your house alarm, book travel, rearrange car insurance. Yet for tracking your medication adherence, only a very few companies have really adopted connected technology early.

> "We are now creating the third generation of our connected health platform using world-leading technology that includes the most commonly used health integration engine and a very rich analytics tool … I've been involved in healthcare IT for 22 years now and this cloud platform that we're building out is far more advanced than anything we've seen on the market."

There is a big challenge with adherence. Only 50-60% of patients, even with chronic diseases, are adherent to their drug delivery. Non-adherence results in a huge burden – such as emergency department admissions – and ultimately death in many instances. The death of 125,000 Americans per annum is associated to medication non-adherance.

You have to look at who are the risk-bearing entities in this process. It's not so much the payers or insurers, it's the pharma companies … and obviously the patients themselves, who make lifestyle choices based on the information they get. More engagement, more connected drug delivery, should push up life expectancy for patients.

Patients live in a more connected world so they find it quite unusual, for example if they are using a prefilled syringe, that they have document their doses manually. It's another burden and one that in most other aspects of their lives they just don't see because things are increasingly done electronically, often automatically.

The accelerating migration of care from hospital facilities to the home is evident in all advanced care systems around the world. We need to be able to capture data in the home just as well as we would if the patient had come to the clinic for treatment. All of these things are accelerating towards a more connected ecosystem outside the hospital.

Q Please could you give us an overview of Medicom's offering in this field?

A The broad offering presented by Medicom is that we work with clients to manage product lifecycle right from Phase II or early Phase III to prepare for launch, to prolonging their opportunity with a drug when it comes off patent. We do that by creating a very specific user experience, directly related to the medication, to the patient and to the disease they have, and a strong engagement with the patient, using drug delivery device design.

There are various companies who you can go to and buy, for example, a ready-made autoinjector "off the shelf". We don't do this. We have more than 1000 technology accelerators that we can apply to designing a device for drug delivery. So the first point of contact is to create a great drug delivery device for particular patient groups that addresses specific needs, rather than trying to apply one system universally to different patient groups with different diseases and different lifestyles. We can get a device designed and developed often in a shorter time than it takes to get an "off-the-shelf" device through the applications and approvals process.

Additionally, we are now creating the third generation of our connected health platform using world-leading technology that includes the most commonly used health integration engine and a very rich analytics tool that allows our clients to assess data from patients globally. It complies with all of the privacy laws. It creates a highly structured, codified database so our clients can do global comparators, look at different behaviours in different markets, do some behavioural science. It provides the means to compile data that is solid enough to be used for publishing research, for reporting Phase III studies etc, with the aim of really improving adherence. It supports US 510(k), combination product submissions, the medical device data system (MDDS). It uses the same technology that underpins some of the world's most successful hospital electronic medical record systems and is used by health systems around the world to empower integration.

I've been involved in healthcare IT for 22 years now and this cloud platform that we're building out is far more advanced than anything we've seen on the market. It will be fully released during 2018 but it's being made available to some clients now; we're already working with organisations that are adopting it.

Figure 1: Medicom is evolving enterprise-wide technology platforms that support healthcare.

A big problem with many of the connected medical technology platforms available on the market right now is that they are monolithic solutions, created around a drug, which are expensive and cannot be repurposed. Medicom too has taken this approach in the past. What we are creating now is an enterprise-wide connected health solution that allows patient identifiable information and device data all to be integrated into a common platform. It functions across a client's entire business, so it's not franchise by franchise.

Other systems that are out there are either monoliths, pure device data repositories or offer limited regulatory flexibility, don't support enterprise wide "multi franchise" data management and lack the powerful analytics needed for population health. You need to then create a separate clinical database, and to get meaningful data you need to connect the two, and the device data becomes patient identifiable. This all just sounds very old-hat compared to what the latest technology makes possible in connected health. What we see a demand for, and will bring to market, is something that really specifically addresses the biopharma need for an enterprise-wide connected health solution.

> "Privacy is a really important issue, and trust is an equally important issue. In the end, the patient needs to be in full control of what they share and with whom. That's the only ethical position to take."

We have deep understanding of privacy laws, and extensive experience too, having taken connected solutions to market in more than 30 countries already. We'll deliver our cloud platform uniquely to clients so that you will never have data belonging to pharma company one located in the same place as data belonging to pharma company two – they will always have separate environments.

To summarise Medicom's offering, it goes from enterprise-wide connected health, covering all franchises with one common platform, to delivering unique patient experiences by franchise and designing unique drug delivery devices by franchise based on our extensive technology accelerator portfolio.

Q Why did Medicom opt for parenteral and pulmonary devices in the first instance?

A I think it's because we saw these routes of delivery as the highest revenue risks to biopharma companies. About six or seven years ago, Medicom realised that particularly injectables were going to become a challenge, especially as the biosimilars world was developing very rapidly. A lot of those drugs were being developed for rare diseases, as orphan drugs, and of course a lot of CMOs weren't really geared for dealing with low volumes. We focused on that niche of rare diseases, complex delivery, etc. We also have extensive experience in the inhalation segment and, additionally, have done a lot of work in smart pill packets.

Q A strength of Medicom now, through its parent company Phillips-Medisize, is industrialisation know-how. How does this know-how add to the mix when it comes to connected devices?

A Since June last year Medicom has been part of Phillips-Medisize. Historically, Medicom was geared towards low-volume manufacturing, rare diseases for example. Now we're extremely well integrated with Phillips-Medisize and of course Molex, a global electronics leader. In our projects now we include all aspects of the entire business and we can now engage with projects that go to volume. We've got clients that require more than 100 million units a year. So we go from small scale, which we produce at Medicom's own facilities in Denmark, through to full global production at facilities around the world.

The challenge we had historically is that, whilst we have a very talented resource in Denmark and Cambridge, UK, with which we'd have gone through a great design process with a planned manufacturer, we would have had to have done a technology transfer and there is always a bit of pain in doing that tech transfer. Whereas nowadays we have Phillips-Medisize as part of the team right from the beginning. It really works as one company. And if we need electronics insight, who better than Molex to have as a go-to partner! So we can handle everything – full board design, full-scale manufacture and all the interconnects. We have great experience in Medicom around wireless connectivity and app design. We're building the truly differentiated cloud platform as I mentioned just now.

We're still the only company with a combination product connected auto-injector, the BETACONNECT™ (Figure 2), that's launched in both the US and the EU. We have other technologies that will reach the market with other clients during 2018.

Since the acquisition, our capability to do things on a global basis and set up manufacturing facilities around the world puts us in a completely different space to where we were in say early 2016.

Q In today's drug delivery business, whilst the drug formulation, the pharma company, regulation and numerous other factors are naturally all critical considerations during device design, the patient is always front and centre. Can you talk about what benefits Medicom's technology and expertise bring specifically to the patient?

A There are a couple of points I'd make here. First, from Medicom's perspective, no experience is "generic". We create unique experiences by disease, by drug and we can even tailor that further by, for example, age group. The requirements that a six year old girl has of her treatment are different from those of a sixty year old man. Their experiences are different, the education and training during their treatment are different, the way they are encouraged during the course of their treatment is different. We tailor that specifically.

We engage with patients right at the beginning of the process and we do a huge amount of usability work. Typically we get that done quickly – in about three to six months, and before we go into design controls.

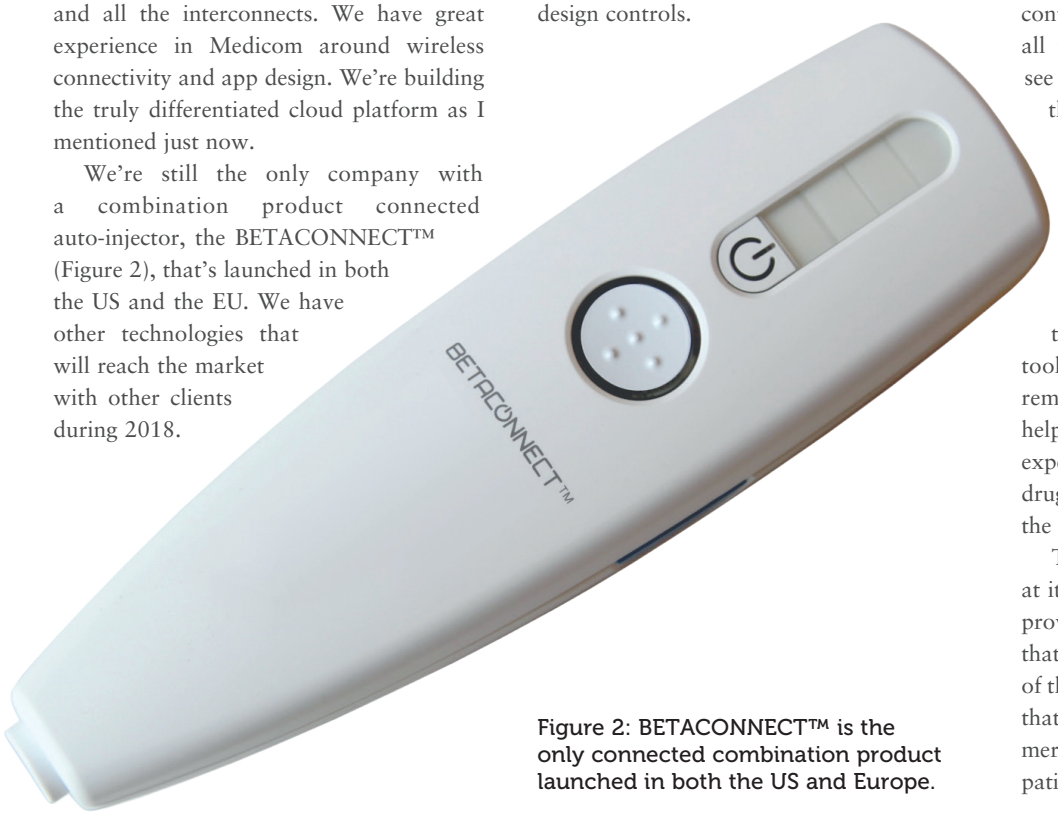


Figure 2: BETACONNECT™ is the only connected combination product launched in both the US and Europe.

Second, privacy is a really important issue, and trust is an equally important issue. In the end, the patient needs to be in full control of what they share, and with whom. That's the only ethical position to take. There's no need to restrict somebody from using a tool if they're anxious about where the data goes, so in all scenarios we give the patient the opportunity to choose whether they share their data back to the pharma company, whether it is anonymised or identifiable. If they want to be considered for research projects then by default they will have to identify who they are.

Patients can also decide who else they want to share their data with. They may have a loved one or a carer who they want to give access to their data. There's also alerting. For example for emergency medication or something unusually episodic you might share data on that but no information about your background dosing. Results can also be shared. We integrate with testing technology and patients can put their results into various tools. Also connected technology can be used to help create what are known as "legitimate relationships" with healthcare providers so patients may wish to share their data with their provider network.

Increasingly we see providers setting contracts with patients to share the data if they want to continue to use smart devices, but the ultimate result is that it must be really and totally in the individual patient's control. They have the option to switch all these things on and off. They should see the pharma company as a sponsor for them to use their technology, whether or not they share the data. If they don't share their data they can still use the connectivity between their device and their smartphone.

It's not a philanthropic venture on the part of the pharma company though. Biopharma are providing a tool that offers education, engagement, reminders for adherence etc, which all helps make sure the patient has a good experience while being treated using their drug. But the patient does not need to share the data at all.

Today, when a pharma business is looking at its patient population, the product that's provided is not just the drug, it's the services that are provided around it, and certainly all of the organisations we work with recognise that patient engagement is more than a mere marketing tool. It's about making sure patients adhere and that they get the best

results possible from the medication that's been prescribed to them.

From our perspective, because of our third-generation connected health platform, data can potentially go straight back into the care provider network, almost bypassing the pharma business and going straight to the clinician.

Privacy is a big challenge. Obviously the EU GDPR [General Data Protection Regulation] will be in effect from May 2018 which creates an additional burden on the pharma companies. There are massive differences between North American privacy laws and those in the EU. The EU is more stringent. For example, under CFR21, in the US patients shouldn't be able to fully delete their data in case there's a legal challenge later in life. They can suspend access to their data but they cannot delete it. In the EU though, you have the right to have the data removed. Even different markets in Europe have a different view on privacy. The GDPR regulation is trying to harmonise this but our experience is that there was an EU-wide standard beforehand but implementation in each market changed – sometimes because of privacy and sometimes because of clinical practice. As a business, Medicom understands this complex area well and we know how to create regional variations of a configuration.

Q How does Medicom fit with the wider Phillips-Medisize and Molex organisational structures and strategies?

A For legacy Medicom projects already underway at the time of the acquisition, Phillips-Medisize and Molex have added substantial additional insight. A number of projects started almost immediately after the acquisition because the deal really caught the industry's attention. On these we have teams of people across all of the business units but we all work as one. A decision is made early on for each project as to where is the best place to lead it from. But the businesses work together. So if we need electronics insight we bring Molex in early.

Molex have fantastic technologies – flexible boards (they can even print circuit boards on paper that you can wrap inside drug delivery devices like pens), tiny interconnects, great power management – things that are beyond what Medicom alone would have been able to deliver in-house. Phillips-Medisize is well-known for being accomplished at producing at volume. They really understand design for volume. And so everyone is involved right from the beginning.

One of the key things we offer to clients is something we call "Jump Start". We simply run a workshop for a couple of days with them. There are usually two weeks' work ahead of that during which we learn as much as we can about the client's needs from the information they provide to us. But during the workshop with them we really assimilate all of that, capture all their needs and by the end of a couple of days we've reached a point where we're visualising what their device and software solution could be. This approach saves a lot of time and money for the clients. They are very quickly in to working out the art of the possible, not trying to be on bleeding-edge technology but on the leading edge. All of the value-add components across the Medicom, Phillips-Medisize and Molex business units are applied to the client when they need to be.

Looking at how it works commercially, there are things that come to Medicom because clients see a need for a complex design and technology solution. There are things that go to Phillips-Medisize where, for example, clients are quite advanced in their design concept and are asking questions around going to volume. Each of us pulls bits of the business in as needed.

On the level of the people the integration has been really smooth. We're all on first name terms across the business units, we genuinely work together closely and you'll often see people from across all three divisions attending conferences together as one team. I've been through M&As before elsewhere and there's typically a struggle and some pain and, often after acquisitions on this scale, you'll naturally see a human impact on the business evidenced by quite a number of people leaving. This just hasn't happened in the case of Medicom, Phillips-Medisize and Molex because everything has been additive.

The acquisitions are a really good story. Medicom strengthens the organisations in the connected drug delivery space. Medicom have advanced connected drug delivery insights, Philips-Medisize bring advanced, global, volume manufacturing and additional device design capability, Molex are a leading design and manufacturing electronics business.

Q Finally, please could you tell our readers a little about yourself, your career, and what it is about Medicom in particular that, for you, makes it an attractive organisation to be a part of?

A I've always worked in healthcare. I used to work in Critical Care and was often engaged in medical education by the Department of Resuscitation Science at Leicester University Hospitals. I left there 22 years ago to work in medical devices, clinical decisions support, healthcare IT, health analytics and care pathway design. I joined Medicom Innovation Partner two years ago to evolve their connected health offering that will emerge next year as our third-generation connected health platform. I'm based in Cambridge in the UK but have worked all around the world.

I have been involved in drug delivery previously – I used to run marketing for devices for Hospira in the EMEA. I also have experience working in patient engagement, having worked for Microsoft for some time looking after their HealthVault platform across EMEA.

I saw Medicom as a really interesting business that was growing well, had really good leadership and a good vision of where it wanted to be. To me, Medicom just presented an opportunity to solve many of the problems that pharma was facing.

I remember the first pharma conference I attended after joining the company and listening to all the fear, uncertainty and doubt in the room about privacy, liability, pharmacovigilance, all of those challenges. I thought to myself, we fixed all of this in healthcare IT years ago. No-one expects their MRI to turn up on YouTube! There are lots of rules, processes and standards already in place that you can take from the care delivery network and use because it's well proven, well developed and tested over many years. You can apply it to what is in effect an expanded care delivery network, moving medication delivery from the clinical facility into the home. We've discussed the benefits of this move already, but for the patient it is simply better to resort to hospital treatment only when it is really needed, because people who stay in hospital longer than necessary are more like to get sicker. If patients who can be treated at home are treated at home they are more likely to recover.

For me, looking at Medicom I saw that this was a great company because it was

pushing the boundaries in that space. They had already created great technology, they had a good foundation, and I thought, this is somewhere we can really make some impact and create value for stakeholders. The acquisitions just enhance that. Molex is itself part of Koch Industries and so the reach and capabilities, and the level of investment we're now making, were never possible in the Medicom only days. It's an even stronger business than the one I joined two years ago – and the level of interest and the pipeline of work has expanded dramatically. It always was an exceptional business with talented people and these days there are more than 500 talented engineers that we have access to around the world, all focused on drug delivery. It's a great place!

ABOUT THE COMPANY

Medicom Innovation Partner (a Phillips-Medisize Company) is a leading global innovation, development and low-volume production provider focused on drug delivery devices and connected health solutions. Medicom Innovation Partner was established as a technology venture of Bang & Olufsen A/S in 1989 and the company has been a dominant player within the drug device world for more than 25 years. Medicom holds a dedicated staff of more than 90 high-calibre innovation specialists, mechanical, hardware, software, quality assurance, regulatory and production engineers based in Struer, Denmark, and Cambridge, UK. Medicom has experienced considerable growth over the last five years.

As of May 31, 2016, Medicom became part of Phillips-Medisize Corporation. Phillips-Medisize is a leading global outsource provider of design and manufacturing services to the drug delivery and combination products, consumable diagnostics and medical device, and speciality commercial markets. The company has annual sales of over US$700 million with 80% of the total revenue coming from drug delivery, medical device, primary pharmaceutical packaging and diagnostic products, such as disposable insulin pens, glucose meters, speciality inhalation drug delivery devices, single-use surgical devices and consumable diagnostic components.

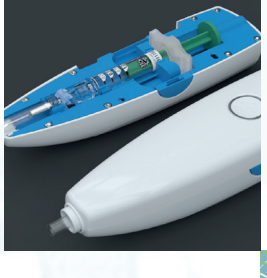
Together Phillips-Medisize and Medicom are becoming one of the leading players within the growing drug delivery device and connected health market.

Medicom Innovation Partner
a Phillips-Medisize Company

Mr Neil Williams
Director Front-End Innovation
Head of Connected Health
T: +44 1223 786953
E: nwi@medicomip.com

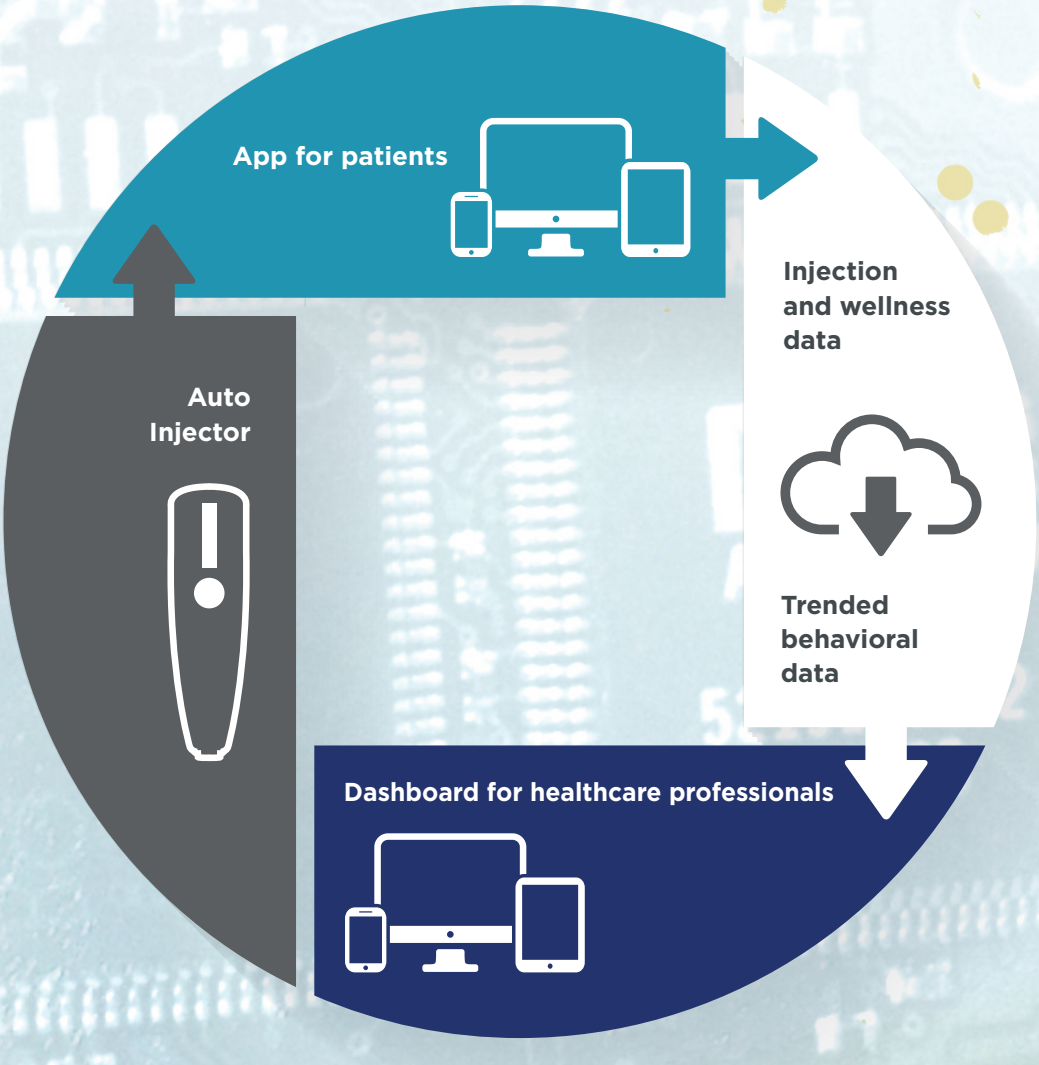
Medicom Innovation Partner Ltd
a Phillips-Medisize Company
Milton Hall, Ely Road
Milton, Cambridge
CB24 6WZ
United Kingdom

www.medicomip.com



World leaders in patient centric drug delivery systems

Devices
Connectivity
Connected Health Service Solutions



Medicom Innovation Partner
a Phillips-Medisize Company

Phillips Medisize
a molex company

ENERGY HARVESTING: POWERING CONNECTED DRUG DELIVERY DEVICES

Here, Charlotte Harvey, Consultant Mechanical Engineer, Sagentia, examines the opportunities and practicalities of using energy harvesting technologies in drug delivery devices. With a specific focus on enabling connectivity functionality, Ms Harvey runs through the various aspects of energy harvesting and offers insight on whether it is the right choice for a new device development.

INTRODUCTION

Connectivity has become a watchword for the drug delivery industry, but it's more than just the latest trend. There are many benefits to a device that can communicate externally; some are obvious, providing the ability to monitor patient behaviour and compliance with a treatment plan for example, but other benefits are less so. Connected users might be given access to a specialist portal, through which they can manage their condition and get advice remotely from healthcare professionals. The proliferation of smartphones and ubiquity of wireless technology makes connectivity an essential tool for doctors, who are increasingly involved in post-diagnostic care. With Bluetooth Low Energy (BLE) and near field communication (NFC) technologies now readily available, the race is on to connect drug delivery devices and so help improve patient outcomes.

Drug delivery devices have not traditionally been designed with a built-in power source. However, without power the device is unable to support the electronics required to incorporate BLE or NFC and enable connectivity. Next generation connected devices will therefore need printed circuit boards (PCBs) and batteries or an alternative means to generate energy. The product development process for such next generation devices will need to evaluate the trade-off between the benefits that connectivity offers versus any impact on usability, the environment, shipping and regulatory compliance.

> "In some cases, the optimal solution may be simply to avoid the use of a battery altogether. Instead the energy required to power the device could be generated by 'harvesting' the energy in-use."

Introducing a battery to a device can create new design challenges, such as reducing shelf life, creating complications around disposal and determining the device's size. In some cases, the optimal solution may be simply to avoid the use of a battery altogether. Instead, the energy required to power the device could be generated by "harvesting" the energy in-use (Figure 1). Most connected device functions require low levels of power and thus are well-suited to energy harvesting, which provides energy naturally in small packets. However, to make the most of these energy harvesting technologies, it's best to keep the connectivity subsystem relatively simple. This article explores how energy harvesting could be applied to drug delivery devices to provide the power required for connectivity. It recognises that, rather than having broad applications, energy harvesting is most effective when applied in specific circumstances.

There are other methods which can be considered when batteries have been ruled out. These often require conversion to electrical power at point of use:

- Gas canister
- Osmotic drive
- Compressed spring
- Biocell.

The design of an energy harvesting subsystem can be broken down into source, storage and use. The energy must be sourced from either the environment or the user

Charlotte Harvey
Consultant Mechanical Engineer
T: +44 1223 875200
E: info@sagentia.com

Sagentia
Harston Mill, Harston
Cambridge
CB22 7GG
United Kingdom

www.sagentia.com

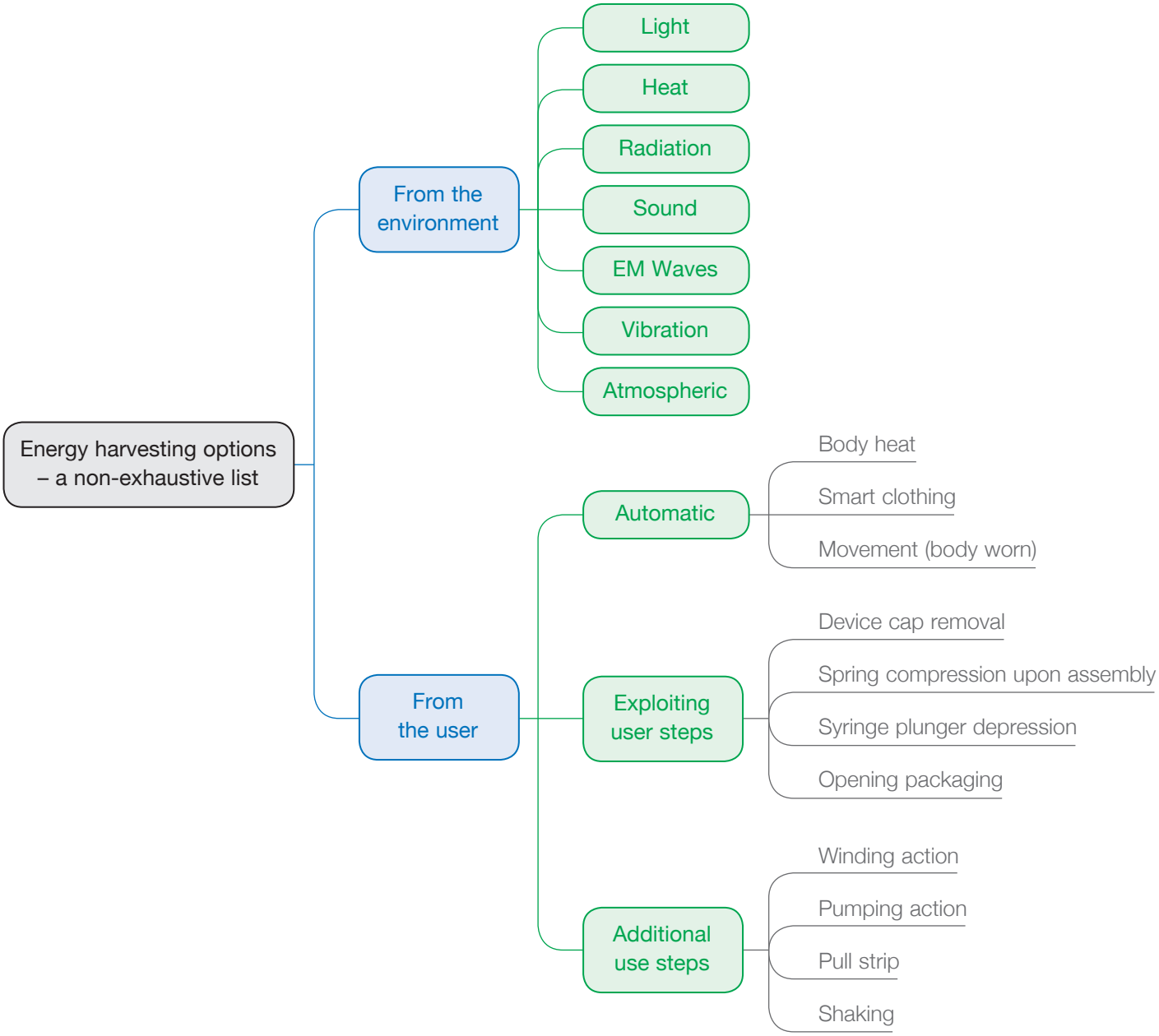


Figure 1: Sources of energy with the potential for harvesting.

themselves. Then it needs to be stored for use at the appropriate time and employed in a way that maximises its efficiency. Consideration also needs to be given to the disposal of the device and how the new embedded technology affects the end of the product lifecycle.

ENERGY SOURCING

There are a number of options when it comes to deciding where to source the energy needed. However, when the typical use case and environment for the device are taken into account the options quickly narrow. Energy harvesting should be the preferred option only when the overall device design will benefit.

Questions to consider:

- How much control do we as designers have over the use environment?
- Do we even know enough about the use environment at this point to ensure consistency and reliability?
- How much do we want to rely on the user to ensure that the energy harvesting technology is working properly?

Heat and light are the two most common forms of waste energy found in everyday environments.

Heat energy is primarily harvested through the use of thermo-electric generators (TEGs). TEGs are able to produce electrical energy when there is a temperature gradient across them, therefore care is needed not to allow the TEG to completely warm to ambient temperature as the necessary heat flux would be lost.

Due to the development of flexible TEGs, it is now easier to harvest heat from the body. These flexible TEGs can conform to the skin, improving the thermal interface. Human skin temperature is typically about 34°C, whilst room temperature is typically about 18-25°C. A drug delivery device held against a patient's skin could leverage this gradient and harvest the energy.

An alternative way to use heat energy would be if a drug cartridge is taken from a fridge and left to warm prior to injection. It may be possible to harvest enough energy as it warms to send a message

"The simplest way to harness energy from the user is to exploit activities the user would have performed anyway. For instance, the action of opening packaging or pushing a syringe plunger could be used as an energy source."

via BLE that the drug is ready to inject. Additionally, such a signal could double as compliance monitoring.

Light can be transduced into electrical energy through the use of photovoltaic (PV) cells. In recent years the price per square metre of PV cells has come down significantly, due in part to national governments seeking to increase their renewable energy generation capability. There now exists a package that is capable of transmitting BLE signals using just the energy from indoor fluorescent lighting.

A solar powered device has an availability issue however, in that the device may be stored in a dark place (fridge, bathroom cabinet), or may typically be only used at night (user injects before bed). It might be possible to require the user to leave the device in the light to charge, for they would charge any other device, but this risks the user forgetting to do so.

THE USE ENVIRONMENT

Previous examples illustrate the importance of fully understanding the use environment prior to designing the device. To control for the edge cases, we should also consider how much responsibility is entrusted to the user. The standard in human factors engineering is to reduce user responsibility and, certainly for devices a patient is more dependent on, this should be the aim. In such cases, the reasons behind any decision to design out a battery should be re-assessed to consider whether other options present different, more onerous challenges.

By focusing on the user and their interaction with the device we can arrive at alternative solutions. The simplest way to harness energy from the user is to exploit activities the user would have performed anyway. For instance, the action of opening packaging or pushing a syringe plunger could be used as an energy source. If so, it is likely that this natural step in operating the device may need to be designed in a way which ensures it produces the required energy. This, however, may be at odds with the need to keep operation of the device as simple as possible. For example, care must be taken not to over-exert particular patient populations with manual dexterity or strength issues.

Where more power is required (or on a device where there are only a few user steps), a user action might need to be added solely for the purpose of harvesting energy. This could be in the form of a manual step such as winding, pumping or shaking. Although these methods will create more energy, they are also more taxing for the user and have knock-on effects on usability. It may be difficult for users to accept this approach therefore, particularly in cases where there is a competing device which asks less of them. On the other hand, if there is a clear pay-off for the user the device is more likely to be more readily adopted.

Many devices already take advantage of energy harvesting from user actions for functions other than those related to connectivity. The most common is priming a spring for the delivery of a drug product using a rotary or direct pull/push motion. The energy stored in the spring is then released by a button press, or similar, when the energy is needed. Such an approach could also be used to both harvest energy and store what's generated.

With all user-based energy harvesting technologies, careful consideration will have to be given to the ISO 62366 guidelines which specify the usability requirements around the development of medical devices. Any design approach which could be seen as compromising usability will need to be justified. Since batteries already exist as a safe technology option, this could be a challenge.

ENERGY STORAGE

In an ideal world, the generation of power via energy harvesting would occur just before the energy is needed. For instance, a Bluetooth signal triggered and powered by the user attaching a vial to a high-volume pump. Unfortunately, in practice there will frequently be a delay between when the energy is harvested and when it is needed. Storage solutions must account for this.

Considerations when looking for a storage solution:

- Efficiency – not losing the energy which has been gathered.
- Availability – connectivity applications typically require small bursts of energy at specific times. The energy must therefore be readily available for use.
- Delivery parameters – there will be power requirements dependent on the specific use of the energy. Storage solutions vary in how they perform.

At first glance, supercapacitors seem like an ideal energy storage medium for energy harvesting – they bridge the gap between traditional electrolytic capacitors and Li-ion cells. This makes them capable of much more rapid charging than a traditional cell whilst having a much greater energy density than capacitors. This capability to rapidly absorb power is important since the power available for harvest can be highly unpredictable and may feature large spikes.

On further inspection, supercapacitors have some noteworthy disadvantages which make it important to consider their use carefully. Whilst they are far more energy dense than electrolytic capacitors, they typically have 1-5% of the capacity of Li-ion. They also suffer from a high self-discharge rate. This combination makes them unsuitable for use as long term storage, and as such should be restricted to situations where energy is harvested and used in a similar time frame. Beyond this scenario they tend to be significantly more expensive than a battery. Typically, the maximum allowable voltage of a supercapacitor is around 2.7 V which can create the need for DC-DC converters,

"Even devices with rigid or high power requirements can benefit from an energy harvesting approach. It may be possible to compartmentalise different activities within a device and use energy harvesting for some of those functions."

as the voltages required for BLE can be higher, or additional supercapacitors and a balancing network. All of this can increase size, cost, inefficiency and complexity.

These considerations imply that, if a device needs to communicate often and straight off the shelf, a supercapacitor would not be the correct storage medium. For applications where power is only required for a short duration or enough energy can be harvested from the environment to perform infrequent tasks, a supercapacitor may be the right choice.

The optimal choice of supercapacitor and/or battery for the application will depend upon how the energy is generated and used. In the instance where energy harvesting is being used to make way for a smaller battery, it may be difficult to match the energy harvesting output generated to the battery specification. In the cases where user activity is the source of energy, direct transference to a supercapacitor is difficult if the user action is slow and steady because a supercapacitor is better at storing energy released in a burst. To get around this issue the energy generated from harvesting could be stored in an intermediary, such as a spring or a compressed gas, and then transferred to the battery at the appropriate rate.

ENERGY USE

Harvesting energy in a handheld drug delivery device is far easier if the manner in which the generated power is put to use is kept flexible. For example, ideally data transmission would wait until the requisite energy is available.

If the device has strict power requirements, or requires a significant amount of power to function, it may be tempting to rule out energy harvesting as an option. However, even devices with rigid or high power requirements can benefit from an energy harvesting approach. It may be possible to compartmentalise different activities within a device and use energy harvesting for some of those functions. This may then enable simplification of the overall system. Alternatively, it may be sensible to separate a device out into its re-usable and disposable components. The disposable element can operate independently if an energy harvesting technology is used, dramatically reducing instances of battery disposal.

Finally, it is important to ensure that any critical device functions are being powered by a reliable energy source. As many connectivity functions are not typically critical, they may be well suited to energy harvesting. However, this design decision should be well understood as it can be tempting to then expand the use of this energy to other functions which are essential to the effective use of the device, which could put the patient at risk.

DISPOSAL

The fact that batteries can be difficult to dispose of is often the reason for their exclusion from a new product design. If that is the case it is vital that any alternative option for powering the device does not present similar challenges.

Disposal of some of these alternative technologies is also poorly catered for, particularly in domestic settings. For instance, it is easier for a user to recycle a battery than it is to recycle a biocell. Furthermore, consumers will also find solar cells challenging to dispose of, as this normally takes place on an industrial scale. If the disposal process becomes part of the device manufacturer's responsibility these problems can be dealt with effectively, although it would place an additional burden on the manufacturer.

Whilst Li-ion cells are classed as hazardous waste and require special disposal processes, supercapacitors are classed as non-hazardous waste and could be disposed of with the rest of the device.

Disposal concerns are not the only reason to remove batteries from a device design. Whatever the deciding factors for excluding batteries are, the new energy harvesting technology needs to be analysed against those same criteria. As these technologies are typically fairly novel and complex to implement (in comparison with a battery), there should be a clear benefit to their introduction.

HOLISTIC DESIGN

Energy harvesting is not an approach which should be universally adopted across all drug delivery devices; it supplies only small amounts of energy and can introduce design complexities. A thorough review of all the options available must be carried out for each project to ensure that energy harvesting is right for the design and that the correct technology is being implemented for maximum efficiency. It is important to match the technology with the right system design and use case, using energy harvesting in place of battery technologies for the right reasons. In specific applications, such as when the only powered device function is connectivity, it can be exactly what is needed.

ABOUT THE COMPANY

Sagentia is a global science, product and technology development company, assisting companies in maximising the value of their investments in R&D. Sagentia partners with clients in the consumer, industrial, medical and oil & gas sectors to help them understand the technology and market landscape, decide their future strategy, solve complex science and technology challenges and deliver commercially successful products.

Sagentia employs more than 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and cutting-edge product development services focused on science and technology initiatives. It has seven offices globally, two UK-based dedicated R&D innovation centres and more than 470 employees. Other Science Group companies include OTM Consulting, Oakland Innovation, Leatherhead Food Research and TSG Consulting.

ABOUT THE AUTHOR

Charlotte Harvey is a consultant mechanical engineer at Sagentia. Her experience lies predominantly in managing medical product developments, specifically those in the surgical and injectable drug delivery fields. As such, she has recently experienced the issues related to incorporating connectivity functions into these devices first-hand. Recent projects have included front-end innovation in the drug delivery space, user interviewing for human factors, and development of reconstitution-based auto-injectors. Ms Harvey graduated from the University of Cambridge (UK) with a Masters in Mechanical Engineering.

Drug Delivery & Packaging

Pharmapack

INNOVATION • NETWORKING • EDUCATION

EXHIBITION & CONFERENCE 7-8 FEBRUARY 2018 PARIS EXPO, PORTE DE VERSAILLES

Pharma's dedicated packaging & drug delivery event

- Innovation Gallery
- Pharmapack Awards
- Innovation Tours
- Pharmapack Start-up Hub

- Networking Areas & Events
- International Meetings Programme

- Conference
- Symposium
- Workshops
- Learning Lab

FREE to attend!

REGISTER NOW!

Follow the link: bit.ly/2uJnYTF

#PharmapackEU

UBM

NEWS, WHITEPAPERS & EVENT PROGRAMME AT WWW.PHARMAPACKEUROPE.COM

THE PROMISE OF VOICE: CONNECTING DRUG DELIVERY THROUGH VOICE-ACTIVATED TECHNOLOGY

In this article, Chris Franzese, Lead Clinical Analyst, and Marty Coyne, Principal and Founder, both of Matchstick, discuss the vast potential that voice-activated technologies, such as Amazon's Alexa, have in the healthcare market. Running through the challenges posed by data security and human factors, they go on to explain how the rewards voice-activation offers are well worth the effort, spanning the drug delivery experience.

MARKET PENETRATION, USER TRUST & POTENTIAL FOR HEALTHCARE

Since the introduction of Apple's Siri, the first voice-activated assistant installed on a smartphone, voice-activated technology has become increasingly accessible to users. The voice-activation market has expanded to encompass technology from other tech giants like Google (Home), Amazon (Echo) and Microsoft (Cortana). According to a recent projection, by the end of this year 35.6 million Americans will use such technology at least once a month, a 128.9% increase over last year.[1] This interest continues to build – a 2017 report by Parks Associates found that 56% of US households with broadband access find it appealing to use voice assistance to control smart home devices.[2]

Amazon, as the first company to embrace the technology, has dominated the market, having an estimated 70.6% share of consumers using its Alexa-enabled devices.[1] According to data on recent internet trends, Amazon shipped approximately one million Echo devices in the first quarter of 2016 alone, with the total number of devices installed in the US to date quickly approaching 12 million.[3,4]

Amazon has also pioneered the employment of voice-activation beyond consumer use, notably having been behind some of the early applications of this technology in healthcare. Some examples include Kids MD, a program (termed an "Alexa Skill" by Amazon) designed by Boston Children's Hospital to deliver advice about fever management to parents of sick children; WebMD, which employs the well known website to answer basic health-related queries; and, most recently, Sugarpod, an integrated scale and mobile app concept developed by Wellpepper for patients with type 2 diabetes.[5-7]

> "As the technology moves into healthcare it also takes its first steps into a far more regulated environment than that of consumer products."

PATIENT PRIVACY & DATA SECURITY

Thus far most applications of voice-activation have been targeted towards consumers, rather than the healthcare market. This is starting to change however, and as the technology moves into healthcare it also takes its first steps into a far more regulated environment than that of consumer products. For instance, in the US, where voice-activation adoption has occurred most rapidly, the biggest questions surround the privacy and security of protected health information (PHI), as detailed in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and Security Rule.

In short, the Privacy Rule provides legal protections for individually identifiable health information held by HIPAA "covered entities" (healthcare providers, health plans or healthcare clearinghouses) and their "business associates" (those who are authorised to use this information on a covered entity's behalf). This includes giving patients the right to obtain a copy of their PHI, know the identity of those who have received their information and request limits on who may access it.[8]

The Security Rule, on the other hand, specifies a series of administrative, physical

Chris Franzese
Lead Clinical Analyst
T: +1 973 753 0383
E: chris@matchstickllc.com

Marty Coyne
Founder & Principal
T: +1 973 753 0383
E: marty@matchstickllc.com

Matchstick, LLC
712 Main Street
Boonton NJ 07005
United States

www.matchstickllc.com

"In practice, patients may misname, mispronounce or use a number of different terms to describe their drug delivery devices, treatments or laboratory measures. Failure to test for these nuances during human factors studies and anticipate these events during actual use could pose significant risk to patients where voice-activated technology is involved."

and technical "safeguards" that covered entities and their business associates must implement to prevent unauthorised or inappropriate access, use or disclosure of electronic PHI. This involves assuring clear policies and procedures are in place, risk management is conducted and data is appropriately encrypted both at rest and during transmission.[8]

Whilst many components of Amazon's ecosystem are currently HIPAA-compliant, Alexa is not. This fact has shaped, and effectively limited, the capabilities of currently marketed healthcare Alexa Skills. Firstly, because HIPAA regulations strictly apply to covered entities, Amazon's voice-activation cannot yet be employed in clinical settings where patient information is collected and used (e.g. via integration with electronic medical records). Secondly, without access to a patient's full clinical picture (e.g. medical history, medications, laboratory values), Alexa cannot act on the information it receives to deliver true medical interventions. Instead, it is currently limited to activities like patient self-monitoring and simple data retrieval. For example, Alexa may be able to tell a diabetic patient what their last blood glucose reading was and how many carbohydrates their lunch contains, but it cannot instruct them on how many units of insulin they should take to accommodate their meal, given other factors like insulin sensitivity, concomitant anti-diabetic drugs or recent exercise.

With the recent shift in drug delivery towards patient self-medication, the limitations on voice-activated technology seem likely to change. A 2016 report to Congress serves as an early indicator, where the US Department of Health and Human Services highlighted significant gaps that exist in current legislation with regard to digital health.[9] Still, there are more than technological and policy barriers that must be overcome to ensure voice-activation is ready to realise its healthcare potential.

UNIQUE HUMAN FACTORS OBSTACLES

If voice-activation is to be used alongside, or in conjunction with, medical devices in a clinical setting, it must receive rigorous scrutiny from a human factors perspective. As with medical devices, voice-activated technology must account for specifics of the intended user and use environment to ensure safe and effective use. Unlike most medical devices, where the user interfaces with the device in a primarily tactile and visual manner, voice-activation is an inherently intangible interaction and singular mode of feedback, therefore presenting distinct usability challenges. Some of these challenges were highlighted in a recent analysis of Amazon Alexa user reviews.[10]

User Specific Human Factors

In traditional medical device human factors studies, user specific requirements typically take into account variables like physical dexterity, cognitive abilities/limitations, literacy/language skills and mental/emotional state, all of which may be influenced by an individual patient's disease or comorbidities. Where voice is concerned, these considerations could manifest as differences in pronunciation (including accent), volume or word choice, all of which are factors that may be specific to, or influenced by, an individual's disease.

In practice, patients may misname, mispronounce or use a number of different terms to describe their drug delivery device ("injector", "pen", "needle", "shot"), treatments ("metformin", "medformin", "met") or laboratory measures ("blood glucose", "BG", "sugars"). Failure to test for these nuances during human factors studies and anticipate these events during actual use could pose significant risk to patients where voice-activated technology is involved, especially if easily mistaken terminology is involved – such as look-alike and sound-alike medications.[11]

To reduce the potential for errors, human factors research must not only allow for synonyms, but also consider the importance of interpreting what is said in the appropriate context, which will require significant clinical knowledge and input during testing. For example, the drug Celebrex, an oral anti-inflammatory agent, should never be confused with Cerebyx, an intravenous anti-epileptic, if a patient is asking for help managing their osteoarthritis. Similarly, Lantus, a long-acting basal insulin typically taken once daily, should never be recommended in lieu of a rapid-acting insulin to a patient asking how many units they should take to cover their mealtime carbohydrates.

Use Environment Specific Human Factors

Use environment specific human factors considerations are complicated by the voice interface as well. Location and distance relative to the voice-activated device must be taken into account. If the device resides in the kitchen for instance, medications must be taken in close proximity for voice-activation to be maximally utilised. The most significant use environment challenge for voice-activation involves managing unauthorised interactions, either inadvertent or intentional, in different settings. As mentioned previously, accidental disclosure of PHI is not of particular concern when it comes to self-medication in home use environments. In this setting, human factors considerations may be more focused on eliminating accidental input of information from unintended sources, such as a television advertisement or casual conversation. On the other hand, the potential for breach of PHI must be taken very seriously if the intended use environment is a busy clinical setting, where several patients are being treated in close proximity (e.g. doctor's offices, hospitals, assisted living facilities or long term care settings).

POTENTIAL TO IMPROVE THE DRUG DELIVERY EXPERIENCE

Although the voice interface creates specific human factors challenges, it also holds tremendous promise to enhance the user experience. More than any other interface, voice facilitates a more natural, human, intuitive and instinctive interaction with technology. Preliminary research has shown that voice-activation is already being used to both improve the healthcare experience

Scenario	Goal	Patient/Caregiver Interaction	Example Voice-Activated Technology Response
Onboarding and training	Increase confidence and "walk through" use steps	"Alexa, what do I do next?"	"Okay, now that you have the injector pressed against your skin, it's time to inject. Whenever you're ready, press the green button on top with your thumb – you might feel a quick pinch when the needle goes in…Good job, the medication is being injected now. Keep holding, and I'll let you know when it's done."
Medication reminders	Manage medications inclusive of entire therapy regimen and routine	"Alexa, I just took my metoprolol. When is my next dose?"	"Great, I'll log that. Your next metoprolol dose is at 7 pm – I'll remind you when you get home from your staff meeting today. Also, don't forget today's a Humira day too. What time do you want to do that?"
Symptom management	Capture and deliver ancillary information related to diseases and treatments	"Alexa, my peak flow is 60% after being outside all day. Can you add ragweed as a trigger?"	"Sure, I added it with today's date and your peak flow reading. Do you need me to read through your asthma action plan?"
Caregiver engagement	Monitor patients and their self-care	"Alexa, did Dad take his Sinemet today?"	"He took Sinemet at 8am but is one hour late for his second dose. Would you like me to remind him? I'll get back to you when he takes it."
Patient support	Incorporate conversational and motivational elements	"Alexa, why am I even taking this lisinopril? It does nothing for me."	"You may not feel your lisinopril working, but it's still important to take it. It keeps your heart and kidneys healthy."

Table 1: Hypothetical voice-activation and patient/caregiver interactions.

and build trust with patients and that, moreover, voice offers unprecedented device accessibility to those with physical or neurological disabilities.[10] These benefits are of particular note when it comes to drug delivery, where patients are faced with increasingly complex medication regimens and unfamiliar delivery devices. Table 1 summarises examples of interactions that could be possible as technical and voice recognition capabilities improve.

Onboarding and Training

Therapy initiation often tends to provoke anxiety due to the unfamiliarity and uncertainty associated with starting a new therapy, especially if that medication requires a delivery device (e.g. an auto-injector, on-body injector, nebuliser or inhaler). Even with oral medications, the prescribed regimens can be complex and involve different medications taken at different times.

Voice-activated technologies show great potential to improve the process of initiation. Rather than the patient relying on written instructions for use, voice-activation could be employed to walk patients through the injection process from start to finish. With the advent of connected drug delivery devices, voice-activation could also be programmed to acknowledge specific steps, such as needle guard removal, skin contact, injection initiation and end-of-dose. Several studies have demonstrated the benefit of such multisensory interaction (i.e. the combination of visual, audio and tactile stimuli) on improving learning capacity.[12,13] Other studies have correlated more intensive device education and training with reduced rates of use errors.[14,15]

Medication Reminders

Non-adherence to medication is a well known and perennial problem across multiple disease states and medication regimens. A myriad of technologies, including hundreds of mobile applications, currently exist to help patients remember to take their medications consistently. Although forgetfulness is only one of many contributors to non-adherence, voice-activation has clear potential to help facilitate medication tracking and reminders in a way that is more patient-friendly, encompasses all of that patient's medications (i.e. polypharmacy) and is more compatible with their daily routine.

Symptom Management

Patients with some chronic diseases (e.g. psoriasis, asthma, COPD, migraine, heart failure, cystic fibrosis, lupus) often experience symptomatic periods or disease exacerbations that may be associated with specific triggers or have defined management strategies. These patients may find it useful to capture trigger information and be reminded of how they've alleviated symptoms in the past. Those who experience side effects due to one or more of their medications may benefit from a similar practice. Voice-activated technology has the potential to deliver this information whenever patients need it.

Caregiver Engagement

Caregivers play a significant role in helping patients manage their disease, particularly if the condition is debilitating or complex. Unfortunately, caregivers often carry the full burden of a patient's condition, which may negatively impact their own lives. Voice-activation could play an important role as an intermediary between caregivers and their patients, potentially lessening the load. An ongoing study is currently exploring whether voice-activation could reduce the demands on caregivers for patient with learning disabilities.[16]

Patient Support

Perhaps the most impactful aspect of the voice interface is its unique ability to provide a feeling of personal interaction with users. In the aforementioned analysis of Amazon Echo reviews, a large percentage of users

consistently saw "her" (Alexa) as a friend or family member. This sense of trust and companionship makes voice-activation a promising medium for delivering motivation and support to patients in a way regular smartphone applications cannot.

THE FUTURE OF VOICE

The regulatory space around voice-activated technology is still evolving, and will be a significant inhibitor or accelerator of voice technologies for more sophisticated interventions. It is currently unclear whether voice-activation will require a similar degree of FDA regulation to that of mobile medical apps (MMAs) where delivering medical interventions is concerned. Regardless of emerging regulatory frameworks, early research has revealed that "do it yourself" voice approaches are already being implemented by patients, and these solutions highlight clear, unmet human factors needs. However, this research also provides indications that, for at least some patients and caregivers, voice-activation provides an added layer of companionship, conversation and assistance that, when executed well, is perceived as authentic and authoritative. Manufacturers cannot ignore the opportunity to add additional tools that complement existing investments and drive patient engagement, and must begin to consider voice-activation approaches, trusting that regulations will "catch up" to the promise these technologies offer.

For voice-activation in the drug delivery space, it is clear that maximum value will be provided when the entire system is context-sensitive to individual patients, diseases and therapies. Clinicians, such as those with experience in patient counselling, medication therapy management and clinical decision support, will play an increasing role alongside traditional human factors practitioners in navigating the permutations that lead to potential use errors.

ABOUT THE COMPANY

Matchstick is a speciality consultancy focused on pre-concept and concept stage development of combination products including devices, patient support and engagement programmes, training and lifecycle strategies. Matchstick helps firms understand unmet patient and caregiver needs, invent useful and relevant product and service solutions to those needs and help clients deliver compelling business cases to drive programmes forward within their organisations.

REFERENCES

1. *"Alexa, Say What?! Voice-Enabled Speaker Usage to Grow Nearly 130% This Year". eMarketer, May 2017.*
2. *"Voice Assistants and Technologies: Ecosystem and Market Leaders". Report, Parks Associates, March 2017.*
3. *Meeker M, "Internet Trends 2016". Report, Kleiner Perkins Caufield & Byers, June 2016.*
4. *Meeker M, "Internet Trends 2017". Report, Kleiner Perkins Caufield & Byers, May 2017.*
5. *Comstock J, "Boston Children's Hospital Launches Amazon Alexa App KidsMD". Healthcare IT News, April 2016.*
6. *Mack H, "WebMD integrates with Amazon Alexa to offer health information through voice assistant". MobiHealthNews, March 2017.*
7. *Weiler A, "Introducing Sugarpod by Wellpepper, a comprehensive diabetes care plan". Wellpepper Blog, July 2017.*
8. *"HIPAA Administrative Simplification Regulation Text". US Department of Health and Human Services Office for Civil Rights, March 2013.*
9. *"Examining Oversight of the Privacy & Security of Health Data Collected by Entities Not Regulated by HIPAA". US Department of Health and Human Services, July 2016.*
10. *Coyne M, Thomas C, Collimore A, Franzese C, Hwang C, "Early user centered insights on voice integrated technologies through retrospective analysis". iproc, 2017, Vol 3(1), e49.*
11. *"ISMP's List of Confused Drug Names". Institute for Safe Medication Practices, February 2015.*
12. *Shams L, Seitz AR, "Benefits of multisensory learning". Trends Cogn Sci, 2008, Vol 12(11), pp 411-417.*
13. *Shams L, Wozny DR, Kim R, Seitz A, "Influences of multisensory experience on subsequent unisensory processing". Front Psychol, 2011, Vol 2, article 264.*
14. *Sicherer SH, Forman JA, Noone SA, "Use assessment of self-administered epinephrine among food-allergic children and pediatricians". Pediatrics, 2000, Vol 105(2), pp 359-362.*
15. *Arkwright PD, Farragher AJ, "Factors determining the ability of parents to effectively administer intramuscular adrenaline to food allergic children: Injectable adrenaline for food allergy". Pediatr Allergy Immunol, 2006, Vol 17(3), pp 227-229.*
16. *Gidley S, "Smart speaker technology trial to aid supported living". BBC News, November 2017.*

ABOUT THE AUTHORS

Chris Franzese is the Lead Clinical Analyst at Matchstick. He manages a team of clinicians supporting client projects related to combination product and medical device development and usability testing, leads the company's clinical training and is accountable for making clinical knowledge relevant to client projects. An experienced clinical trial researcher, Mr Franzese has numerous peer-reviewed publications related to usability research for connected medical devices, antiplatelet therapies in coronary artery disease and clinical laboratory testing. He has a BS in Biology from Loyola University (US) and is pursuing a concurrent PharmD and MHS in Health Informatics from Fairleigh Dickinson University (Teaneck, NJ, US).

Marty Coyne is Principal and Founder of Matchstick. He has 20 years of experience with implantable and disposable medical devices, particularly drug delivery devices used in acute care, ambulatory and home settings. A thought leader on sharps injury protection, safe injection practices and healthcare worker and patient safety, he has innovated extensively in these areas individually and for clients, with 11 patents issued and over 40 patents pending. Mr Coyne has a BE in Mechanical Engineering from Stevens Institute of Technology (Hoboken, NJ, US) and an MBA from Columbia University (New York, NY, US).

CONNECTED HEALTH – AN EFFECTIVE SOLUTION TO IMPROVE PATIENT ADHERENCE

Here, Sai Shankar, Director for Connected Devices Business Development, Aptar Pharma, details the problem of non-adherence, in particular in asthma and COPD, and how its solution, along with myriad other benefits, can be found in digital healthcare and connected devices.

THE PROBLEM: NON-ADHERENCE

The success of any medication is dependent on the individual patient's adherence to the dosing regimen and, in unfortunate reality, 60% of patients fail to take their medication properly. The impact of these compliance issues does not merely begin and end with the patient – it extends throughout the supply chain, from pharmaceutical companies, through hospital services, all the way to the physician.

The Scale of the Problem is Significant

To illustrate, let us examine the prevalent conditions of asthma and COPD. We know that there are 334 million people worldwide who suffer from asthma and 100 million who suffer from COPD.[1] We know that symptoms in around 50-60% of asthma patients are uncontrolled[2] and adherence rates to daily controller medications are under 30%.[3-6] It is predicted that another 100 million people will suffer from asthma by 2025,[1] so the need to manage patient adherence better will only accelerate. This is an issue we need to address urgently today.

> "Around 50-60% of symptoms in asthma patients are uncontrolled and adherence rates to daily controller medications are under 30%. It is predicted that another 100 million people will suffer from asthma by 2025, so the need to better manage patient adherence will only accelerate."

The Cost of Non-adherence is Equally Enormous

The treatment cost of asthma and COPD is approximately US $100 billion (£75.6 billion) per year in the US alone. A further £100 billion a year is spent on managing respiratory disease in Europe.[7-9] Annually, it is estimated that pharmaceutical companies in the US lose $188 billion in revenue because of poor adherence, with the overall cost of non-adherence to the healthcare system closer to $300 billion.

So, the impact is felt at all levels. Non-adherence accounts for approximately 50% of avoidable health costs, with about two-thirds of said avoidable costs attributable to hospitalisation. With an ever-increasing geriatric population, particularly in developing countries, the incidence of non-adherent hospitalisations will increase – as will, inevitably, the cost of healthcare in the future.

Mr Sai Shankar
Director for Connected Devices Business Development
E: sai.shankar@aptar.com
T: +1 847 800 6058

Aptar Pharma
475 West Terra Cotta
Crystal Lake, IL 60014
United States

www.aptar.com/pharma

"Aptar Pharma believes that a demonstrable and significant difference can be made through the provision of digital health solutions."

The real cost, however, is to the patient – to their health, wellbeing and quality of life. While there are substantial gains to be made to the healthcare economy by improving patient adherence, we should be mindful that the real motivator must always be in improving patient quality of life, both now and in the future.

THE ANSWER: DIGITAL HEALTH

There are, of course, numerous components that will contribute to improved adherence, from the choice of device to the clarity of the patient information leaflet. Aptar Pharma believes that a demonstrable and significant difference can be made through the provision of digital health solutions (Figure 1). Aptar's definition of digital health is "the convergence of digital technologies with healthcare to enhance the efficiency of delivery and make medicines more personalised and precise". The starting point is connected devices.

Improving Patient Outcomes & Reducing Healthcare Costs

So, why does Aptar believe connected devices and digital health are the answer? Current trends will see mobile phone ownership grow to 70% by 2019 (even higher in more developed countries) which means more people will have access to data-driven mobile technology. A digital health approach will help to identify the target patient population with the highest levels of non-adherence. By effectively targeting problem patients and providing them with precise information and prompts to take medication, greater levels of patient engagement and improved dose adherence can be expected, and therefore improved health outcomes. Improved adherence will consequentially reduce hospitalisation events in chronic disease, and a reduction in hospitalisation rates will lead to a decrease in healthcare costs to payers – patient, physician and insurer.

It is also anticipated that connected devices will help create a supportive, informed and transparent ecosystem whereby the patient, the physician, the healthcare provider and the pharmaceutical company will have real-time access to information which will immediately improve adherence for the patient. In the short term, it will help physicians assess patients more accurately based on data, rather than patient interpretation. Longer term, it will enable healthcare providers to shape care provisions more appropriately and help pharmaceutical companies deliver more effective products.

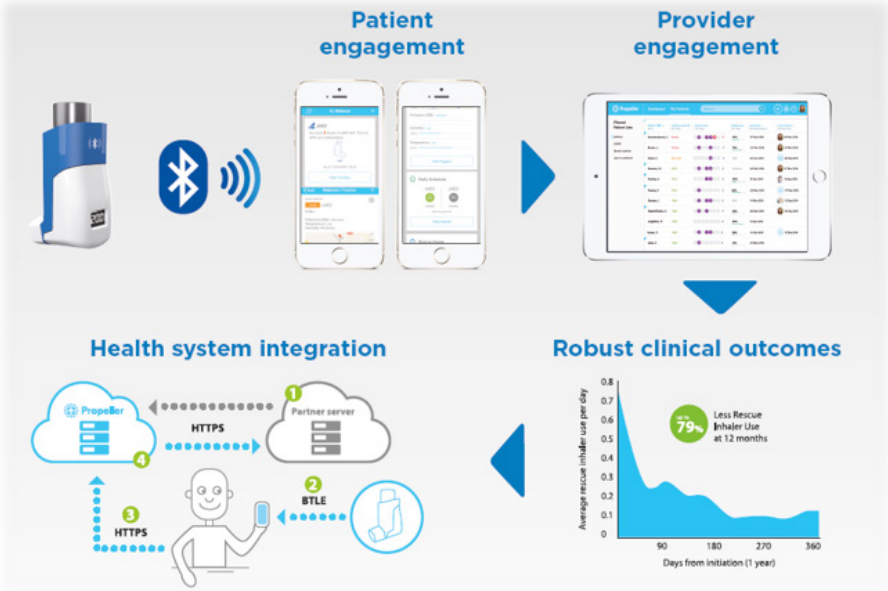


Figure 1: How connected devices can help improve patient outcomes and reduce healthcare costs. (Image courtesy of Propeller Health)

"By effectively targeting problem patients and providing them with precise information and prompts to take medication, greater levels of patient engagement and improved dose adherence can be expected, and therefore improved health outcomes."

Digital Health is Rapidly Changing the Drug Delivery Landscape

Greater levels of collaboration are being seen between drug delivery device manufacturers and digital health solution providers. Aptar Pharma is partnering with cutting-edge software providers, such as Propeller Health (Madison, WI, US) for asthma and COPD and Kali Care (Mountain View, CA, US) for eye care, to deliver truly connected drug delivery solutions. It is also being witnessed that US FDA and EMA regulatory requirements are demanding more of new products, for which digital solutions can aid compliance.

Which Patients Can Benefit Most from Digital Health?

The simple answer, of course, is that everyone can benefit from a digital health solution. That being said, there are some groups that are in clear and absolute need.

For example, in the asthma space patients seeking a digital health solution generally have poorly controlled asthma and want to improve their asthma control for themselves. They may also want to learn more about what triggers their asthma, so they can mitigate the onset or respond appropriately.

What Benefits Will People See from a Digital Health Solution?

In simple terms, an improvement in quality of life. For example, people could be more in control of their asthma and have fewer attacks as a result. They could also avoid missing work or school days, and generally not miss out on everyday life.

CONCLUSION

We are living in a world where there appears to be an irreversible increase in asthma and COPD. Predictions suggest

there could be a further 100 million asthma sufferers by 2025 – that's almost a 33% increase expected in just eight years.

There is clear data to show that the overwhelming majority of patients cannot or do not control their asthma effectively, with adherence rates to daily controller medications under 30%. The cost this presents to the entire healthcare community is significant, with the treatment cost of respiratory diseases being $206 billion in the US and Europe. Ultimately, however, it is the patient who suffers the most, with high levels of hospitalisation and readmission, alongside the increases in their healthcare costs.

As an industry, we can respond to this need today with the provision of connected devices – either as a modification to existing drug delivery devices or as an integrated device. For example, Aptar Pharma has a portfolio of devices that already help mitigate against adherence and compliance issues, with connected inhalers and ophthalmic devices currently being tested.

There is a clear desire from everyone in the supply chain – from pharma companies and healthcare providers, to physicians and patients – to improve patient health outcomes. By creating a connected ecosystem, real changes can be affected at an individual and global level, whereby patient engagement increases, dose adherence improves and overall health outcomes benefit. Not only would patients manage their medication better, they would also reduce the financial burden on themselves and healthcare providers.

ABOUT THE COMPANY

Aptar Pharma is part of AptarGroup, Inc (NYSE: ATR), a leading global supplier of a broad range of innovative dispensing and sealing solutions for the beauty, personal care, home care, prescription drug, consumer healthcare, injectables, food and beverage markets. AptarGroup is headquartered in Crystal Lake, IL, US, with manufacturing facilities in North America, Europe, Asia and South America.

ABOUT THE AUTHOR

Sai Shankar is Director for Connected Devices Business Development at Aptar Pharma. Mr Shankar has 15 years of product development and business strategy experience in the pharmaceutical industry. He joined Aptar in April 2017, with previous stints at Allergan and Sanofi.

REFERENCES

1. *"Chronic Respiratory Diseases". World Health Organization, 2007. (www.who.int/gard/publications/chronic_respiratory_diseases.pdf)*
2. *Stanford RH, et al, "Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the Asthma Control Characteristics and Prevalence Survey Studies". J Asthma, 2010, Vol 47(3), pp 257-262.*
3. *Barnes CB, Ulrik CS, "Asthma and adherence to inhaled corticosteroids: current status and future perspectives". Resp Care, 2015, Vol 60(3), pp 455-468.*
4. *Bender BG, Pedan A, Varasteh LT, "Adherence and persistence with fluticasone propionate/salmeterol combination therapy". J Allergy Clin Immunol, 2006, Vol 118(4), pp 899-904.*
5. *Williams LK, et al, "A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma". J Allergy Clin Immunol, 2010, Vol 126(2), pp 225-231.*
6. *Wu AC, et al, "Primary Adherence to Controller Medications for Asthma Is Poor". Ann Am Thorac Soc, 2015, Vol 12(2), pp 161-166.*
7. *Guarascio AJ, et al, "The clinical and economic burden of chronic obstructive pulmonary disease in the USA". ClinicoEconomics and Outcomes Research, 2013, Vol 5, pp 235-245.*
8. *Barnett SB, Nurmagambetov TA, "Costs of asthma in the United States: 2002-2007". J Allergy Clin Immunol, 2011, Vol 127(1), pp 145-152.*
9. *Gibson GJ, et al, "Respiratory health and disease in Europe: the new European Lung White Book". Eur Resp J, 2013, Vol 42, pp 559-563.*

Together, we can tackle patient adherence. Let's connect.

Aptar Pharma – delivering connected, intuitive devices to improve patient health outcomes

As the leader in respiratory drug delivery systems, Aptar Pharma is focused on supporting customers and patients to effectively treat respiratory diseases including asthma & COPD.

Today, 60% of patients fail to comply with their medication regimen. At Aptar Pharma, we strongly believe that patient behavior can be changed through connected and intuitive, user-friendly devices. This can significantly increase dose adherence and improve patient health outcomes. That's why we are partnering with digital health solution providers to develop a portfolio of connected devices such as MDIs and DPIs.

To find out more about how we can help you deliver better patient health outcomes via connectivity, call **Chris Baron**, Associate Director, Business Development, at Aptar Pharma on **+33 6 3095 5331** or email **chris.baron@aptar.com**

Delivering solutions, shaping the future.

Aptar pharma

CONNECTIVITY IN DRUG DELIVERY: CONFERENCES REVIEW

Here, Napoleon Monroe, Managing Director, New Directions Technology Consulting, summarises the intensifying coverage of connectivity as a key theme at two recent drug delivery conferences he attended, Partnerships in Drug Delivery and PDA's Universe of Prefilled Syringes and Injection Devices.

The drug delivery Autumn conference season began at the Seventh Annual Partnerships in Drug Delivery Conference (PODD), which took place on October 19-20th, 2017 in Boston, MA, US. As a hub for medical innovation and connected drug delivery device development, Boston is a great, convenient venue for tapping into emerging connected technologies. Most of the PODD sessions featured discussions of connectivity. Also, many of the exhibitors introduced new refinements and extensions of their connected product platforms.

In her opening "Year in Review" talk, PODD Chair, Barbara Lueckel, PhD, Global Business Development Director, Roche, briefed on US FDA clearances of connected health solutions. Actual clearances show the reality and importance of connectivity for drug delivery systems and related diagnostics, and Dr Lueckel covered:

- the FDA clearance of Adherium's SmartTouch monitoring device for AstraZeneca's Symbicort inhaler (510(k))
- the FDA clearance of Bayer's app-connected Betaseron (interferon beta-1b) injector for multiple sclerosis, BETACONNECT (developed by Medicom Innovation Partner)
- Glucose monitoring systems: clearance of several connected systems, including Ascensia's CONTOUR NEXT ONE, Smart Meter's iGlucose and Abbott's new FreeStyle Libre
- Otsuka Pharmaceutical and Proteus Digital Health's resubmission of the FDA application for sensor-embedded formulation of Otsuka's antipsychotic pill, Abilify (aripiprazole). This product was subsequently cleared in November 2017.

Other connectivity highlights of the conference included a panel dedicated to connected delivery devices chaired by Kevin Deane, Executive Vice-President, Medicom, and a very interactive panel chaired by Paul Jansen, Board Member, Haselmeier, on platforms.

> "The question of who advocates with regulators and legislators for connected drug delivery devices was raised in the final conference Q&A."

Kurt Sedo's (Vice-President, PharmaCircle) slides "Injectables are Taking Over the Pipeline" and "Innovator Drug Approvals Since 2012" highlighted what we all know about the growing importance of injectables and other combination products. Kurt advised that one can search the PharmaCircle database to find which products are connected.

Jeffrey Karp, PhD, Associate Professor of Medicine / Director of the Laboratory for Accelerated Medical Innovation Harvard Medical School / Brigham and Women's Hospital, discussed personalised medicine targeting and led me, a layman, non-scientist, to a far better beginning understanding of the related complexities. Lars Rebien Sørensen, Former President and Chief Executive, Novo Nordisk, gave a "Fireside Chat" that showed why he is so widely respected a leader.

Connectivity will undoubtedly feature strongly again at the 2018 Eighth Annual PODD, which will take place again in Boston, at the Westin Copley Place Hotel, on October 17-18, 2018. The conference staff at PODD were super, by the way!

The conference season continued in Vienna, Austria, with the PDA's 14th Universe of Prefilled Syringes and Injection Devices Conference. PDA Universe, too, was largely about connectivity. A Pre-

Mr Napoleon Monroe
Managing Director
T: +1 718 427 3038
E: nap.monroe@newdirectionsconsulting.net

New Directions Technology Consulting, LLC
1442 Drake Ln
Lancaster
PA 17601
United States

www.mmedhealth.com

Conference Workshop focusing wholly on "Connected Health & Drug Delivery" was very well attended.

During the workshop, Markus Bauss, Managing Director of SHL Connect, covered his research on market trends and introduced two fascinating patient centric diabetes presentations.The first was by a very informed type 1 diabetes patient. The second by another type 1 patient, the founder of mySugr. He discussed their creative approach – business-to-consumer for product development, followed by business-to-business with insurers and pharma being target partners to bring product sales. mySugr claims 1.1 million registered users and growth of 1,000 users per day. Bauss cited the importance of pens, auto-injectors and infusions and industry plans to invest in connecting these devices.

In their pre-conference presentation, West Pharmaceutical Services included a quote from Prescriptions for a Healthy America in their presentation: "Medications cost the healthcare system approximately $325 billion annually, and research indicates that suboptimal medication use—including taking too much or not taking enough—leads to avoidable annual healthcare costs totaling $300 billion. People who don't take their medicines are more likely to end up back in the hospital or in the emergency room than those who do." One audience member (me) noted that Prescriptions for a Healthy America is part of the Horizon Group. Horizon also advocates for interoperability.

A recurrent theme of both the pre-conference and main conference presentations was the benefits of connected devices. The regulatory status of several connected devices was discussed. The exhibition was far larger than prior years and many exhibitors featured connected products this year.

The emphasis on adding connectivity to devices is being driven by the need to improve patient outcomes and add value to delivery devices. One noted gap in the US healthcare system was the lack of interoperability of information systems across the stakeholder communities.

A number of presenters shared their experiences. Sub themes included: the need for collaborations; the concept of device platforms; potential pitfalls; human factors; and other regulatory issues.

In the final presentation, "The Future of Parenteral Drug Delivery in a Connected Health Ecosystem", Divakar Ramakrishnan, PhD, Executive Director of Manufacturing Science and Technology at Eli Lilly, provided predictions. His top three predictions were:

1) Auto injectors and pens will remain key for parenteral delivery
2) On-body devices will gain share
3) Connectivity will become standard.

The question of who advocates with regulators and legislators for connected drug delivery devices was raised in the final conference Q&A. PDA advised that it would consider how this might best be addressed. The PDA organisers and staff again did a masterful job in 2017.

In 2018, PDA Universe of Prefilled Syringes and Injection Devices will return to the US, taking place on October 8-9th, 2018, at Loews Royal Pacific in Orlando, FL, US.

The current conference season continues at Drug Delivery Partnerships (DDP), which also takes place in Florida, on January 22-24th, 2018. My presentation at DDP is entitled: "Breaking News", and will be one of several covering the emergence of connectivity in drug delivery. We look forward to learning from our colleagues there.

DATA IS DRIVING THE FUTURE OF NEUROTECHNOLOGY WITH CRANIALCLOUD

Will Rosellini, Chairman and Chief Executive Officer, Nexeon Medsystems, and Pierre-Francois D'Haese, PhD, Founder and Chief Executive Officer, Neurotargeting, discuss the neurotechnology market and how the Internet of Medical Things is creating exciting opportunities in the space. Looking at the collaboration centring Nexeon's Deep Brain Stiumulation technology and Neurotargeting's CrainialCloud, they expand on the untapped potential in the sector and how it might be realised by a platform type business model.

INTRODUCTION

The past decade has ushered in an explosion of neurotechnology designed to measure, improve and repair nervous system function in patients suffering from chronic diseases. Newly developed implantable neurostimulators, wearable stimulators and imaging techniques provide rich data to fuel further refinement of therapies. In parallel, a global rise in the "Quantified Self" concept has gained traction, enabled by Internet of Things (IoT) technology. More recently, leaders of the neurotech revolution are adopting an emerging sub-sector of IoT for use in neurotechnology – the Internet of Medical Things (IoMT).

IoMT refers to a connected infrastructure of medical devices and software applications that can communicate with various healthcare IT systems. IoMT is being leveraged to improve medical care by integrating neurological data with other biometric diagnostics, thus providing medical professionals with richer information with which to make their decisions. Successful usage of IoMT will require a vast and layered database of neurological information, including real-time neural recordings that enable medical treatment to be customised to specific patients. Linking nervous system recordings with the IoMT facilitates the alleviation of chronic pain, stopping of tremors or improvement of mood disorders, all at the touch of a button. Once this level of connectivity is achieved, the addressable neurotechnology market is expected to widen significantly as these therapies start to improve patient outcomes whilst also reducing the overall burden of management.

"Successful usage of IoMT will require a vast and layered database of neurological information, including real-time neural recordings that enable medical treatment to be customised to specific patients."

DEEP BRAIN STIMULATION

Deep Brain Stimulation (DBS) therapy is one of the most common technologies that modulates a patient's neuronal activity. Worldwide, it has been prescribed in over 150,000 patients with Parkinson's disease (PD), a neurodegenerative disorder

Mr Will Rosellini
Chairman and CEO
T: +1 214 414 0454
E: will@nexeonmed.com

Nexeon MedSystems, Inc
1910 Pacific Avenue, Suite 20000
Dallas
TX 75201
United States

www.nexeonmed.com

Dr Pierre-Francois D'Haese
Founder and CEO
T: +1 615 835 2386
E: pf.dhaese@neurotargeting.com

Neurotargeting, LLC
1315 16th Ave S
Nashville
TN 37212
United States

www.neurotargeting.com

which leads to a progressive deterioration of motor function. DBS has also shown great potential in alleviating symptoms of patients suffering from other movement disorders. Unfortunately, evaluation of long term studies shows that neuromodulation technologies, such as DBS, have not received major improvement since arriving on the market 30 years ago.

While DBS therapy does improve a patient's quality of life, compared with other medical technologies such as pacemakers, it is in a state far removed from its potential. At present, DBS involves empirically selected stimulation parameters arrived at through trial and error over a number of clinical visits. Identification of the appropriate DBS stimulation parameters can take up to six months, followed by up to twelve months of intermittent adjustments during outpatient visits. Oftentimes the stimulation parameters are not fully optimised to maximise patient outcomes, falling short of the potential improvements a patient could receive. To date, DBS device manufacturers have yet to provide neurologists with the robust tools needed to assess a patient's quality of life continuously and enable them to fine tune the stimulation parameters. The technology implanted for the last 30 years provides a static or pseudo-static stimulation scheme that does not adjust to a patient's disease state, medication status or side-effects. DBS therapy will only reach its full potential once the therapeutic output adapts to a patient's neurological state automatically.

Recognising this gap in the market, Nexeon MedSystems has created a DBS device that records local field potentials (LFPs) of the neuronal activity where known biomarkers of the disease can be detected (Figure 1). These recordings can then be extracted, analysed and used to create self-adjusting algorithms that automatically optimise the therapy. Stimulation will be delivered and signals will be collected using a bidirectional DBS system instead of setting static parameters that do not account for the numerous changes a person goes through during the course of a day. Just as a pacemaker dynamically adjusts to keep the heart at a healthy, appropriate rate, the Nexeon DBS system adjusts to keep the brain in a healthy, optimally functioning state. It will also enable physicians to manage patients remotely to reduce or avoid disruption to quality of life.

Thus far, the benefits of LFPs have remained a mystery, since no DBS devices have enabled robust, sustained recordings of these LFP biomarkers. Physicians and neuro-engineers are cautiously optimistic that this never before collected data will provide the basis for "closed-loop" systems that automatically adapt to a patient's clinical state, therefore improving the efficacy of the therapy and minimising undesirable side-effects.

Figure 1: Nexeon's synapse device.

> "Observing directly how the brain reacts to stimulation in real-time opens the door to closed-loop control, refining stimulation to the true physiological state. Such control is preferable to using manual adjustments, which are time consuming, prolonged and often subjective."

Furthermore, as the MedTech world is connecting us to an ever increasing number of wearable sensors, Nexeon is setting up the path for the brain stimulator to correlate its data with external information about a patient's state or actions in order to produce more sophisticated insights to how a specific disease effects a patient. Observing directly how the brain reacts to stimulation in real-time opens the door to closed-loop control, refining stimulation to the true physiological state. Such control is preferable to using manual adjustments, which are time consuming, prolonged and often subjective.

Nexeon's vision is for neurotechnology to integrate with IoMT technologies that address all aspects of medical treatment to maintain a comprehensive picture of patient health. This means neurological data will combine with the IoMT system that tracks patient medications, hospital visits, data from wearable devices, caregiver input, patient vital signs and other key indicators for comorbidity management (i.e. diabetes, COPD, dysphagia, etc). The goal is not the singular treatment of, for example, Parkinsonian tremor, the goal is complete interconnectivity on all aspects of a patient's healthcare to improve their overall wellbeing.

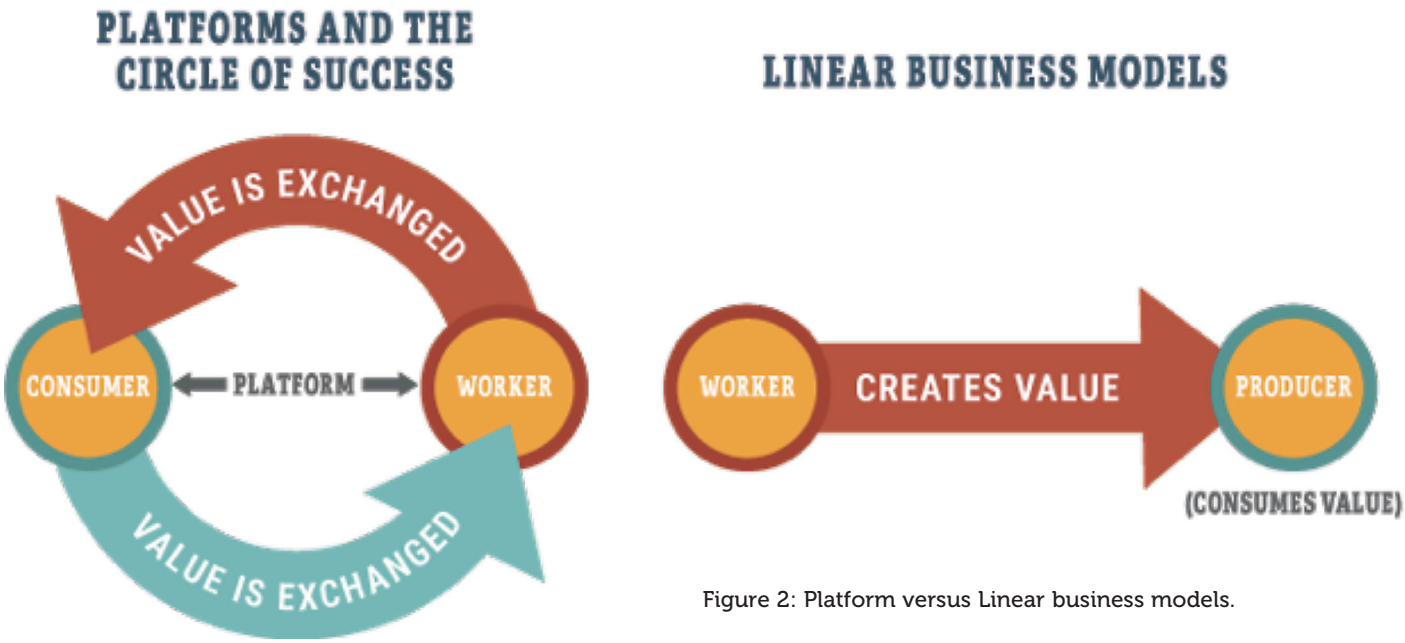


Figure 2: Platform versus Linear business models.

DATA-DRIVEN NEUROTECHNOLOGY PLATFORMS

Revolutionising neurotechnology requires a new way of doing business. The 20th century was dominated by the factory business model, in which companies create a commodity and push it in one direction toward the customer at the end of the supply chain. Internally owned and controlled resources are a factory's most valuable assets. It is now the case that platform business models are starting to replace these traditional linear models by enabling a multi-directional exchange of value between two or more user groups. Platform businesses use external networks, such as the IoMT technology, data and users, as the aggregator of business value rather than investing in and growing their internal resources or supply chain (Figure 2).

A useful analogy would be General Motors, which manufactures cars, versus Uber, which "manufactures" transactions between drivers and riders. Uber does not provide the ride service, instead it merely facilitates the exchange of value between drivers and passengers. When a linear business gains a new customer, it adds only one new relationship. But when a platform adds a new user, that person adds potential relationships with all the platform's users. Platform companies grow exponentially rather than linearly, which is why platform businesses can expand at an unprecedented pace. This is how Alibaba, Facebook and Google continue to grow at an exponential rate regardless of their current size.

> "CranialCloud handles the management of neurological diseases by collecting images of a patient's brain and spatially relating their information to these images, facilitating improved clinical decision making."

Although a platform model enables transactions, it does not directly control the behaviour of its users. In the context of neurotechnology, the users are patients, caregivers, researchers and healthcare providers. The challenge for neurotech companies going forward is directing user behaviour toward effectively improving patient care.

The answer lies in the four core functions of a platform:

1. Audience building
2. Matchmaking
3. Providing core tools and services
4. Setting rules and standards.

If a neurotech platform can handle these four functions well, it would be able to facilitate transactions that reduce the burden of neurological diseases.

Data-driven decision making is the revolutionary neurotechnology platform upon which improved neurological disease management can be delivered. With the development of IoMT connected neurotechnology, data collected on patient disease management will facilitate an outpouring of analytics to improve decision making by healthcare providers. Leveraging data on patient disease holds the potential to eliminate redundant or predictable decisions, saving valuable physician time and focusing their attention on what only they can do: diagnose, plan treatments, perform procedures and care for patients. With these tools, quality patient care can expand beyond specialised centres into more rural or underserved areas. Smart neurotech devices, paired to data supported decision making algorithms, could support physicians who are less experienced or less knowledgeable about a therapy by providing therapeutic parameters developed from the data of thousands of other patients managed by leading physicians worldwide.

THE CRANIALCLOUD PLATFORM

Nexeon has combined its state-of-the-art neurostimulaton with an IoMT platform called CranialCloud designed by Neurotargeting, a specialist software company. The primary goal of the collaboration is to achieve data-driven decision making in neurology and neurosurgery. More specifically, CranialCloud is a centralised

neurotechnology data platform that enables the visualisation and exchange of clinical data between researchers and healthcare providers. At its core, CranialCloud handles the management of neurological diseases by collecting images of a patient's brain and spatially relating their information to these images, facilitating improved clinical decision making. It consists of a network of databases and associated processing pipelines that are fully integrated into the clinical flow.

The CranialCloud framework permits spatial normalisation of the data, data sharing across institutions and handles the issue of data ownership, privacy and compliance with the US Health Insurance Portability and Accountability Act (HIPAA). Each research group or medical centre owns a single CranialCloud account in which clinical data is stored. Neurotargeting works with each account owner to create contracts and analyse risk, thereby integrating CranialCloud smoothly into the hospital workflow. To assuage industry concerns of safety in data management, Neurotargeting maintains compliance with HIPAA and ISO-27001 standards, as ensured by the monitoring of two external companies. Once CranialCloud accounts are opened by a hospital or research group, the platform becomes a legal extension of that institution's IT network. Because data within the platform is managed on the institutional level, any stakeholder within that institution (clinician, researcher, etc) can store their data in a structured way during the clinical care or clinical research.

The integration of CranialCloud into healthcare IT networks allows access to patient data collected with regulated neurotechnology and other medical devices. Key patient data include (but are not limited to):

- Signals recorded directly from the patient's brain
- Images from surgical planning systems to extract lead locations and location in the brain of electrophysiological data
- Patient responses to therapy.

Neurotargeting has developed multiple applications that feed into CranialCloud to utilise these data sources.

CranialSuite is the surgical planning tool used for patients who require neurosurgery to implant neurostimulators, such as DBS devices. It combines basic trajectory planning to obtain frame settings with advanced planning and navigation capabilities that improve operating room workflow and localisation of anatomical and functional areas.

The CranialDrive application is a client-based application used to acquire and transfer data to the archive. Similar to file hosting platforms like DropBox, CranialDrive runs on a computer and listens for new clinical and research data to sync with the archive. The CranialDrive application has a complex mechanism of data anonymisation and multi-level encryption to ensure HIPAA compliance.

Sharing anonymised patient data across institutions is perhaps the most crucial component of CranialCloud, because advancing the treatment of neurological diseases cannot be done in a vacuum. CranialCloud collects data from CranialSuite and CranialDrive, which then enables cross-institutional data collection and analysis. Neurotargeting has developed effective methods for data sharing by incorporating requirements or constraints on data structure to enable a common data storage and labelling. These standard structures are able to acquire and manage complex, multi-dimensional data, including real-time LFPs streamed from implantable neurostimulators.

The CranialCloud platform enables multidirectional flow of value between healthcare providers, between companies and patients, from patients to healthcare providers and from healthcare providers to companies. As clinicians grow and share their patient database, companies can access data that will enable them to refine features of their technology. Clinicians can share smart algorithms to deliver more efficient and effective patient care. Patients can provide improved, less subjective feedback to their caregivers and providers. By combining neurotechnology and IoMT through platforms like CranialCloud, connectivity can be increased, opening up possibilities for unprecedented advances in healthcare.

ABOUT THE COMPANY

Nexeon Medsytems is a global medical device company focused on providing innovative neurostimulation products that improve the quality of life of patients suffering from debilitating neurological disease. It was originally founded in 2005 with the goal of changing how innovative ideas in the medical device industry move from concept to reality with a focus on creating solutions for clinicians in their pursuit of improving patient outcomes.

ABOUT THE AUTHORS

Will Rosellini is a 15 year veteran of the neurotechnology space with expertise in accelerating the development of emerging technologies using minimal at-risk capital, holding five Master's degrees and a law degree. From 2005 to 2012, he was a founder and CEO of Microtransponder, a company developing vagal nerve stimulation therapies for treatment of stroke and tinnitus. He went on to serve in other Board and C-level positions for various biomedical device companies and research programmes. Mr Rosellini joined Nexeon MedSystems in 2016.

Pierre-Francois D'Haese conceived of and became the key architect of the CranialCloud system as part of his PhD, already having Master's degrees in Electrical Engineering and Business Administration. He co-founded Neurotargeting in 2007 and successfully secured funding from the US NIH to translate this technology to create a product that would impact patient care. Dr D'Haese also holds a faculty position at Vanderbilt University (Nashville, TN, US) as Research Assistant Professor in Electrical Engineering and Computer Science, as well as in Neurological Surgery.

IMPROVING PATIENTS' LIVES THROUGH CONNECTIVITY

In this article, Eric Dessertenne, Chief Operating Officer, and Matthieu Hamon, Business Development Associate, both of Biocorp, look at the importance of increasing the connectivity of drug delivery devices to improve patient compliance in the area of chronic disease management. Biocorp aims to use innovations such as Datapen™ and EasyLog™ to help create patient-centric, interconnected care, known as 4P medicine.

RECENT MOVES TOWARDS CONNECTIVITY

At a time when many industries have taken huge steps forwards into the implementation of connectivity, progress has remained slower in the pharmaceutical industry – particularly with drug delivery devices. However, the need to promote patient compliance has never been so great and technology is now more affordable, so increasingly moves are being made in the industry towards e-health.

A programme launched by the US FDA in 2016 states that "these advancements [in digital health] are leading to a convergence of people, information, technology and connectivity to improve healthcare and health outcomes". Last month, for example, Otsuka and Proteus (Redwood City, CA, US) announced the first FDA clearance of a digital medicine system combining a pill and a sensor. This represents a big leap forwards in compliance monitoring.

In addition, both European and US agencies are working towards a simplification of the regulatory path for many connected drug delivery devices and the barriers that have surrounded such devices are vanishing.

There have also been countless connected innovations including electronic health record software, heart rate monitor patches, wrist bands that monitor blood pressure and insole sensors that measure weight, balance or temperature. It is clear that connected drug delivery systems are going to be a key part of healthcare in the future.

"...the need to promote patient compliance has never been so great and technology is now more affordable, so increasingly moves are being made in the industry towards e-health."

OPTIMISING THE MANAGEMENT OF CHRONIC DISEASES

In this context, Biocorp has developed a line of connected drug delivery systems with the main objectives of enhancing patients' medical compliance and ultimately changing the way treatments are managed, without adding any burden to their daily lives.

Ongoing partnerships within the pharmaceutical industry, studies among patients and multiple awards given to our devices have shown that there is abundant enthusiasm for our products. In October 2017, Biocorp was awarded the CPhI award for "IT, mHealth and digitalisation" on its whole line of connected products. This award recognises of several years' worth of work and acknowledges that there is a real need for connected drug delivery.

Biocorp's line of connected devices is composed of innovative smart drug delivery systems, mostly dedicated to the injectable route of administration.

Matthieu Hamon
Business Development Associate
T: +33 684 512 109
E: mhamon@biocorp.fr

Eric Dessertenne
Chief Operating Officer
T: +33 608 021 451
E: edessertenne@biocorp.fr

Biocorp
Parc Technologique
Lavaur-La-Bèchade
63500 Issoire
France

www.biocorpsys.com

This includes the smart reusable pen injector Datapen™ and the connected cap EasyLog™ and that connects major pen injectors (Figures 1 and 2). We also develop connected medical devices in the respiratory field; including Inspair™, a smart sensor and communicator compatible with all pressurised metered dose inhalers (pMDIs) (Figure 3).

These devices are designed to be a cornerstone of future treatments for chronic diseases such as diabetes, multiple sclerosis, infertility, Parkinson's, asthma and COPD.

Improving Compliance

Biocorp aims to improve patients' lives by improving their medical compliance. Many patients suffering from chronic diseases must manage their treatment by themselves. Our connected devices are designed to give patients support and comprehensive tools that lead to a better understanding of their disease.

For instance, patients suffering from diabetes need to keep track of several factors, such as the last time they took their treatment or the quantity of insulin they injected. Using EasyLog™ helps by providing information such as exact dose injected, time, date and production concentration, as well as reminders and alerts. Trackers will also detect with 100% accuracy if the injection was not fully administered.

Furthermore, sensor devices from Biocorp can link with diagnostic tools such as blood glucose monitoring (BGM) or continuous glucose monitoring (CGM). The integration of blood glucose level together with the patient's insulin information from EasyLog™ will revolutionise the way patients are managing their chronic condition. This is an exciting innovation and Biocorp is the only player in the market at this level of maturity.

MAKING DEVICES USER-FRIENDLY AND TRANSPARENT

The connectivity function needs to be available without adding burden to patients' daily lives. Connected devices must be easy to use and simple to understand so that they can improve compliance. All our devices and applications are user-friendly and convenient. For example, with EasyLog™, patients only need to take their pen injector, clip EasyLog™ on the top of it and inject as per normal. It is an innovative product that, once attached, can give connectivity to all major pen injectors on the market without requiring any additional steps from patients.

Figure 1: Datapen™ is a smart reusable pen injector compatible with standard cartridges.

Figure 2: EasyLog™ connects all pen injectors and captures exact dose with 100% accuracy.

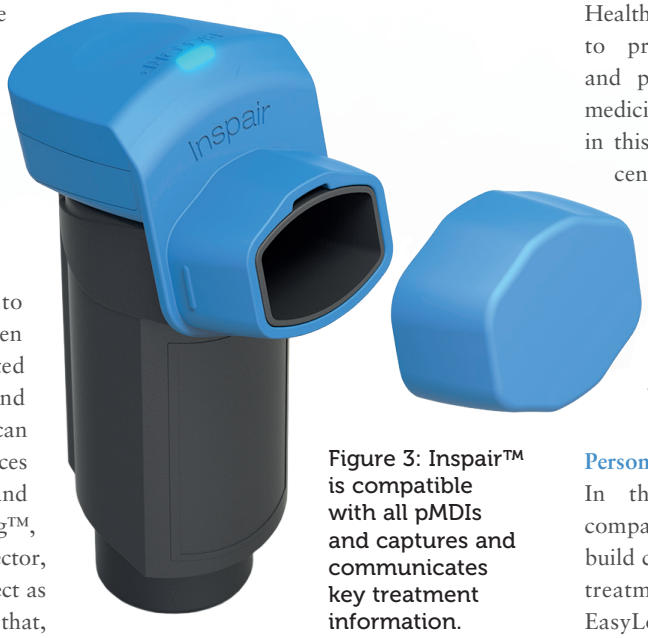


Figure 3: Inspair™ is compatible with all pMDIs and captures and communicates key treatment information.

> "Adjusting patient behaviour will be a new strategy that HCPs can use before having to increase the dosage, leading to a more effective and cost-efficient system."

The technology used by these smart devices is simple in appearance, yet the functionalities added through the implementation of connectivity are highly advanced. Biocorp has developed smart sensors and innovative ways to capture data that are trailblazing. Being able to connect to a pen injector and capture the exact dose with 100% accuracy depends on cutting-edge technologies (Figure 4, next page).

Security is a key issue as well; all data are encrypted in the device and thereafter transferred to a secure platform. No data is stored on the mobile phone and a strong authentication system is utilised. This offers a very high level of protection, compliant with European and US data protection laws. Therefore, Biocorp's smart devices aim to bring "transparent connectivity" in order to improve the patient's experience and medical compliance.

"P4" MEDICINE CONCEPT

Healthcare is evolving from reactive care to predictive, preventive, personalised and participatory care, known as "P4" medicine. Biocorp aims to play a key role in this type of care by creating a patient-centric, interconnected environment to which many stakeholders can contribute. To do this, we want to leverage connectivity to bridge the gaps between these different stakeholders and provide accurate information that will benefit everyone.

Personalised Medicine

In the field of diabetes, healthcare companies have been working hard to build closed-loop systems that will optimise treatment management for diabetics. EasyLog™, by automatically recording

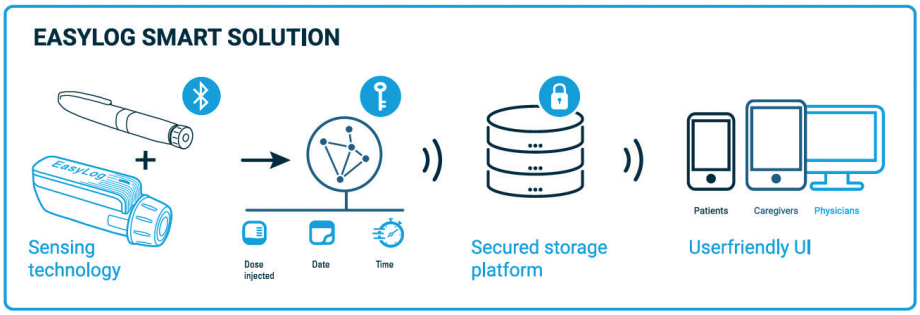


Figure 4: EasyLog™ is a simple solution that depends on cutting-edge technologies.

each amount of insulin delivered by the patient, with the exact time and date, produces key data that were previously missing. It allows healthcare professionals (HCPs) to better understand their patients and tailor treatment plans based on individual characteristics to guarantee maximum efficacy, fulfilling the promise of personalised medicine.

Participatory Medicine

This new data will be available for patients and sharable with HCPs and other stakeholders, at patients' discretion. It is designed to be centralised in a single platform to make sure that everyone involved can have the best level of information to optimise their contribution. Biocorp truly believes in the benefits of participatory medicine and has been working hard on its interoperability with other systems to promote it.

Preventive Medicine

Accurate information will help preventive medicine by quickly identifying patients that are losing interest in their treatments and moving away from optimal treatment adherence. Easylog™ data will encourage HCPs to discuss the treatment experience with patients, potentially adapt the medication plans to remedy the situation, and set up treatment adherence goals to get them progressively back on track. Adjusting patient behaviour will be a new strategy that HCPs can use before having to increase the dosage, leading to a more effective, and cost-efficient, system.

Predictive Medicine

The ultimate step of this new era will be predictive models. To build such models, you need accurate, consistent and relevant data. EasyLog™ is the only sensing system that collects 100% accurate insulin delivery information, with high robustness and repeatability. The quality of predictions is only as good as the data behind them, therefore Biocorp is highly committed to providing this level of precision. If predictive medicine manages to wipe out contingency and uncertainty, then the risks of severe complications, incidents and all their consequences (relapses, emergency doctor visits and hospitalisations) will be reduced to a minimum.

CONCLUSION

Patients face many challenges in the management of chronic diseases and this leads to poor compliance. Pharma companies must find ways to integrate connectivity into drug delivery systems to meet the challenges of patient compliance. Connected drug delivery devices are the missing link that makes automated chronic disease management possible as they bring real benefits to patients without adding additional burden.

Biocorp's connected devices improve the patient experience and are designed to fit seamlessly into people's daily lives, with the final objective of supporting the shift from a curative healthcare model to a preventive and predictive one.

ABOUT THE COMPANY

For 20 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 NewGuard™, an integrated passive safety system for PFS compatible with existing Nest & Tubs, 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 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). Biocorp's innovative connected products have received multiple awards: Pharmapack 2015, Pharmapack 2016, Frost & Sullivan 2016, E-health Summer University 2017 and CPhI award 2017.

On top of its R&D capacities, Biocorp also provides manufacturing services for plastic injection, process assembly and blister packaging.

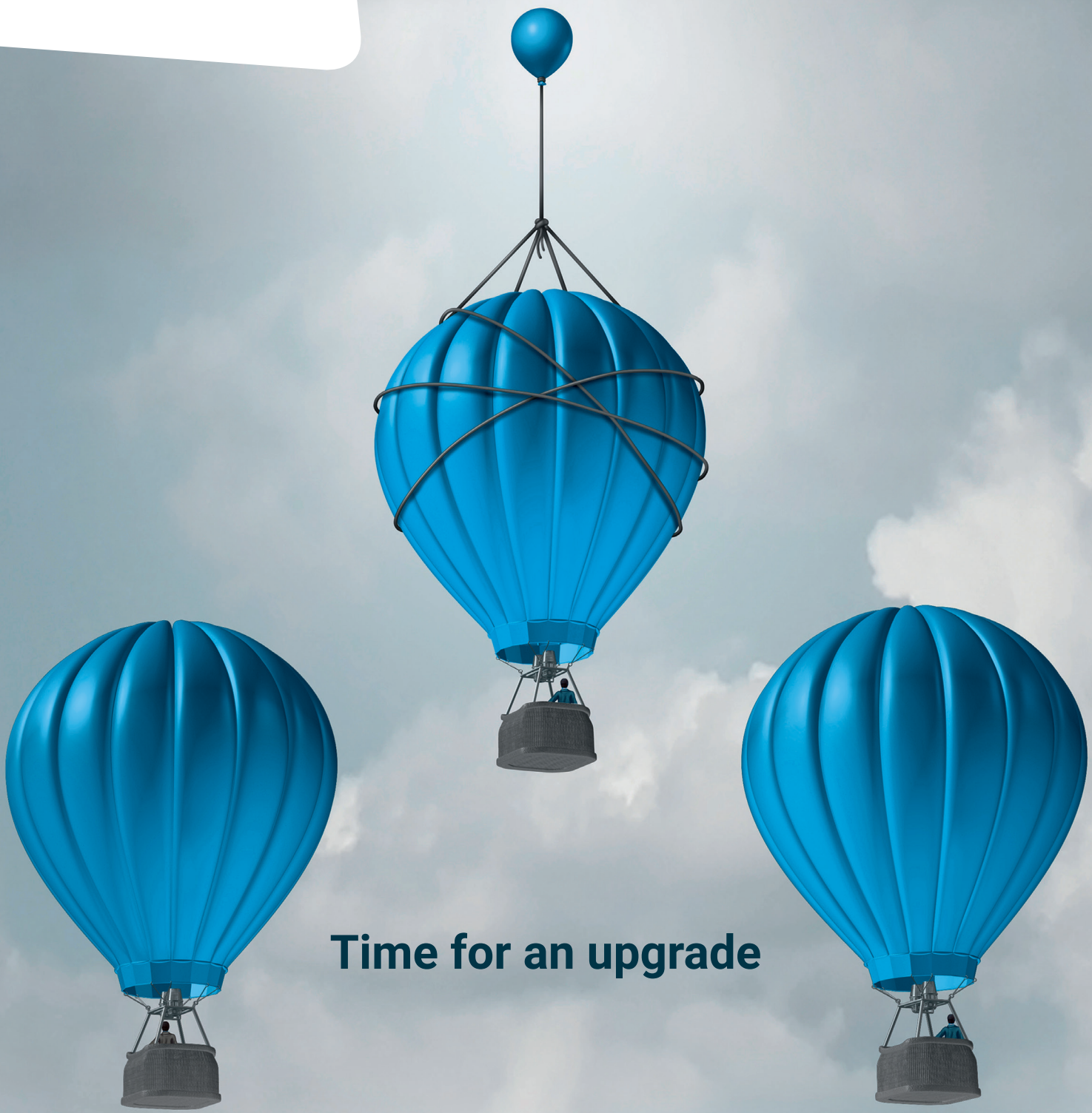
ABOUT THE AUTHORS

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 (Cergy-Pontoise, 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.

Matthieu Hamon is a graduate from SKEMA Business School (Lille, France) with a Master's in International Marketing and Business Development. He has previously worked for various organisations as a business development associate, and specialises in digital products. During his studies and career he had the opportunity to experience multicultural environments and has lived in the US and China. He joined Biocorp in early 2017 as a Business Development Associate to find new partners for Biocorp's connected drug delivery devices.

BIOCORP

Design • Develop • Manufacture Medical Devices



Time for an upgrade

Give your existing device the benefit of connectivity.

With over 20 years of designing and manufacturing medical devices for the pharmaceutical industry, Biocorp knows precisely how connectivity gives you better data, leading to better treatment and better patient outcomes.

info@biocorp.fr **biocorpsys.com**

YDS SmartPilot YpsoMate

Go for smart guidance.

swissmade

10130479-MSTR-en/V01

Reusable add-on transforms the YpsoMate® autoinjector into a fully connected device.

- Reusable add-on with built-in status sensor and wireless interface
- Tracking of injection events including successful completion of YpsoMate® usage
- Step-by-step patient guidance throughout the injection process
- YpsoMate® is compatible with SmartPilot™ without further modifications
- Flexible ergonomic design to accommodate disease-specific usability requirements

For more information visit www.ypsomed.com/yds

Ypsomed AG // Brunnmattstrasse 6 // 3401 Burgdorf // Switzerland
T +41 34 424 41 11 // info@ypsomed.com

YPSOMED
SELFCARE SOLUTIONS