CONNECTING DRUG DELIVERY

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CONNECTING DRUG DELIVERY

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12 MONTH EDITORIAL CALENDAR

Jul	Novel Oral Delivery Systems
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Front cover image, "Elements of a typical connected drug delivery device system", supplied by New Directions Technology Consulting, LLC. (Design by Kelly Barkhurst/smartpr) . Reproduced with kind permission.

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Device training happens here.

There's life beyond chronic conditions. Distractions, anxiety and understanding correct administration technique can all affect compliance. Studies suggest 61% of patients don't completely read the IFU[1] and 12% of patients have proficient health literacy.[2]

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Reference: 1. Noble. (2015, November). The link between device training and patient compliance. Poster session presented at PDA - Universe of Prefilled Syringes 2015, Vienna, Austria. 2. Kessels, R. P. (2003, May). Patients' Memory for Medical Information. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539473/

CONNECTED COMBINATION PRODUCTS: PAST, PRESENT & FUTURE

By Napoleon Monroe, with supporting author Guy Furness

THE PAST: THROUGH CHANGING TERMINOLOGY & ADVANCING TECHNOLOGIES

In the first part of this article I would like to show that Connected Health has not suddenly emerged out of nowhere but, rather, how it has been (often quietly) developing and evolving over many decades, even centuries. Over the years, various approaches have been used across a wide range of applications, and a number of terms have arisen that describe and define a situation where, essentially, healthcare is being delivered and managed by one person or group of people to the recipient, but the person receiving the care is not in the same vicinity as the person or people providing and overseeing that treatment.

Perhaps the broadest term is telemedicine. In its early manifestations, African villagers used smoke signals to warn people to stay away from the village in case of serious disease. In the early 1900s, people living in remote areas of Australia used two-way radios, powered by a dynamo driven by a set of bicycle pedals, to communicate with the Royal Flying Doctor Service of Australia.[1]

Definitions of telemedicine differ. Some, such as that given by the WHO, include all aspects of healthcare including preventive care: "The delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities."[2] The American Telemedicine Association uses the terms telemedicine and telehealth interchangeably although it acknowledges that telehealth is sometimes used more broadly for remote health not involving active clinical treatments. Its definition is: "The use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telemedicine includes a growing variety of applications and services using two-way video, email, smart phones, wireless tools and other forms of telecommunications technology."[3]

> "The potential for consumer products using communications technology was enhanced by the development of many technologies: the internet; ever smarter phones with digital cameras and geo location; low-cost processing power; miniature, ruggedised sensors; small long-life batteries; app development tools: big data; cloud storage; numerous standards; encryption capabilities; and other technologies."

The first interactive telemedicine system, operating over standard telephone lines, designed to remotely diagnose and treat patients requiring cardiac resuscitation (defibrillation), was launched in 1989 by MedPhone Corporation (Paramus, NJ, US). A year later it introduced a mobile cellular version, the MDPhone. Twelve hospitals in the US served as receiving and treatment centers.[1]

Earlier still, in 1977, Dr Stanley Sarnoff invented and patented a mobile analog cardiac monitoring system.[4] That was

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preceded by his filings as early as July 1970. This early telemedicine product anticipated the future of telemedicine.

An interesting early link between telemedicine and the drug delivery space emerges at this point in the story because Stanley Sarnoff became most famous not for his cardiac remote monitoring products, but for an earlier achievement – the invention and manufacture of the first prefilled auto injector. US Patent 2832330 was granted on April 28, 1958 for the AtroPen, which contained atropine for self-administration in the event of nerve agent poisoning. This was the first drug delivery combination product.

Continuing development of auto injectors, Sarnoff followed the suggestion of a pioneering allergist, Dr Stephen Lockey Sr, and asked his engineering team to modify an injector to deliver epinephrine. This eventually led to the life-saving EpiPen, the most famous invention of Survival Technology, Inc, the company Stan Sarnoff founded, now owned by Pfizer. Today the EpiPen remains incredibly successful. It is, by quite some margin, the leading product in its category and, in 2015, became US distributor Mylan's first billion dollar product. The EpiPen was also the reason for a recent induction into the US National Inventors' Hall of Fame. Sheldon Kaplan, one of the engineers on Sarnoff's team, was posthumously inducted this year. While Kaplan's contributions were significant, like most great technology innovations, the development of EpiPen was very much a team effort. Three other people were named on the Kaplan patent cited by the National Inventors' Hall of Fame and there were other patents on the device. Also, suppliers pushed the limits of their technologies to make required components.

eHealth is another related term, used particularly in the UK and Europe, as an umbrella term that includes telehealth, electronic medical records, and other components of health information technology.

With the arrival of mobile phones came mHealth, an abbreviation for mobile health, the practice of medicine and public health supported by mobile devices. The term is most commonly used with reference to mobile communication devices, such as mobile phones and tablets, for health services and information, but also to affect emotional states. The mHealth field has emerged as a sub-segment of eHealth, the use of information and communication technology

Figure 1: The elements of a typical connected drug delivery device system. (Image courtesy New Directions Technology Consulting, LLC. Design by Kelly Barkhurst/smartpr.)

(ICT), such as computers, mobile phones, communications satellite, patient monitors, etc, for health services and information. mHealth applications include the use of mobile devices in collecting community and clinical health data, delivery of healthcare information to practitioners, researchers, and patients, real-time monitoring of patient vital signs, and direct provision of care (via mobile telemedicine).[1]

The potential for consumer products using communications technology was enhanced by the development of many technologies: the internet; ever smarter phones with digital cameras and geo location; low-cost processing power; miniature, ruggedised sensors; small long-life batteries; app development tools: big data; cloud storage; numerous standards; encryption capabilities; and other technologies.

Most recently, came standardised automated identity and data capture. Having these technologies available at reasonable cost provides capabilities for managing the internet of medical things. These technologies are now bundled together into connected healthcare devices. First came monitoring and diagnostic devices. Now we have moved on to connected combination products for remote monitoring and logging of drug delivery. These are sometimes called medication therapy management devices or medication telemanagement devices.

THE PRESENT

It is recognised that patients often do not follow directions. This leads to concerns about medication adherence (picking up the script/buying the medications), medication compliance (following the prescribed dosing regimen) and medication management (the two above and following all administration, storage and disposal directions).

Nerve agent antidote and epinephrine for treating anaphylaxis were the beginning points for combination products, but the drivers for the recent growth of connected combination products are based upon the following factors:

- The emergence and growth of the bio-technology/specialty drug industry
- Biotech products are often fragile and cannot survive the digestive system and first metabolic pass therefore parenteral administraton is required

Figure 2: Veta smart cases for each EpiPen® the patient (or their parents) need to track will work together with the app as an integrated system. (Image courtesy Aterica, Inc.)

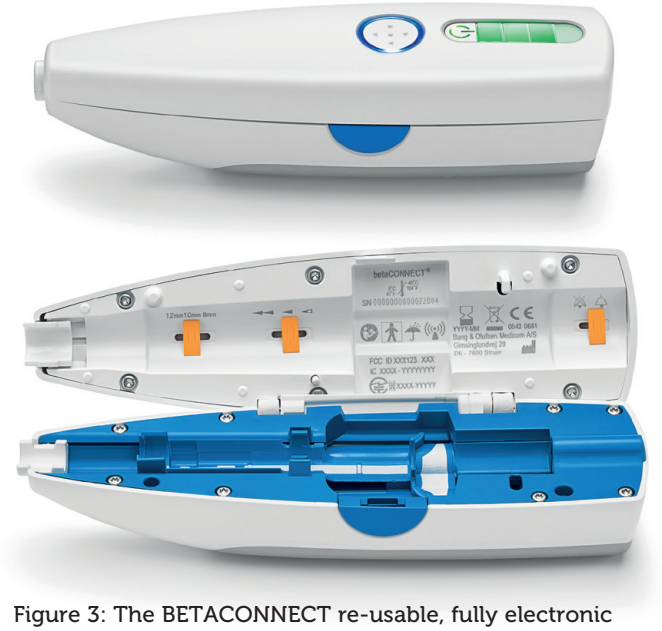

Figure 3: The BETACONNECT re-usable, fully electronic auto-injector can be used as part of a complete software-based system designed to track injection history and share important treatment information with healthcare providers. (Image courtesy of Bayer.)

- Specialty drug products often require special handling
- Desirability of administering drugs wherever the patient can conveniently dose (ie at home is preferable to hospital and primary care settings)
- Patient compliance with treatment regimens is poor
- Payment and procurement models have changed and will change more
- Stakeholders are demanding real world evidence regarding performance
- Human factors are recognised to be highly important for patient self-administered products…
- …Therefore, training and patient support are highly important, and
- Pharma has now recognised the value of connected combination products.

The essential elements of a system surrounding a connected combination product are shown in Figure 1. The claims made will determine whether a product is a combination product from a regulatory perspective.

There are numerous dosage forms under development with connected dispensers and delivery systems. This issue of ONdrugDelivery Magazine features connected devices for:

- Oral dosage forms (Balda Healthcare, Page 44)
- Inhalers (Biocorp, Page 20; and Adherium, Page 32)
- Re-usable and disposal auto injectors (Biocorp, Page 20; Medicom, Page 52; SHL Group, Page 38; and Ypsomed, Page 56)
- Wearable, large-volume injectors (Enable Injections, Page 12; West Pharmaceutical Services, Page 48; and Ypsomed, Page 56).

The examples that follow here provide an additional selection and represent only a fraction of the products already available or in development and heading towards the market.

AUTO-INJECTION

Veta™ Smart Case

Aterica, Inc (Waterloo, ON, Canada) has developed Veta™, a Bluetooth® Smart-connected case for the EpiPen, which is due to reach the market imminently. The case is transparent with sensors and electronics to monitor and communicate. Functionality, via the app, includes: locating a misplaced device; separation alerts; auto-injector removal from case alerts; temperature monitoring; expiry reminders; and connecting with patient-defined support circles which can include a private support circle (for example, parents, close friends, caregivers) and extended support circle (such as teachers, coaches). The patient determines how much or how little information about their location and daily habits each circle's members receive.

Veta can support up to eight EpiPen auto-injectors within the patient's network simultaneously meaning that Veta smart cases for each EpiPen the patient (or their parents) need to track will work together with the app as an integrated system, managing each auto-injector (see Figure 2).

Bayer BETACONNECT™

In 2014, Bayer Healthcare (Leverkusen, Germany) launched the first and, to date, only fully electronic auto injector, for its multiple sclerosis product, Betaferon (interferon beta-1b). The BETACONNECT auto injector (Figure 3), which was developed and is manufactured by Medicom Innovation Partner (Struer, Denmark; now part of Phillips-Medisize), can be used both independently (not connected) and as part of a complete software-based system designed to track injection history and share important treatment information with healthcare providers.

An app, called myBETAapp™ provides Bluetooth or USB connectivity and automated uploading of injection data and also allows patients to record other injection and general health information. Users will be able to connect electronically across multiple platforms (Windows, Apple Mac OS X, iOS, Android) to provide continuous feedback and notifications to help Betaferon® patients achieve and maintain their treatment goals. Patients can choose to share information via the myBETAapp™ dashboard with healthcare providers.

GrowJector® 2

Panasonic (Osaka, Japan) and JCR Pharmaceuticals (Hyogo, Japan) collaborated on the development of a connected digital auto injector for human growth hormone (hGH), which won the 2012 "Good Design Award" sponsored by the Japan Institute of Design Promotion. The device, called GrowJector 2, has data-logging and communications capabilities. Panasonic has worked on other versions of the device for other companies' products.

Unilife's LISA™

The LISA platform of smart disposable auto-injectors (Figure 4) from Unilife Corporation (York, PA, US) allows a range of ergonomic shapes and sizes and a series of options that can be tailored to the specific needs of an individual therapy and its target patient population. Options include the heating of the molecule to room temperate prior to an injection, the ability for a patient to control the speed or depth of each injection, and the pairing of the device with Bluetooth LE connectivity as well as a related app. The LISA connected injector platform has attracted various multinational pharma partners.

INHALATION

Propeller Health

Propeller Health (Madison, WI, US) is developing an add-on with associated app, which connects asthma and COPD inhalers (MDIs, DPIs and others) and has already partnered with GlaxoSmithKline (Brentford, UK) and Vectura (Chippenham, UK), amongst others.

The process of using Propeller's device, from the use point-of-view, is straightforward. They sign-up online / download the app, the Propeller device ships immediately and arrives within days, the patient attaches it to their inhaler and then continues using their device as normal. The app is designed to "learn" and the company intends that patients using the product's mobile apps, desktop web apps and messaging and notification tools gain insights into their triggers, reduce the hassle of managing their asthma or COPD, and become better connected (in terms of their disease management) with their care team (including family members and healthcare professionals). For the healthcare professional, Propeller says it helps focus on patients most in need of attention, increasing efficiency through smart notifications, a patient dashboard and communication tools.

The company has developed a body of evidence, and published substantial trial data, including in peer-reviewed journals, linking the use of their connected product with increases in inhaler adherence and compliance and, going further, suggesting a causal link between the use of their connected product and significant improvements in disease outcomes. For example, earlier in 2016, results were published of a 12-month, randomised, controlled clinical trial conducted by Dignity Health (San Francisco, CA, US) investigating short-acting beta agonist (SABA) use in 495 asthmatics. The paper concluded that, compared with the control group which received routine care without the connectivity of the Propeller platform, "the study arm monitoring SABA use with the Propeller Health system significantly decreased SABA use, increased SABA-free days, and improved ACT scores (the latter among adults initially lacking asthma control).[5]

> "FDA believes that providing patients with access to accurate, useable information about their healthcare when they request it (including the medical products they use and patient-specific information these products generate) will empower patients to be more engaged with their healthcare providers in making sound medical decisions."

Figure 4: Unilife's LISA™ platform of smart disposable auto injectors allows pairing of the device with Bluetooth LE connectivity as well as a related app.

Figure 5: The eMDI from Presspart and Cohero.

Cohero and Presspart

Partners Cohero Health (New York, NY, US) and H&T Presspart (Blackburn, UK) have developed a connected metered-dose inhaler, eMDI (Figure 5) which incorporates electronics to track and communicate medication utilisation passively. A sensor records the date and time medication is actuated, which is then stored in onboard memory, as well as shared wirelessly via Bluetooth. It works seamlessly with Cohero Health's platform of connected devices and mobile applications, which actively engage and empower respiratory patients by tracking medication adherence and measuring lung function. The companies announced the completion of their device in April 2016, making it available to pharmaceutical industry partners.

Cohero has numerous partnerships and announced a US$2 million (£1.4 million) seed financing in December 2015.

Qualcomm Life / Novartis

In early 2016, Qualcomm Life partnered with Novartis on the development of a connected version of Novartis' Breezehaler™ inhaler, which is used to deliver the company's COPD products Onbrez (indacaterol maleate), Seebri (glycopyrronium bromide) and Ultibio (indacaterol + glycopyrronium).

With launch of the next-generation, connected Breezehaler planned for 2019, Novartis aims to be the first company in respiratory medicine to offer "a completely integrated, connected delivery device to provide a seamless, easy to use and simple experience for patients".

A small, disposable, low power module contained within the inhaler detects and reports usage, the time that the inhaler is used, as well as additional relevant information for patients and physicians. The module then wirelessly sends the data to the patient's smartphone and a Novartis COPD mobile app, which sends the data to the cloud, allowing patients and potentially their healthcare providers to monitor their COPD.

Qualcomm Life, a subsidiary of chip-maker Qualcomm, is to develop the design for the module containing the connectivity tech. Qualcomm Life is a very active player in the connected health sector, with numerous initiatives and partnerships with hospitals, pharma companies and other organisations (see Qualcomm Life's article in this issue, Page 27).

ORAL SOLIDS, SMART PILLS & PACKAGING

Proteus / Discover

Probably the most publicised company developing connected tech for oral delivery is Proteus Digital Health (Redwood City, CA, US). The company's platform (Figure 6) comprises four elements: sensor-enabled pills, containing an ingestion sensor the size of a grain of sand; a body-worn patch which receives a signal from the pill when it reaches the stomach; monitors patient activity and rest patterns, and communicates with the cloud relaying information to the patient's smartphone and, with their permission, to their doctors too; the Discover App, which enables patients to keep track of their medications, steps, activity, rest, heart-rate, blood pressure and weight, set multiple medication taking schedules and receive reminders; and the Discover portal, which allows doctors access to patient data helping them allocate resources to those who need them most and optimise tailored treatment decisions for each patient.

Figure 6: The Proteus platform comprises four elements: sensor-enabled pills, containing an ingestion sensor; body-worn patch (pictured) which receives a signal from the pill; the Discover App (pictured); and the Discover portal, for physicians. (Image courtesy Proteus Digital Health.)

Like Propeller Health in the inhalables sector as previously mentioned, in the oral delivery sector Proteus is building a body of robust evidence to support its claims that its platform improves clinical outcomes. Most recently, at the 65th Annual American College of Cardiology meeting in Chicago, IL, US, in April 2016, the company reported interim results from a randomised, controlled clinical trial in 96 patients with uncontrolled hypertension and type-2 diabetes, which revealed that patients who used Proteus Discover achieved statistically greater reduction in blood pressure and low-density lipoprotein cholesterol, known risk factors for cardiovascular events, and were more likely to achieve their blood pressure goal compared with those receiving usual care.

IMC Med-ic

The smart blister pack, Med-ic, from Information Mediary Corporation (Ottawa, ON, Canada), utilises a CPU and attached printed sensor grid embedded in the blister package (Figure 7). The CPU records the time when a given tablet or capsule is expelled from its blister, and stores the data for later display and/or analysis.

At the time of refilling the prescription or during a clinical trial follow-up visit, the patient's compliance data are downloaded to a PC via a CertiScan® RFID Reader, or downloaded using any NFC-enabled

Figure 7: Med-ic smart blister pack utilises a printed sensor grid embedded in the blister package to record when a given tablet or capsule is expelled from its blister. (Image courtesy IMC.)

smart phone or tablet. CertiScan Software displays the information immediately on a PC using an intuitive graphic interface featuring point-and-click, drill-down capabilities ranging from daily to annual at-a-glance views. Using an NFC-enabled smart phone or tablet, compliance data can similarly be displayed directly on the device. The software extends electronic record compliance with 21 CFR Part 11 back directly to the patient source.

No patient information is stored on the CPU, ensuring confidentiality. CPU-resident data comprise simply a sequence of numbers representing time-events that can only be related to a patient when the study code is broken by the sponsor. Inputting compliance data collected by the traditional methods of patient reports, medication diaries and pill counts is costly. Med-ic eliminates the need for the double entry compliance data phase, dramatically reducing data entry costs while offering researchers the most reliable and valid records of patient adherence to the study regimen.

West Rock's Smart Packaging

WestRock (Norcross, GA, US), which was formed in 2015 from a combination of MeadWestvaco and RockTenn, is developing a range of connected smart packaging for oral dosage forms. MEMSCap for example, is a connected, child-resistant cap with integrated circuits that fits most standard pill vial sizes and can record up to 3,800 dosing events (Figure 8).

Figure 8: MEMSCap is a connected, child-resistant cap with integrated circuits that fits most standard pill vial sizes. (Image courtesy of WestRock.)

Whilst MEMSCap works on the assumption that a pill is removed each time the container is opened, other WestRock products can detect when individual pills or capsules are removed from blister packaging. CarePak features a tiny, hidden microprocessor and printed, conductive inks which record the date, time and location of each pill removed from the package. Tracking the removal of each specific tablet is critical for dose titration (pill dosage changes) and for regimens with a mix of placebo and active drugs.

Dispensers and Pouches

Many companies are now developing smart pill dispensers and organisers. Vitality Health (Los Angeles, CA, US), for example, was an early introducer of smart pharmaceutical packaging and has developed a pill vial cap (along the same lines as MEMSCap described above) called GlowCap. It is also developing a smart, resealable pouch, GlowPack, which can hold oral solids (including blister packs), injectables, inhalers, drinkables, and topical ointments. It provides both visual and audible reminders, glowing at dosing time and glowing and playing a melody one hour past dosage. It includes an automated reminder call to the patient two hours past missed dosage. The device communicates via an AT&T wireless cellular connection and allows for detailed weekly and monthly reporting to patient, clinician and manufacturer.

THE FUTURE OF CONNECTED COMBINATION PRODUCTS

As can be seen from the small sample of projects and products described here, and elsewhere in this issue, many well-informed stakeholders are funding the further development of connected combination products. Some are simple informational products which are not medical devices. Others combine state-of-the-art technologies. Future developments will utilise legacy and new technologies in ways beyond current dreams.

As with consumer products, to be successful, connected combination products should be simple to use and meet real needs. A May 2016 Wall Street Journal article entitled, "Smart Tampon? The Internet of Every Single Thing Must Be Stopped", cautioned that not every object should connect to our smartphones – and if it does, it should at least work. Whilst it described a number of so-called smart devices as actually being dumb, not smart – for example, the smart umbrella that reminds you not to leave it behind, or the smart tampon that reminds you when to change it – the article conceded that there were truly smart devices out there with real potential, and specifically mentioned medication telemanagement devices as serving real needs.[6]

In the coming months, market needs will drive individual stakeholders and their trade and professional associations to push towards reimbursement, resolving regulatory and security issues. Indeed as this article was going to press, the US FDA Center for Devices & Radiological Health (CDRH) issued a Draft Guidance for Industry entitled, "Dissemination of Patient-Specific Information from Devices by Device Manufacturers".[7] The fact of the draft guidance itself is telling and suggests that the regulators are coming up to speed on the benefits of engaging patients in their treatment by providing them with data.

The Draft Guidance says: "FDA is issuing this guidance to clarify that manufacturers may share patient-specific information recorded, stored, processed, retrieved, and/or derived from a medical device with the patient who is either treated or diagnosed with that specific device."

> "Pharma has now recognised the value of connected combination products."

It continues: "FDA believes that providing patients with access to accurate, useable information about their healthcare when they request it (including the medical products they use and patient-specific information these products generate) will empower patients to be more engaged with their healthcare providers in making sound medical decisions."

While the Draft Guidance suggests no additional regulation of devices regarding providing data to patients, industry should follow the development of this and other guidances, and be cautious about any labelling, which might be regulated.

In the near future, the value in connected combination products will be clearly demonstrated. As with consumer products, this will further stimulate demand. Partnering activity will increase because few, if any, stakeholder organisations have all the required capabilities in house. As with technology and consumer industries, firms will co-operate using shared IP to secure freedom to operate. They will acquire/license/cross license and co-operate to exclude infringers as elsewhere in these industries. Thus the sale and licensing of medication telemanagement IP will become strategically important.

As the market for connected combination products grows, new entrants will appear and challenge the early developers. For example, Chinese firm Delfu Medical (Changzhou City, Jiangsu Province, China) showcases a large range of electronic devices on its website including electronic syringes, auto injectors, insulin pumps and more.[8]

Service beyond the script and real world data will be used to extend pharmaceutical product life and reach. Stakeholders will enjoy revenue streams from new products/services grown from medication telemanagement, and pharma product service and support will improve pharma's stakeholder relations.

Developing countries will explore more creative uses of connected combination products. Just as with the smart phone and the internet, developing countries may enjoy greater benefits because they are not bound by legacy customs and systems. A number of US leading companies including Cardinal Health have already partnered with non-profit organisation Trek Medics International (New York, NY, US) which is dedicated to improving emergency medical systems in communities around the world without reliable access to emergency care. Imagine a connected drug kit with interactive instructional capabilities in the situation pictured in Figure 9.

Figure 9: The difficulties involved with delivering emergency care to a remote location in the developing world (Image courtesy Trek Medics)

The world is just waking up to the promise of connected health and specifically in drug delivery systems and other combination products. It is truly exciting to contemplate its full potential and what might be achieved by applying connectivity in healthcare over the coming years and on into the future.

ABOUT THE AUTHOR

Napoleon Monroe is Managing Director of New Directions Technology Consulting, LLC. His diversified background extends from developing and producing emergency pharmaceutical delivery systems to managing private brands for a Fortune 500 company, to building and managing the IP portfolio for a company that is now part of Pfizer. His expertise includes product development, licensing, regulatory processes, risk management and international marketing, with experience managing business relationships in more than 30 countries.

As Vice-President of Corporate Brand Development for global healthcare distribution and service company Henry Schein, Inc, Mr Monroe was responsible for all aspects of the company's private brands. He grew annual sales by more than 500% to more than US$500 million. While there, he also began filing medication telemanagement patents.

Before Henry Schein, Mr Monroe spent more than 20 years at Survival Technology (now the Meridian Medical Technologies division of Pfizer) where, as a Corporate Vice-President, he was responsible for product development and systems strategy. While at Survival, with colleagues he invented three medical devices that were patented and commercialised; two were for auto-injectors and one was for a transtelephonic, peak-flow monitoring device.

There, he also led teams that invented, prototyped, tested, commercialised and scaled-up such products as: the EpiPen, still the leading product for treatment of anaphylactic shock; the Antidote Treatment Nerve Agent Auto Injector delivery system, which still protects US and allied military and civilian personnel; and products that supported the formation of Shahal Medical Services in Israel (acquired by Shanghai Jiuchuan) and Raytel (now part of Philips in the US).

Mr Monroe has been cited in a number of industry publications. He is active in the Parenteral Drug Association, HIMSS, Prescription for a Healthy America, Health IT Now, National Defense Industrial Association and other groups. He is a longstanding member of the American Telemedicine Association. He supports East Carolina University where he did his undergraduate degree.

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ENABLE CONNECTIONS: A BLUETOOTH-CONNECTED WEARABLE, ON-BODY INJECTOR

Last year, Enable Injections announced the development of a Bluetooth-connected Enable Wearable Injector. In this article, we explore the vast potential for improving patient care that comes from adding connectivity to devices that deliver biotherapeutics for the treatment of chronic conditions and, in particular, the synergy that exists when wearable on-body injectors are combined with connectivity technology.

Written by ONdrugDelivery Magazine, for and on behalf of Enable Injections.

The steady uptake of digital technologies within healthcare continues to improve diagnosis, treatment and patient management in the clinical setting. It produces a large amount of data – the manifold uses and value of which industry stakeholders are just coming to terms with. An opportunity exists to produce far more, increasingly valuable data from digital technologies if the healthcare sector is able to direct the necessary resources towards building the infrastructure to connect digital health technology to the cloud, for true connected health (CH).

> "Connected Health allows the patient and other stakeholders to enjoy all of the benefits of self-administration without it having to be at the expense of the benefits of clinical oversight and monitoring. Having the best of both worlds – convenient, intuitive administration at home and clinical monitoring – becomes an achievable goal."

The area of consumer health is moving ahead on this, with connected biometric devices already becoming widespread. The growth of the smartphone industry has clearly been a key enabler and monitoring our own health outside the clinical setting with mobile and wearable clinical and fitness devices has become popular. For consumers, this represents a powerful tool, providing the ability to access, analyse and share their data from connected devices and apps.

The medical and pharmaceutical segments of the healthcare industry are on the verge of harnessing these developments and taking advantage of the benefits CH can bring. The potential to create a better, more efficient and cost-effective healthcare system is substantial.

CONNECTED HEALTH IN BIOLOGICS DELIVERY

Biologic-based therapeutics have been reaching the market in steadily increasing numbers, with biologics-rich pharma

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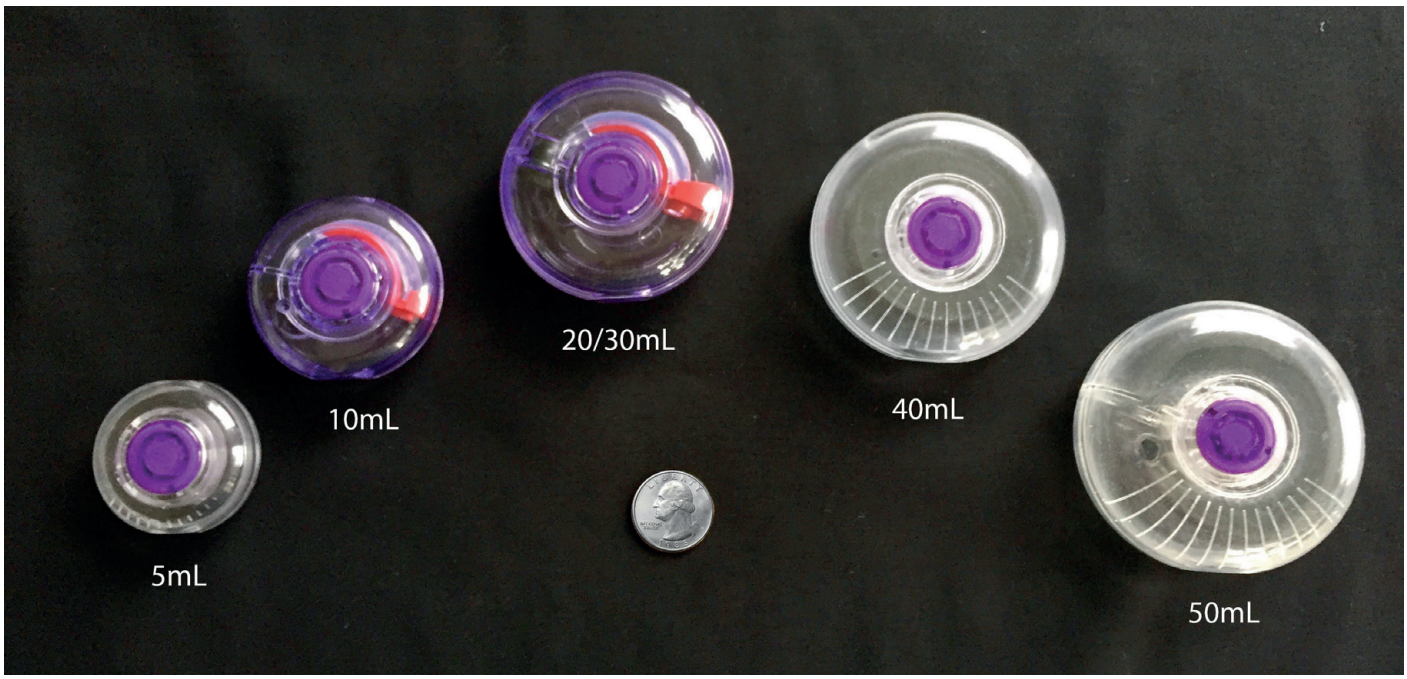

Figure 1: The Enable Wearable Injector can deliver volumes from 5 mL up to 50 mL.

company R&D pipelines promising more to come in the medium and longer term. Biologics typically treat chronic conditions requiring a long (often life-long) treatment regimen, and such indications are on the rise due to advances in medicine and people living longer. What were once fatal diseases have become chronic diseases. The underlying growth in global population is also a factor. The rampant growth in the development of biologics has been driven by the need to meet this rise in chronic conditions.

Almost all biologics require delivery via infusion or injection and traditionally the hospital setting was the location for their administration, by healthcare professionals. On one hand, these sophisticated medications are highly effective in treating difficult diseases. But on the other hand the nature of many of these medications introduces further complexities most notably: the high viscosities arising from high protein concentrations, giving rise to large injection volumes; the frequency of required dosing can be inconvenient; there are larger volumes of drug to monitor and, due to their high price, reducing excess and waste is important. The burden and inconvenience of complex treatment regimens threaten patient compliance/adherence, with consequent negative impact on clinical outcomes.

"The connected Enable Wearable Injector features passive monitoring. The monitoring software is integrated with the device to deliver a fully automated monitoring process. This removes all requirement for user input and for the user to carry out process steps with applications as far as recording the data is concerned, avoiding the user retention issues that have caused other mobile monitoring projects and therapy adherence apps to fail in the past."

Self-administration at home is clearly a highly favourable means to increase convenience, and over recent years we have seen the emergence of enabling technology capable of taking treatment out of the hospital and into the home. For small volumes of less viscous formulation, pens and auto injectors often suffice, making administration simple, intuitive and safe enough for self-injection at home.

For the more complex, viscous formulations with high dose-volumes, which are often the biotherapeutics that are effective in difficult-to-treat indications, auto-injectors are not usually suitable delivery devices. However, wearable, on-body injectors like that under development by Enable Injections do overcome the technical restraints that previously inhibited use of these difficult-to-deliver biologics outside the hospital setting in the past.

A principle advantage of wearable bolus large-volume injection devices is essentially that they take the time pressure off the administration procedure. With a syringe or an auto injector, the injection needs to be completed quickly – seconds rather than minutes. Whereas once you move to a device that is worn on the body, the process can take a few minutes, or more, without any problems.

The very significant advantages and possibilities that open up if you can take more time, slow down the rate of injection, and allow a higher dose volume are summarised in the boxed text at the end of this article. The specific advantages of Enable Injections' wearable device, which can now deliver volumes from 5 mL right up to 50 mL (see Figure 1) were discussed in greater detail in Enable's article, "*People Power: Inspiring & Delivering a Unique Wearable Bolus Injector*", which appeared in ONdrugDelivery Magazine, Issue 51, July 2014, pp 31-33.

The cost savings that wearable large-volume injectors bring are not limited to those arising from enabling self-injection compared with the more expensive clinic- and hospital-based treatments. "The benefit for biopharma companies is they can get their product into clinical evaluation quicker as there is no need to spend time on additional formulation to achieve low volumes," explained company Chief Executive Officer, Mike Hooven.

Nevertheless, whilst huge benefits stem from moving injected therapeutics, even those requiring large volumes or highly viscous formulations, out of the clinic and into the home setting for self-injection, there is one element of compromise – because of course moving treatment home and out of the clinical setting also means moving the patient and their treatment away from the close oversight and monitoring that healthcare professionals provide in the clinic where they are present.

> "In connecting the Enable Wearable Injector via mobile devices to the cloud, Enable Injections is demonstrating that its founding principles of patient-centric innovation, promoting adherence, technology-enabled therapeutics and cost reduction endure."

As more biologics reach the market, and the trend for their self-administration as injectable therapeutics in combination with drug delivery devices accelerates, this presents an obstacle: self-administration at home diminishes the ability of healthcare providers to track and monitor the use of ever larger amounts of therapies being prescribed to a large and growing number of patients.

It is this undesirable compromise that connecting delivery devices to the cloud can really help to avoid – CH allows the patient and other stakeholders to enjoy all of the benefits of self-administration without it having to be at the expense of the benefits of clinical oversight and monitoring. Having the best of both worlds – convenient, intuitive administration at home and clinical monitoring – becomes an achievable goal.

In addition to allowing clinicians to monitor and oversee treatment at home, CH has the potential to aid in patients' accountability for their own home treatment. A connected drug delivery system increases patients' engagement with their treatment since: 1) they know they're being checked and 2) there is a sense of gratification from meeting the marks required of them.

The same human psychology applies with treatment adherence goals as with mHealth products such as Fitbit, which works because we want to meet our target of, for example, taking a certain amount of steps a day, and to see our achievements displayed visually on our phone screens via the app. It is well understood that patients who engage in their healthcare decision-making process tend to have healthier outcomes.

Self-managed health and wellbeing using a connected delivery device brings with it numerous additional benefits including: the sharing of essential data with doctors/physicians; the ability to alert healthcare providers to potential problems; using the data to facilitate more informed clinical decisions and efficiently manage populations. Connected devices can help accommodate different patient populations and instil confidence with self-administration – for example patients with different disease states; patients experienced with using injections *versus* self-injection-naïve patients; variable cognitive abilities; differing physical dexterities; and patients of different ages.

CONNECTING THE ENABLE INJECTION DEVICE

In 2015, recognising the enormous potential that the synergy of CH and wearable on-body injectors holds, and the rising need for compliance monitoring and data capture with a mobile app, Enable Injections announced a Bluetooth-connected Enable Wearable Injector. Mike Hooven said: "Now pharmaceutical companies, physicians and patients can each have the tracking data they need by using a mobile app or Bluetooth-connected device. The ultimate goal is that the new drug delivery technology will not only benefit patients by improving their health outcomes, but also lower costs by streamlining drug development and replacing costly hospital-based infusions."

The connectivity hardware (chipset), which is developed in partnership with Flextronics International Ltd ("Flex"), is conveniently packaged inside the Enable Wearable Injector's button (see Figure 2). The operation of the drug delivery device function remains wholly mechanical and independent from the electronic components used to capture data. Therefore the connectivity aspect is optional and if, for example, the chipset malfunctioned, the drug delivery device would still function completely normally.

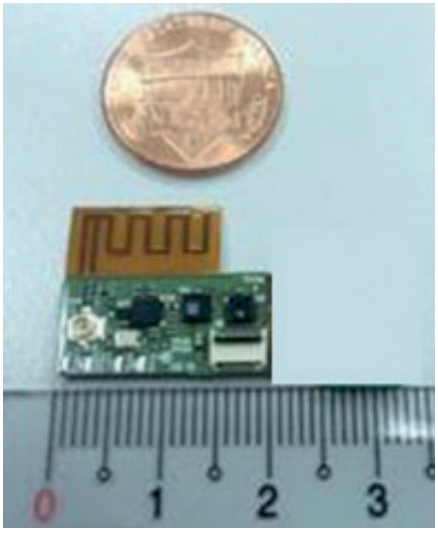

Figure 2: The chipset for the Bluetooth-connected Enable Wearable Injector, which will be packaged conveniently inside the injector's button.

Whilst the delivery device functions mechanically and independently of the connectivity electronics in the button, the connected Enable Wearable Injector features passive monitoring. The monitoring software is integrated with the device to deliver a fully automated monitoring process. This removes all requirement for user input and for the user to carry out process steps with applications as far as recording the data is concerned, avoiding the user retention issues that have caused other mobile monitoring projects and therapy adherence apps to fail in the past due to the need for active user input. But at the same time, once the data has been collected automatically, it can be processed and actively delivered in a useful format to the patient via mobile app notifications and alerts, driving incentive, engagement,

and patient accountability when using wearable on-body delivery devices.

The possibilities for improving treatment outcomes arising from having the ability to collect real-time and historic data from the Enable Wearable Injector are breathtaking and do not stop at promoting patient engagement, accountability and increasing adherence. For example, in many diseases there is no "one-size-fits-all" care management approach. A variety of nuances related to the disease treatment such as disease progression, genotype, comorbidities, and/or other risk factors drive the need for an optimal, individual approach. Based on data feedback from the Enable Wearable Injector, dosing regimens can be tailored to real individuals' needs.

CONCLUSION

The original, founding principles of Enable Injections were around patient-centric innovation, carrying out detailed user preference and usability studies, and using the insights from these to incorporate innovative device design features that promote adherence. The concept of technology-enabled therapeutics was also crucial, whereby the provision of a wearable, on-body injector capable of delivering high volumes of viscous formulations could transform active biologics into convenient, effective successful therapeutics on the market. These were previously so complex and difficult to deliver that they were not viable as pharmaceutical products. Additionally, as explained previously, the Enable Wearable Injector provides an efficient means to reduce and manage the growing expense associated with the rising incidence of chronic conditions. The over-riding objective is always to improve treatment outcomes from biological therapeutics.

In connecting the Enable Wearable Injector via mobile devices to the cloud, Enable Injections is demonstrating that its founding principles of patient-centric innovation, promoting adherence, technology-enabled therapeutics and cost reduction endure and with it the promise of significant, life-enhancing treatment outcomes for patients suffering from chronic conditions.

SUMMARY OF ENABLE WEARABLE INJECTOR ADVANTAGES

The Enable Wearable Injector provides numerous advantages, including:

- Subcutaneous delivery of up to 50 mL doses of high volume and/or viscous biologics
- Passive warming of drug product, eliminating the 30-minute wait for refrigerated vials to reach room temperature
- Automated mixing and reconstitution, reducing formulation time and drug development costs
- Use of standard vials, cartridges and syringes, and existing container closures
- Facilitation of in-home therapy, reducing healthcare system costs
- Ability to monitor compliance and capture data utilising optional Bluetooth connectivity and a mobile app to provide a connected healthcare solution.

MATHIAS ROMACKER, PFIZER

As well as being a world-leading expert on parenteral delivery systems, Mathias Romacker is a very well-known, respected and much liked personality in the sector. Since the emergence of prefilled syringes onto the market in the 1990s and throughout the parenteral device sector's rapid evolution over the past two decades, he has been at the heart of this industry, working on both the device manufacturer side (including at Becton Dickinson and Gerresheimer) and then on the pharma/biotech side, most recently at Pfizer. Mathias has a true feel for the industry, the markets it serves, and where things are heading.

In this interview, Mathias shares his thoughts with ONdrugDelivery Magazine on the emergence of connectivity in drug delivery devices, from his current big pharma company perspective and also based on his previous industry experience. He explains why he thinks the buzz around connectivity in delivery systems is more than just hype and describes the trends in the pharma sector that mean it makes sense now to connect up devices. He also cautions, though, that connected technology must drive value in order to be successful, and points to some of the areas where he believes it could do so and how it might be done.

Q Connectivity has been called the next big thing in drug delivery. But you and I have both been around long enough to know that whenever we hear about "the next big thing in drug delivery", sometimes it's true, sometimes it is not. What's your feeling about connectivity in drug delivery? How important is it really? And why?

A It's a very good question to raise. Will something that is supposed to be the next big thing really be the next big thing? In this specific case, clearly we are looking at something that is part of the bigger ecosystem – the drug delivery sector is definitely not in a vacuum or a silo here. Think electronic medical records. And we hear more and more that payers need to see outcome-based therapies so they want to have ways to measure outcomes, measure success. So connectivity presents opportunities for diagnostics. And also, of course, connectivity presents the means to determine whether the drug is being taken at the right dose, as prescribed. From that perspective I think that connectivity – really being able to make the connection from a patient taking a drug to healthcare professionals, and beyond to pharma companies and to payers – it will happen. We don't know how fast but it will happen. First of all, the technology is now available and, secondly, the underlying need is also there.

Smart phones are obviously a crucial aspect – people having this technology at their fingertips, truly being connected. The internet of things has become reality and if you look across the board at who is using it, you have young ones but also older folks. People are growing up with it. Somebody who is in their fifties right now will be familiar with their smart phone. Fast forwards two decades and you'll have seniors – people in their seventies – who grew up with this technology and they aren't going to give up on it.

> "Somebody who is in their fifties right now will be familiar with their smart phone. Fast forward two decades and you'll have seniors – people in their seventies – who grew up with this technology."

Q There is this sense of two previously quite separate and distinct industries – digital tech and pharma – really coming together now. It seems like trends in both sectors are pointing to both being at just the right point to combine very effectively. What are the main trends and breakthroughs on either side – the tech side and pharma side – that are making now the right time to connect up our drug delivery systems. I guess I mean, why is this happening now? Why is this the right time – not earlier and not later?

A Explaining why this hasn't happened earlier is easier I guess. The technology was not there, or if it was then it was prohibitively expensive. Now of course the technology is there. I've always been a firm believer, though, that as well as just being available, the technology has to be driving value and it has to be affordable. I think we're seeing that now.

As to why it matters now, again it comes to the overall equation that in the pharma industry we have more and more biologics both being launched and in the pipelines of pretty much every large pharma company, and most smaller ones too. Many of these biologics are antibodies and so the injection frequency is changing. In the past most self-injection drugs – the growth hormones and the insulins – were mostly daily injection events. The more recent biologics coming through are injected less frequently – weekly, biweekly, monthly even.

So the question comes up, what actually happens between those injections? How can we monitor the patient and make sure of what is going on between these less frequent injections and between doctors' visits? How can you set up an individualised intervention system? Another industry that we have seen evolving is patient on-boarding. With so many self-injecting patients now, how do you do the on-boarding best?

Connectivity represents a tool that can help with both the on-boarding and with keeping the patient up to speed. If they are only injecting once a month, for example, the patient might forget how to do the

injection. There are opportunities now to have video on demand, training on demand. There are so many opportunities out there right now – where connectivity, in conjunction with devices and drug delivery systems, could be leveraged.

Q Is now the right time for us to connect in terms of drug delivery device industry trends too?

A As we discussed before, adding connectivity has to make economic sense. It seems to me that patient adherence is an important issue. Obviously it varies according to therapeutic area – it's higher in areas like oncology, for example, and lower in others, especially for asymptomatic indications. At conferences some speakers throw around numbers that are mind boggling! But adherence is definitely a big issue. We can improve adherence through better devices and better, more intuitive technology, for example, the needle should never be visible, pain should be minimised and safety optimised. The industry has made significant progress on this over the past decade or so.

Maybe the missing piece of the puzzle, something that you can't achieve otherwise, is that you want to interact with the patient and, in certain circumstances, monitor and log the use of drug delivery devices, such as inhalers and auto-injectors. But patients can't see their doctor every day and so this level of interaction can only be achieved through connectivity – there doesn't seem to me another logical technology out there. And as we mentioned earlier, the cost of this has come down substantially – think of low energy Bluetooth technology, think of energy harvesting.

Another very interesting question for me as an industry watcher is that historically the trend has been for simple, easy-to-use disposable devices, but is there an opportunity now for a reusable device with all the bells and whistles, patient comfort settings, you name it, and with connectivity, which users might prefer? A device like this could probably do a lot if it makes economic sense or if it can be reused, for example, for a chronic, long-term therapy.

Q There are potential advantages to be gained right across the board from connecting delivery systems – patients, payers, physicians/doctors, pharma companies, regulators, in clinical trials etc. Can you outline some of these advantages? Will connectivity become established in some areas, or for some purposes/functions, more quickly than others? Which groups of stakeholders do you see benefiting first? How will they benefit? Who has the most to gain overall?

A It's a very difficult question so I need to speculate here quite a bit. Clearly with the bond between patients and physicians/doctors this is an area that can definitely take off. Ideally healthcare professionals want to minimise the time they have to spend on training and adherence while still making sure that the patients get it right.

There is potential in the area of clinical trials but this is a little bit different. It's a much more controlled environment and the people in the trials are a little more co-operative than you'd maybe find in the overall population.

> "When you look at infrastructure from a pharma company perspective, how far do you want to go? Does a pharma company want to build up a whole infrastructure, or is this maybe an opportunity for some of the service providers in that space that they may be able to build the infrastructure or the ecosystem and within that space the pharma companies would operate and create value."

In terms of pharma and payers, this is an interesting one. Privacy issues may sometimes present a challenge that needs to be overcome. For example, I understand that with the device from Medicom (see this issue Page 52), Betaconnect, for Bayer's betaferon, patients actually have to opt in to share their device data with doctors/physicians.

It could be that for sharing data with pharma companies the information could be blinded and consolidated in order to anonymise it. So they could have information that tells them here are, say, 100 patients using the device, here are their adherence rates, these are the comfort settings they are using, and so on. For sharing data with payers, this is an interesting one that I've not read or heard so much about but obviously they have quite an interest in making sure patients actually take the drugs, and take themin the way they should, and also an interest in measuring outcomes.

Clearly medical records data is a very sensitive issue for patients so there needs to be some kind of confidence that it's managed in an appropriate way. What the appropriate way looks like still needs to be defined. It's in the interests of payers, doctors/physicians to have this information to enable them to make therapy decisions.

A recent partnership between West Pharmaceutical Services and HealthPrize is interesting (see this issue, Page 48). They are looking at reward systems whereby the patient is rewarded if they use a drug as it's prescribed and on a regular basis. I don't think the verdict on this is out yet. It's very interesting. For instance, in some markets payers could reward users with a co-pay they can manage. So it doesn't have to be that you have to give every patient something like a Starbucks voucher. It's evolving and of course the regulators have to weigh in with what they think is acceptable.

Whether or not the medicines regulators will be the ones making decisions on the issues of privacy and related matters, is an interesting question. I wouldn't say it would necessarily be regulated at that level. Although on the other hand they do listen to patient advocacy groups. Whoever makes those decisions in the end, one would hope it would be very inclusive.

Q What are the main drivers for this growth/emergence of connected drug delivery? And, crucially, what are the main barriers and challenges the industry faces?

A In this industry we like to talk about differentiation and in this instance – I may be totally wrong – I don't think connectivity is necessarily a great differentiation opportunity. A very good technology class comes along, connectivity tech, and it allows us truly to interact with patients, make sure they take their

medication, monitor and intervene if patients are not taking their drug. I think this is more an adherence play than anything. I think it's going to help multiple stakeholders across the board. Obviously the patient benefits from getting a prescribed drug and taking it the right way – best efficacy, best safety. The payer benefits because if the patients stay healthy because they are taking their medication well, this leads to fewer hospitalisations. And of course if patients are taking a medication that is therapeutically beneficial, and they are taking it for longer, then pharma benefits.

> "I've always been a firm believer, though, that as well as just being available, the technology has to be driving value and it has to be affordable. I think we're seeing that now."

In terms of barriers and challenges, I'm not really the expert as far as connected tech is concerned but the conversation about the security of electronic medical records has been going on for some time. I actually read recently that the application of Bitcoin encryption technology could be interesting in this area. My understanding is that for now there are a lot of different systems out there and they are not aligned. It may be a little bit like the VCR industry 30 years ago – with Betamax, VHS and so on. It's not exactly the same but clearly new ecosystems of technology are being established and are evolving and there may be an issue of compatibility.

When you look at it from a pharma company perspective, how far do you want to go? Does a pharma company want to build up a whole infrastructure, or is this maybe an opportunity for some of the service providers in that space? They may be able to build the infrastructure or the ecosystem and within that space the pharma companies would operate and create value.

Q How are large pharma companies such as Pfizer engaging with the developments around connected drug delivery systems, and the opportunities they present? Where do the most exciting opportunities lie for tech and other companies that could offer connectivity-related services, technologies and products as partners to large pharma companies like Pfizer?

A Not being Pfizer-specific, I can say that big pharma companies already have large IT departments, and they have already put quite a few apps out there. But it seems to me their usage is still not that high. People just don't use them much. I'm a strong believer that you need to make these things passive ideally, not active – like opening an app or with NFC holding a device next to a smartphone or the other way around. These are active processes whereas I think the opportunity is to create some kind of passive system, for example when it comes to injection logging.

Another aspect to consider is that device development in our world typically takes around three to five years and this timescale is largely under-appreciated. It looks simple but it takes a while to create and launch a new device! So obviously with the opportunity of connectivity coming we're going to have legacy devices, other devices that are already on the market, devices that are in development and devices whose development has not started yet. So, clearly it's a bit tiered. For delivery systems that are on the market or quite a long way into development you might want to consider add-ons to those devices. Whereas of course if you are starting from scratch or you leverage an existing device platform early, here is the opportunity to integrate connectivity fully at an early stage, and not to make it an afterthought.

> "Down the road the question might be, can you operate in the drug delivery device space without having a take on connectivity, without having a connected aspect to your offering?"

It's an interesting question, where the pharma industry stands on this. I don't have the answer. Is the industry now thinking when a new project starts, how do we actually integrate the connectivity? Or is it more a case of thinking well, we'll deal with connectivity when the time comes because we don't quite know exactly what it means and where the value is.

It's still very much a work in progress but it's an interesting space where we're hearing a lot of new names – companies like Qualcomm (see Page 27) have co-operations with pharma companies now, for example. We're also seeing a lot of the established drug delivery device players starting to adopt connected technologies seriously and to start going out and offering solutions to the industry.

Down the road the question might be, can you operate in the drug delivery device space without having a take on connectivity, without having a connected aspect to your offering? It's happening. There's a lot of excitement about the broad opportunity connectivity offers, to see how it is going to take off, who will be the main players and what will really drive it.

ABOUT...

Mathias Romacker is Senior Director, Device Strategy at Pfizer Headquarters in New York City. He joined Pfizer in March 2015. In this commercial role he focuses on the front end of device technology. He works with multiple functions and sites across the organization to develop a device strategy for Pfizer pipeline and inline products.

Previously Mathias worked over nine years in the device area for Amgen (Thousand Oaks, CA, US). Before joining Amgen he held multiple sales and marketing positions with Becton Dickinson and Gerresheimer in Germany, South Africa and New Jersey, US.

Mathias holds a Masters equivalent degree in Economics from the University of Freiburg, Germany.

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BIOCORP
BEYOND TREATMENT

THE MULTIPLE VALUES OF INTEGRATED SOLUTIONS

In this article, Arnaud Guillet, Business Development Associate, and Eric Dessertenne, Head of Commercial Operations & Business Development, both of Biocorp outline the potential value of the data that can be collected from integrated devices, not only for pharma companies but also for patients and payers.

Switching to connected devices is a much debated topic but what is the real value behind these new solutions?

The shift from product-centered and cost-based medicine to patient-centric and value-based medicine is already in motion. In this new context, Biocorp does not perceive devices as instrumental to the treatment, but as part of the treatment. Thus, a connecting device does not mean adding new functionalities, it means providing integrated treatment solutions, which incorporate:

- A drug delivery system, to meet the primary function of such devices
- A treatment management tool, to embrace this new patient centric era
- Automatic generation of treatment data, to demonstrate treatment efficacy and prove value.

These new treatment solutions must deliver drugs in the most convenient and user-friendly way, support patients in monitoring and managing their treatments (including supporting their relationships with healthcare providers (HCPs) and relatives), and generate reliable treatment data to demonstrate their efficacy, for example, to payers.

When it comes to connected health solutions, there are two key questions to be addressed. Firstly, who should pay? Patients, pharma or payers?

It goes without saying that moving to connected devices generates an extra upfront cost that needs to be supported most of the time by pharma companies. This extra cost can be allocated to the marketing budget and be part of a financial effort to monetise a key product, even though the impact of this shift will go way beyond.

> "Pharma companies are neither data-hosting centres nor data encryption specialists, but they need access to compliant, secure, reliable health data to enhance their operational and strategic capacities. Providing them such access is one challenge that Biocorp is ready to meet."

This extra cost will eventually impact on pricing, which can imply a higher cost for patients. However, if these solutions bring actual added value to the patients in terms of comfort and treatment management, their willingness to pay will go up.

Finally, payers are most likely to be involved if these solutions are proved to be medico-economically efficient. Higher reimbursement by public payers or inclusion in private insurance coverage plans are to be expected. In this context, data generated by connected devices will have a key role to play.

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The second key question to be addressed is, who owns the data generated by connected devices?

This question has provoked a lot of debate among both the healthcare and the big data communities. However, the simple answer to this is that patients own their data.

"Biocorp has built software capacities to provide its partners with secured, anonymised, consistent and reliable data."

Thus, the first step is to obtain patient consent before considering any possible use of the data. To obtain such consent, healthcare companies must follow strict guidelines, which ensure they are not only compliant with regulation, but also meet patients' expectations and are extremely protective of their privacy. Then, the question of ownership is open and depends on various criteria that are beyond the scope of this article.

However, the real question is not data ownership – it is data access and right to use. Pharma companies are neither data-hosting centres nor data encryption specialists, but they need access to compliant, secure, reliable health data to enhance their operational and strategic capacities. Providing them such access is one challenge that Biocorp is ready to meet.

ADDED VALUE TO HEALTHCARE KEY STAKEHOLDERS

Connected devices can improve patient experience, provide pharma with a decisive competitive advantage and support payers in their effort to contain costs related to treatment.

Patients

Patients have requested evolution of devices – initially only to focus on risks (data safety, privacy issues etc) – but they have gradually integrated the potential benefits. Now it is estimated that 75% will sign up for a mobile app to a help them adhere to their treatment and track their health goals.[1]

Patient engagement emerged as a top priority for healthcare organisations. 72% of US healthcare organisation leaders indicate that consumer and patient considerations, such as patient engagement, satisfaction and quality of care would be the business issue that would most impact on their organisation over the course of the next two years.[2]

Connected solutions bring comfort to the patients in managing their treatment and improve care efficacy, thanks to:

- Personalised health: tailored solutions to adapt to each patient
- Simplified treatment management: automatic collection of data, reminders, easy stock management (info on stock of consumables), solutions adapted to their habits (mobility, speed, instantaneity) and tools (tablets, smartphones, applications)
- Treatment accuracy and safety: facilitate reporting, eliminate human errors, prevent patients from missing their shots, avoid double dosing
- Treatment understanding: patients have access to accurate treatment data in real time on their smartphone
- Easy relationship with HCPs and relatives involved in their treatment: options to share reports, simplified and faster communication routes.

"Major big data actors on the market have been developing innovative solutions to process data in the most effective way but they cannot succeed without partnering with healthcare providers, medical research institutes, pharmaceutical companies and device makers."

Payers

Payers can achieve cost savings thanks to patients' better compliance and healthier behaviours:

- Monitoring tools contribute to improve treatment adherence (reminders, alerts, etc). An Oxford study published in the American Heart Association journal *Circulation* in January 2016[8] demonstrates that text message reminders can help reduce blood pressure by significantly improving treatment adherence.
- Direct cost of non-adherence in the US is estimated at US$100-289 billion (£69-200 billion) annually by the Center for Disease Control.[3] Non-adherence to cardio-protective medications increased risk of cardiovascular hospitalisations (from 10% to 40%) and mortality (from 50% to 80%). Improved self-management of chronic diseases results in an approximate cost-to-savings ratio of 1:10.
- Connected solutions make patients responsible for their treatment, creating value-conscious and empowered healthcare consumers. This shift to "behavioural economics" has already been embraced by some payers.

As an illustration of this new trend, South African insurer Discovery has implemented the Vitality programme. This initiative uses financial incentives to encourage members to make healthy lifestyle choices, such as awarding points for physical exercise, discounts on healthy foods and points-based rewards ranging from reduced insurance premiums to travel options and shopping discounts.

As a result of these benefits, gym usage among Vitality members increased by 22% over a five-year period, and the proportion of healthy food being purchased increased by 3% in the first year. The use of benefit programmes to engage members in healthy behaviour change has also led to significantly reduced costs. For chronic conditions, risk-adjusted hospital costs are as much as 30% lower for engaged Vitality members. A fitness study showed that hospital admission rates are 10% lower and length of stay in hospital is 25% lower for highly-engaged Vitality members.

Pharma

Connected solutions creates substantial value for pharma at various levels:

- Increase pharma revenues by boosting medication adherence. A 2012 Capgemini Consulting report[6] showed that the global pharmaceutical industry loses an estimated $564 billion annually due to medication non-adherence and

even a modest 10%-point increase in adherence could lead to a significant rise in pharmaceutical revenues
- Enhance patient engagement and experience
- Engage with HCPs: 85% of US doctors use smartphones and medical apps. 88% would like their patients to monitor their health at home, particularly their weight, blood sugar, and vital signs
- Provide competitive advantage: in a highly competitive market, the device is a key way to differentiate. Connected devices offer substantial benefits over regular devices
- Improve relationship with payers by offering value-based medicine, real-life evidence.

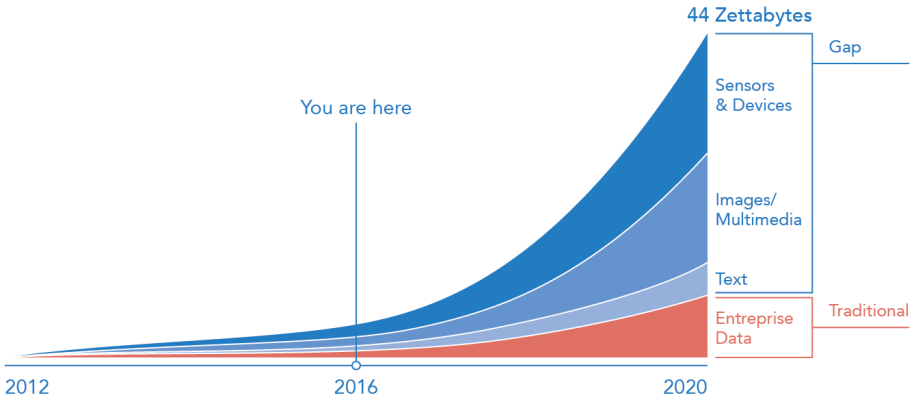

Figure 1: A wealth of data.

THE GOLD MINE BEHIND CONNECTED DEVICES: DATA

Biocorp's vision of connected solutions goes beyond the device itself and its various benefits for patients, payers and pharma. For Biocorp, connected devices means above all else – data. These brand new integrated solutions will generate a vast amount of health data on patient adherence, behaviours with treatment and satisfaction (Figure 1).

Making these data available, intelligible and usable for pharma partners is one key Biocorp objective. Over the past few years, beyond reinforcing Hardware R&D efforts, Biocorp has built software capacities to provide its partners with secured, anonymised, consistent and reliable data. This will fuel pharma business intelligence and bring multiple benefits.

Before describing Biocorp data capacities, let's look at what pharma can do with data.

THE BENEFITS OF QUALITY DATA

Real-World Proof of Value

A new era of healthcare is arising where monetary payments are based on *in-situ*, real-world evidence. It's a small step from direct impact to indirect impacts, such as population-based reductions of comorbidities. Ability to provide such evidence will become a key asset in the relationship with public and private payers.

Another major issue facing pharma is getting pharmacy benefit management companies and insurers to include their products in formularies. Some formularies are being decided on outright cost alone, cutting out competing products. Real-life data can prove that your drug conferred a health advantage and long-term cost savings from a population standpoint over a cheaper competing product. Assessing treatments to enhance health-economic efficiency, data analytics are a key enabler for evidence-based medicine.

AstraZeneca recently implemented a relationship with the Anthem, Inc (Indianapolis, IN, US) data and analytics group. They plan to conduct real-world studies to determine best treatments, including some for chronic diseases, as well as to guide R&D investment decisions. AstraZeneca is working with payers to ensure it has the evidence to obtain coverage for its drugs.

Improves Safety Management

Safety monitoring is moving beyond traditional approaches to sophisticated methods that identify possible safety signals arising from rare adverse events. Furthermore, signals could be automatically detected thanks to connected solutions. This approach provides data on the reach and reputation of different medicines. Bayesian analytical methods, which can identify adverse events from incoming data, could highlight rare or ambiguous safety signals with greater accuracy and speed.

In the context of pharmacovigilance, an automatic collection of data could trigger the alarm instantly whenever an issue arises and allow an early response to physician and patient sentiments, which could prevent regulatory and public-relations backlashes.

Improves Clinical Trials

Data collected can help pharma improve the criteria for including patients in a trial. They could target specific populations, thereby enabling trials that are smaller, shorter, less expensive and more powerful.

Insights gathered in real time can allow rapid responses such as dynamic sample-size estimation (or re-estimation) and other protocol changes. Efficiency gains are achieved by enabling smaller trials for equivalent power or shortening the time necessary to expand a trial.

Real time means quick identification of safety or operational signals requiring action to avoid significant and potentially costly issues such as adverse events and unnecessary delays.

Increased use of electronic data capture could help in recording patient information in the provider's electronic medical records. Using electronic medical records as the primary source for clinical-trial data rather than having a separate system could accelerate trials and reduce the likelihood of data errors caused by manual or duplicate entry.

> "A new era of healthcare is arising where monetary payments are based on in-situ, real-world evidence."

Optimise R&D Investments

Data collected could lead to computational studies and advice on treatable populations, trials design, subject selection (e.g. best-responding patient groups), delivery method (e.g. oral *versus* injectable). It will provide key decision makers with valuable information to define R&D investments better, including drug development.

Early Identification & Better Targeting of At-Risk Subjects

Connecting data from health, genetic, ancestral and other databases, which support preventative lifestyle changes and treatments, and contain information on population-wide healthcare costs through integrated devices, can permit early identification of at-risk subjects. It will automatically improve subject targeting.

Data can help in designing more effective risk management programmes by segmenting patients and stratifying risks. Data analytics make it possible to assess deviations from protocols by region and individual provider. Drug effectiveness can then be improved by targeting programmes and actions at patients who deviate furthest from protocols or who are more likely to change behaviour.

Data gathered in real-life conditions will help identify issues and appropriate actions to be taken in complex cases, including correct tests and properly selected, dosed and timed treatments. Better treatment selection and regimen will lead to better patient compliance

PARTNERSHIPS WITH PROVIDERS

Major big data actors on the market (such as IBM, OptumHealth, Oracle, Verisk Analytics and McKesson) have been developing innovative solutions to process data in the most effective way (IBM Watson Health solutions and Oracle Enterprise Healthcare Analytics, to provide just one example) but they cannot succeed without partnering with healthcare providers, medical research institutes, pharmaceutical companies and device makers.

In this context, Biocorp will help pharma to be a part of big data projects and capture some of this booming market value. The global healthcare data market is expected to reach $18.7 billion by 2020 from $5.8 billion in 2015, at a CAGR of 26.5% during the forecast period.[10]

IBM Watson Health wants to help drug and device companies make that shift from being a product maker to evolving into a company that offers its customers solutions. In line with that thinking, in 2016, IBM Watson Health and Medtronic announced a partnership aimed at improving care in diabetes. "They collect a lot of data through blood glucose monitors and insulin pumps," said Kathy McGroddy-Goetz, Watson Health's Vice-President of Partnerships and Solutions, "but they didn't have the ability to generate cognitive insights that could transform easily into services and solutions." With Watson's help, the two companies are set to release an app by the end of 2016 that could feature a text-message service that tells the patient that a low blood sugar or hypoglycaemic event is likely to occur in the next hour.

Besides device makers, the company has also partnered with Novo Nordisk. This partnership is also centered around how to help patients manage chronic disease better. "In the past, a pharma company wouldn't necessarily know who their patients are. Now they're trying much more to engage patients and find ways to understand more about them. That's become really valuable to them," added McGroddy-Goetz.

Novo Nordisk is working with Watson Health to develop a type of virtual coach to help inform decisions about insulin dosage. Watson will also analyse health data from patients with diabetes to help them ultimately better manage the diseases. That data could end up informing a tool, like a mobile app, that could help take some of the guesswork out of diet, exercise and insulin.

BIOCORP CONNECTED DEVICES

Biocorp offers two options to integrate connected solutions into your portfolio:

- Launch a development programme to replace your device with a brand new connected device
- Equip your existing devices with an add-on, a smart sensor that turns regular devices into connected and communicating devices.

New development Program Approach, Illustrated by DataPen

Compatible with prefilled cartridges, the Datapen is a smart and innovative subcutaneous drug delivery system adapted to chronic disease treatments.

The electromechanical injection simplifies the product delivery and provides maximal user comfort. This system guarantees a high degree of accuracy for the injection and a high repeatability of injected doses. Data are automatically transferred to a treatment mobile app via Bluetooth. Biocorp complies with the highest standards of health data encryption to guarantee maximal data security.

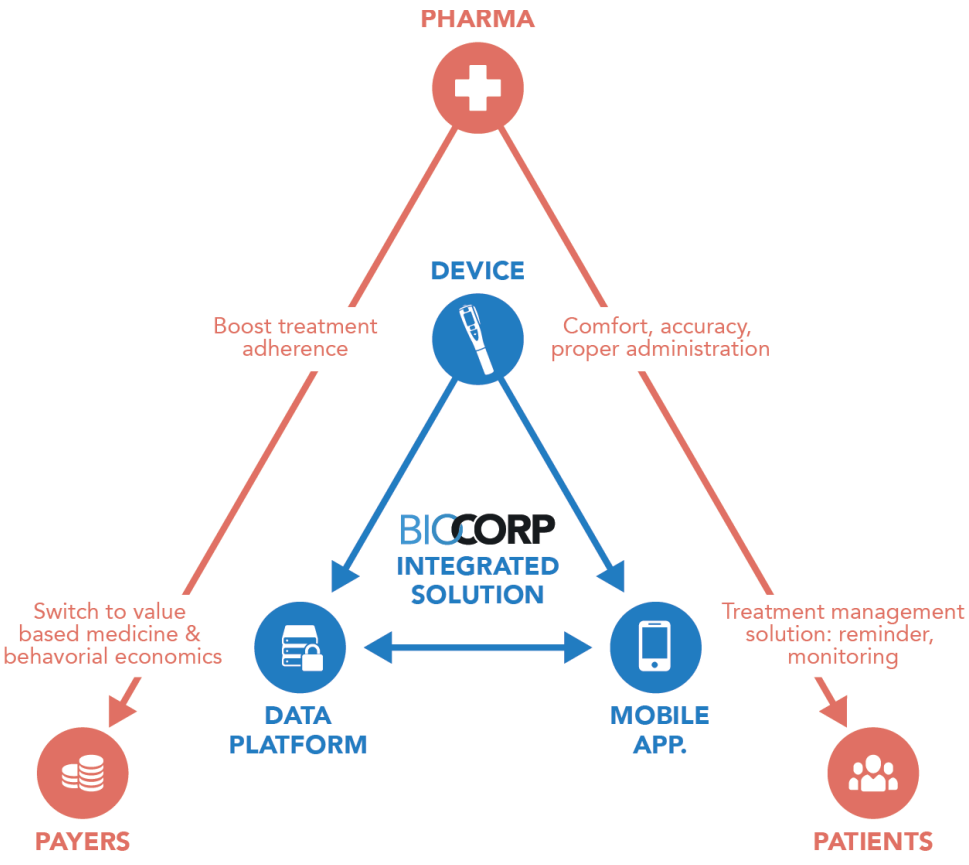

Figure 2: The Biocorp integrated solution.

Add-On Approach, Illustrated by EasyLog and Inspair

Integrating some electronic components into disposable medical devices proved to be cost inefficient due to the cost of technology. However, add-ons answer that unsolved business case. Through add-ons, Biocorp's ambition is to connect existing medical devices by adding smart sensors to regular drug delivery devices.

This new approach provides a shortcut towards integrated drug delivery systems because it fits in the lifecycle management strategy with no impact on industrial process. It also limits the investment needed to convert regular injection devices into connected devices.

In the field of injection devices, EasyLog is a smart sensor that converts all injection pens, reusable as well as disposable, into connected devices.

EasyLog automatically collects injection data (dose injected, time and date). The measure is 100% accurate and can differentiate doses selected and doses actually delivered. Data are transferred via Bluetooth to a treatment mobile app. Successful ergonomics tests in users have proven that the system is easy to understand and user friendly.

In the field of respiratory devices, Inspair is a smart sensor that turns pMDIs into connected devices, records inhalations and guarantees proper inhalation technique compliance.

Inspair features miniaturised sensors and electronic card, and fits on most MDI mouthpieces thanks to specific adaptors.

The system monitors inhalations and guarantees proper inhalation technique compliance. It automatically records daily inhalations, checks the right preparation of the canister (shake before usage), assesses the co-ordination of actuation with inhalation ("hand-mouth" co-ordination) and provides useful guidance throughout the inhalation steps.

BIOCORP MOBILE APPLICATIONS

All Biocorp smart drug delivery systems are connected to medication adherence mobile apps providing patients with real-time information on their treatment, reminders and alerts as well as a treatment calendar, graphics and analytics (Table 1).

Thanks to its software capacities, Biocorp can develop mobile applications specific to a designated pathology (such as diabetes, growth hormone deficiency, asthma or cardiovascular issues) and adapt their content to specific treatment management issues (Figures 3 and 4).

BIOCORP Software Factory	BIOCORP Agile Method
• Automation: no human error for testing/deploying, continuous QC with automated tests and deployment • Standards: internal best practices compliant with the highest market standards • Control of lead times: calibrate to meet deadlines and project requirements • Constant quality check before release for better software quality	• Iteration: build and release new software using iterative processes • Build as you go: easy integration of new product requirements • Quick time to market: quick deployment of new functionalities
Efficiency: quick delivery of product functionalities with the highest standard of quality and control	

Table 1: Biocorp software development approach for apps providing patients with real-time information, reminders, alerts, calendar, graphics and analytics.

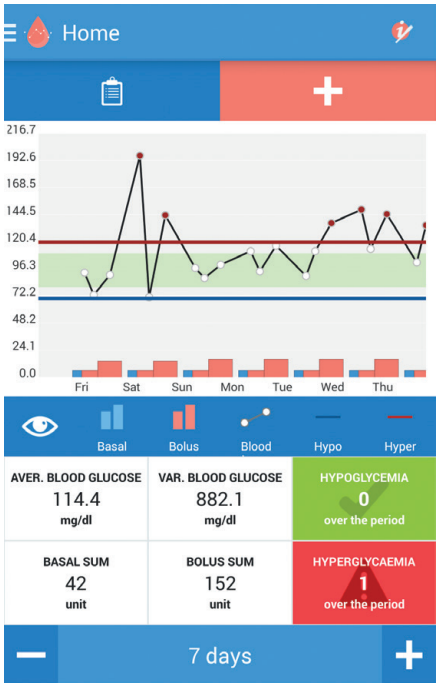

Figure 3: Appli home 7 days

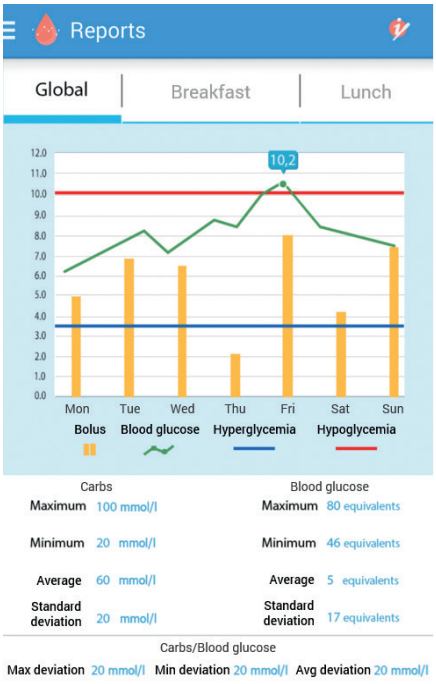

Figure 4: Appli reports

BIOCORP DATA QUALITY

Having data that are consistent, reliable, and well linked is one of the biggest challenges facing pharmaceutical R&D. (See boxed text for details of the data processing platform.)

- Secure data: secure connection process with individual code
- Security: TIER III Data Center, encryption of all flows, doubling of security equipment
- Compliant data: anonymised data, upgradeable privacy settings, formal patient consent required
- Reliable data: tested technologies, automatic collection (no human error), no selection biases
- Specific data: controlled cohorts, related to a specific pathology, related to specific device
- Comprehensive data: all data automatically captured and integrated, no information gaps.

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BIOCORP DATA PROCESSING PLATFORM

Data acquisition

- Data is collected from a unique user account
- Secure connection process is provided with strong factor authentication.

Storage

- Hosting: compatible with government-certified web hosts
- Security: TIER III DataCenter, encryption of all flows, doubling of security equipment
- High availability: fail-over, supervision 24/7, multi-site
- Performance: network connection fibre, high performance storage, servers clusters and application cluster.

Processing

- Designed for Big Data: several billions of transactions are possible
- Big Data management: high level of data quality and accessibility for BI
- Cryptographic anonymisation process, providing the highest level of protection for patients.

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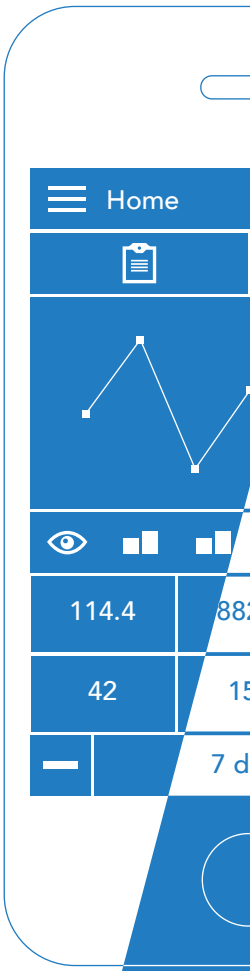
INITIATE A **NEW DEVELOPMENT PROGRAM**

Electromechnical injection: only a slight push, whatever the quantity of product injected

Visual signal to notify the end of injection

Compatible with regular prefilled cartridges



DATAPEN,
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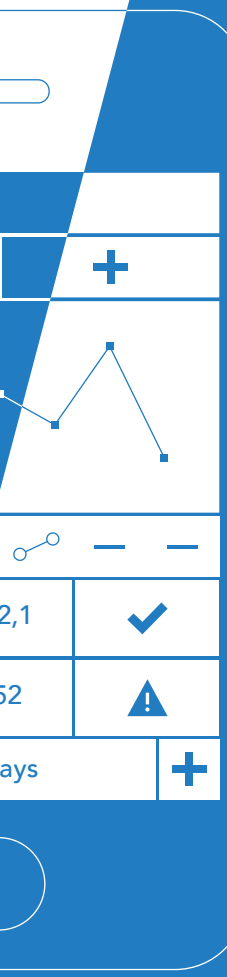

Automatic collection of doses with time and date

Compatible with all injection pens, reusable as well as disposable

ATTACH AN ADD-ON **TO YOUR EXISTING DEVICE**

Compact design, miniaturized sensors and electronic card

Modular concept fits with the majority of MDIs available on the market

INSPAIR,
A SOLUTION TO MONITOR MDI USE

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THE INDUSTRIAL REVOLUTION OF MEDICAL DEVICES

With a focus on the UK, Thomas Olesen, Commercial Director, Europe, Qualcomm Life, provides an overview of the digitalisation of healthcare, and the current status, hurdles and potential benefits of connected devices, from the perspective of a digital technology company. He provides examples of telemedicine and mHealth projects already underway, and explains how Qualcomm Life is building the digital infrastructure required for organisations including national healthcare systems to provide connected healthcare both for patient monitoring and for drug delivery too.

The UK population is 64.1 million and roughly 15 million of those people suffer from a chronic disease. It is also estimated that approximately 42% of patients in the UK have at least one chronic disease – meaning they could be suffering from more. Annually, the UK economy suffers a cost of £7.2 billion from coronary heart disease, for example. Productivity issues account for 47% of this cost while 27% relates to direct healthcare costs.[1] It is thought that if hospitals learned to use hospital beds more efficiently by reducing the length of stay or readmissions, the UK NHS could save at least £1 billion a year.[2]

> "Balance Rewards members can sync selected mHealth devices directly to their Balance Rewards account, earning points which translate to dollars, and enabling pharmacists to access biometrics and health status information electronically."

In light of these figures, there is a call for UK healthcare services to be digitally transformed. Aside from e-records and free Wi-Fi, this mandate extends to telehealthcare. Telehealth, the remote exchange of clinical data between a patient and their clinician, is a fast growing and dynamic market, which holds a lot of potential for the UK.

The UK digital health sector is currently worth £1.3 billion, with the UK being the frontrunner globally in the use of primary care electronic health records. However, acute hospitals have lagged behind and have been the focus of some recent government initiatives.

There have been a number of initiatives designed to improve the evidence base and adoption of telehealth, the most well-known being the Whole System Demonstrator (WSD) study. However, the evidence on cost-effectiveness produced from the WSD was viewed as disappointing, and the adoption is now subject to number of barriers including clinical buy-in.

Markets such as the US are moving ahead with implementation of larger scale telehealth implementation, whereas the UK continues to be in pilot mode. This disadvantages local industry as the UK currently lacks the scale and infrastructure to drive growth.

As the market evolves, the UK becomes at risk over the short- to medium-term. But this could be about to change…

A MARKET EVOLVES

Fixed line and hardware-dependent systems as well as the current focus of large UK providers, are becoming increasingly mobile-based. Consumers are looking to improve their fitness and wellbeing through wearable technology, and patients with chronic diseases are using connected medical devices to monitor their condition continuously and share data seamlessly and securely with their care givers.

Seamless care from hospital to home – and all points in between – is becoming a necessity from many patients suffering from chronic conditions as they look for better quality of life and less trips to the hospital. This is supported by new

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technologies such as smart sensors and apps, generating more intelligent data which in turn allows for better analytics and cost-effective intervention by physicians, which ultimately lowers hospital admissions, while at the same time quality of care is improved and both patients and care givers experience higher satisfaction.

Qualcomm Life, a subsidiary of chipmaker Qualcomm, is helping UK hospitals, and other organisations, remove inefficiencies and improve patient care, through reducing A&E visits, hospital admissions and mortality rates.

Qualcomm Life has established one of the world's largest open connected health ecosystems to deliver intelligent care everywhere, powering connected medical devices, sensors and a secure medical-grade infrastructure across the care continuum. This has been achieved by combining its wireless expertise and ecosystem of connected medical devices outside of the hospital with the expertise of its subsidiary, Capsule (Andover, MA, US), in connectivity and integration inside the hospital. Capsule was acquired by Qualcomm Life in 2015.

Qualcomm Life is today solving several of the challenges historically hindering the ability of connected health to scale. Data is captured anywhere on the care pathway and integrated with any relevant EMR or Health IT system required by the NHS – seamlessly and securely.

Studies have proven that connected health has a positive impact on those suffering from diabetes and heart failure. For example, patients with chronic heart failure using telehealth resulted in a 47.5% lower hospitalisation rate and greater patient satisfaction care compared to those receiving usual care.[3]

CASE IN POINT

Qualcomm Life has been working with leading medical device, provider and pharmaceutical companies across the globe to bring the benefits of connected health as well.

Entra Health Systems (San Diego, CA, US) is developing one of the first US FDA-listed and CE-certified connected blood glucose meters, MyGlucoHealth, working in combination with a near real-time online data collection network to upload and manage blood glucose readings securely, eliminating the need to maintain personal logbooks and enabling patients and providers manage the chronic disease better.

Entra's solution forms an integrated telehealth platform supporting patients and healthcare professionals in the control and treatment of diabetes. Using automated tools, Entra can set up reminders to encourage patients to test more frequently, and notify family, caregivers and clinicians when testing results fluctuate, ultimately giving patients more direct control over their care and providing clear lines of communication with clinicians and caregivers.

Another example of bringing connectivity to healthcare, and specifically potentially to drug delivery too, is Qualcomm Life's work with Walgreens, the largest US retail pharmacy chain, which recently acquired Alliance Boots (parent company of the British retail pharmacy, Boots).

In January 2015, the two companies announced their collaboration to power device connectivity with Walgreens' mobile and web applications and its Balance Rewards for healthy choices® programme. This project is designed to bring the benefits of robust medical device connectivity and care co-ordination capabilities, as well as enable remote patient monitoring, transition care support and chronic care management through a secure and seamless transmission of biometric data from patients' connected medical devices.

Walgreens Balance Rewards members earn points for participating in various health-related programmes and tracking progress towards a goal. With medical device connectivity powered by Qualcomm Life, Balance Rewards members can sync selected mHealth devices directly to their Balance Rewards account, earning points which translate to dollars, and enabling pharmacists to access biometrics and health status information electronically.

Compatible Walgreens devices include a wrist-worn blood pressure cuff, a traditional blood pressure cuff and a blood glucose meter.

Whether patients are transitioning from hospital to the home or managing a chronic condition such as heart disease or diabetes, Walgreens' solution can help patients achieve improved health through regular biometric communication with their providers, as well as being rewarded for participating in becoming more informed and engaged in their healthcare.

IMPLEMENTATION IN THE UK

As previously mentioned, telehealthcare in the UK has not yet had the uptake it has experienced other countries such as US. However, there is one NHS hospital that Qualcomm Life is working with that has embraced digital health as part of its offering.

Through a collaboration with Telematic and Biomedical Services (TBS GB, Southend-on-Sea, UK) and Orla Healthcare (Harlow, UK), Qualcomm Life provided its 2net Platform and Hub (see Figure 1) and saw compelling results with improved health outcomes and patient satisfaction.

> "Qualcomm Life is working to accelerate and enable connected health by providing pharmaceutical companies, medical device manufacturers, and healthcare providers with our scalable, connectivity infrastructure across the care continuum."

TBS GB, a subsidiary of TBS Group, specialises in the management of healthcare technology, provides telehealth technology and logistics support to Orla Healthcare, a private provider of home health services in the UK. Focused on streamlining transitions of care, the 400 patient pilot saved 2,000 hospital bed-stays, had zero unavoidable re-admissions and saw a 99% patient satisfaction rating.[4]

Patients in the pilot were admitted to the Princess Alexandra NHS Hospital (Harlow, UK) and treatment was provided at the patient's home with a telemedicine kit comprised of a blood pressure monitor, a pulse oximeter, a telecare device (GPS location system and alarm button) and a 2net Hub to capture and transmit biometric data from the patient's home to the 24/7 clinical support team. The patient data was visualised using Medixine Clinic, Qualcomm's cloud-based software program that enables biometric data visualisation, triage management, and at-risk patient population management.

Following this success, TBS GB and Orla Healthcare extended the pilot to include early discharge of ward patients, transitioning in-patients from wards and treating them at home.

This service is unique within the NHS and is made possible by Orla's consultant-led team and TBS GB's technology solutions enabled by Qualcomm Life's 2net.

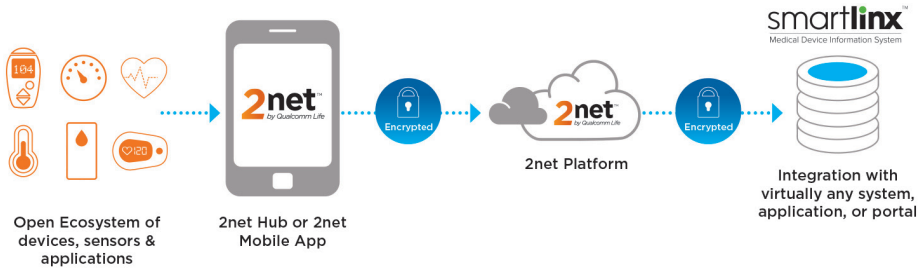

Figure 1: Schematic of Qualcomm's 2Net platform and hub for connecting healthcare.

MOVING AHEAD

As the industry moves ahead with the uptake of digital health, there are several hurdles that need to be addressed, including data interoperability, security and privacy. While the technologies are in place to allow clinicians, GPs and patients access to data anytime, anywhere, the healthcare industry itself just isn't ready. Each institution uses different systems – including payment systems and regulatory frameworks.

Qualcomm Life is working to accelerate and enable connected health by providing pharmaceutical companies, medical device manufacturers, and healthcare providers with our scalable, connectivity infrastructure across the care continuum.

We can also help national health systems, such as the NHS, address some of the challenges of scaling-up telehealth by effectively capturing data across the continuum of care in the UK, compliant with all UK rules for data privacy, and compliant with the medical directive.

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LONDON CONFERENCE

Thomas Olesen will be speaking on this topic at forthcoming the Management Forum "Connectivity in Medical Technology Conference" in London, UK on June 23-24, 2016. He invites readers to join him in London to help find a solution for moving forward with digital health and helping the NHS and other institutions address the challenges that come with embracing digital health initiatives.

CONNECTED INHALERS MAKING A REAL IMPACT ON RESPIRATORY OUTCOMES

Adherium was founded in 2001 (as Nexus6) to develop solutions to help manage asthma better. Now, in 2016, Adherium's Smartinhaler™ platform represents one of the world's largest ranges of sophisticated adherence devices for prescription asthma and COPD medicines, with a robust peer-reviewed evidence base. In this article, Garth Sutherland, CEO of Adherium, describes the problem of chronic non-adherence in asthma and COPD, how Adherium's Smartinhaler™ solutions have proved themselves in the clinic, and why now is the time to move to real-world scale.

The costs of health care and the burden of disease continue to rise, seemingly without limit, putting both healthcare delivery and healthcare payment under extreme pressure.

Driven by escalating need, the opportunities for innovation are escalating in tandem. Digital health is hitting its stride, with record-breaking market values, record-breaking levels of investment and matching levels of hype. A 2015 report[1] valued the global digital health market at US$55 billion in 2014, while an April 2016[2] report highlighted a record $1.8 billion funding into digital health in Q1 2016 alone. This covers many different categories, from financial (insurance) to consumer (wellness, like Fitbit) to analytical (big data) to clinical (from electronic records to decision support).

A source of much frustration in health care has been the inability to maximise the solutions already available, with non-adherence to medications identified as a massive problem. In the US, the overall cost of suboptimal medicine use including non-adherence, under-treatment, administration errors and under-diagnosis, is estimated to be approximately $213 billion annually, or 8% of annual healthcare expenditure (Figure 1).[3]

Chronic diseases are considered especially problematic for adherence, but also promising targets for improvement given the right interventions, hence many digital and mobile health companies are targeting chronic diseases like diabetes, asthma and COPD.

> "Treatment non-adherence is a critical issue in addressing population health from both economic and quality of life perspectives."

THE CONSEQUENCES OF POOR ADHERENCE IN ASTHMA AND COPD

There are two main types of medications used to treat asthma and COPD. The first, commonly-called "relievers" or "rescue" medications, are used to provide near immediate relief from symptoms. The second, referred to as "preventers" or "maintenance" medications, are taken regularly (daily) to control the disease and minimise flare-ups or exacerbations.

Poor medication adherence is common in COPD and asthma, with only approximately 50-55% of US patients taking their medication as prescribed (Figure 2).[4]

The WHO assessed preventer medication adherence could be as low as 28% in developed countries.[5] WHO states that this

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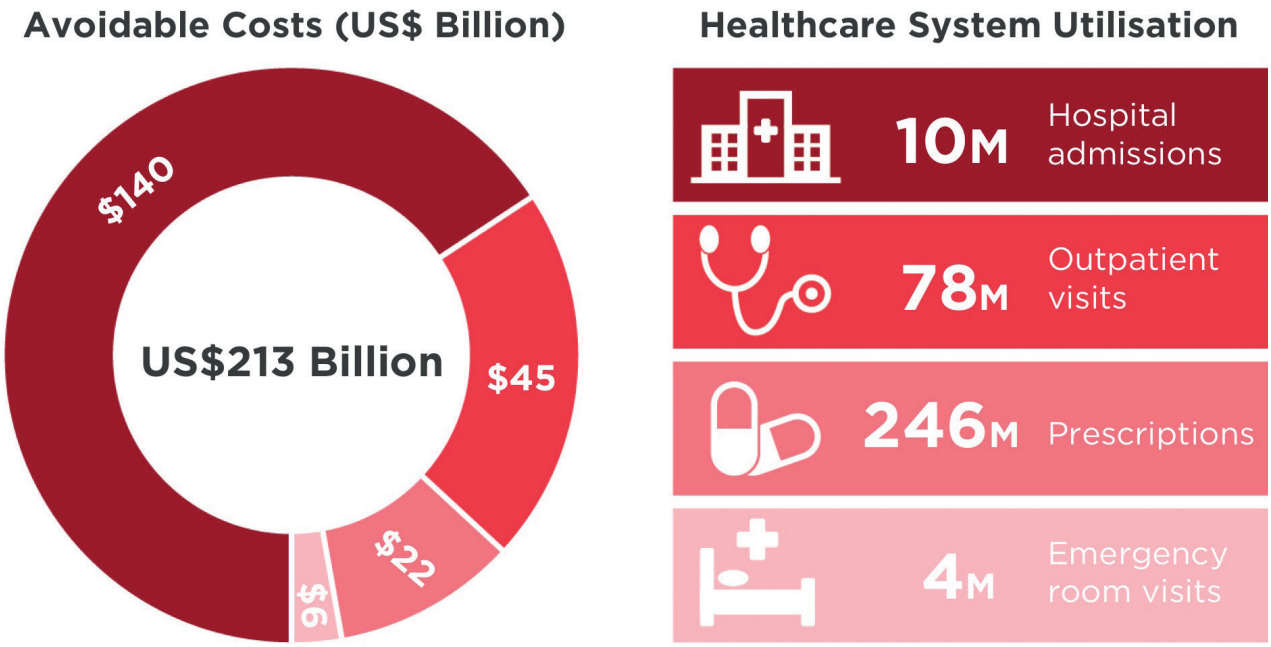


Figure 1: Avoidable costs of suboptimal medicine.[3]

Figure 2: In the US, only 50-55% of asthma and COPD patients take their medication as prescribed.[4]

"results in poor asthma control which has clinical consequences, such as increased hospitalisation and emergency department visits, resulting in unnecessary high costs of health care."

Treatment non-adherence is a critical issue in addressing population health from both economic and quality-of-life perspectives, with patients facing potentially life threatening risks if they are not supported in their medication adherence by the broader health system.

Adherium is a global leader in the design and development of evidence-based digital health solutions that address suboptimal medication use and remote patient management. Adherium's smart health solutions use connected devices, software and data to improve the quality of care – and quality of life – for those with asthma, COPD and other chronic diseases.

"What is new and a cause for hope is the wave of miniaturised, connected and consumerised technology that has washed over all aspects of modern life especially in the last decade."

DIGITAL AND MOBILE HEALTH SOLUTIONS FOR CHRONIC DISEASE

Adherence has long been recognised as a cause of unachieved outcomes, and therefore is an opportunity to address. Over the decades, waves of resources and solutions have been thrown at the problem of chronic non-adherence, to little effect.

What is new and a cause for hope is the wave of miniaturised, connected and consumerised technology that has washed over all aspects of modern life especially in the last decade. This has enabled different solutions for tackling adherence (and other problems) that not only have clinically proven effectiveness but, critically, hold the promise of effective scalability in real-world use. Helping people with asthma or COPD to control their condition better is one of the areas where a critical mass of experience and evidence has been accumulated, and is now tipping from research, development and pilot/small-scale use towards large-scale execution in the real world.

Advanced digital/mobile health interventions comprise multiple parts:

- Sensors and inputs for tracking and measurement, gathering accurate objective data.
- Communication between sensors and devices, software, patients, clinicians and other stakeholders (whether using smartphones, tablets, desktop computers or other).
- Feedback and advice to the patient from their inhaler or smartphone. For adherence, this is the primary intervention channel.
- Feedback and advice to healthcare professionals (HCPs) and other stakeholders. This channel provides for HCP-mediated interventions.

To work, all of this has to be accurate, secure and safe. Furthermore, it must have a low user burden, have good usability and deliver a good overall user experience, for patients and for all other stakeholders involved in delivering or executing such solutions.

Adherium's Smartinhaler™ platform is designed to help patients adhere to their preventer medications and allow clinicians to monitor and manage patients' therapy remotely (including adherence) to improve patient outcomes. The platform comprises a medical device (from the Smartinhaler™ range), specifically designed for each type of inhaler required, and the SmartinhalerLive™ platform, which comprises the wireless communication, mobile and desktop apps, and cloud-based software (Figure 3).

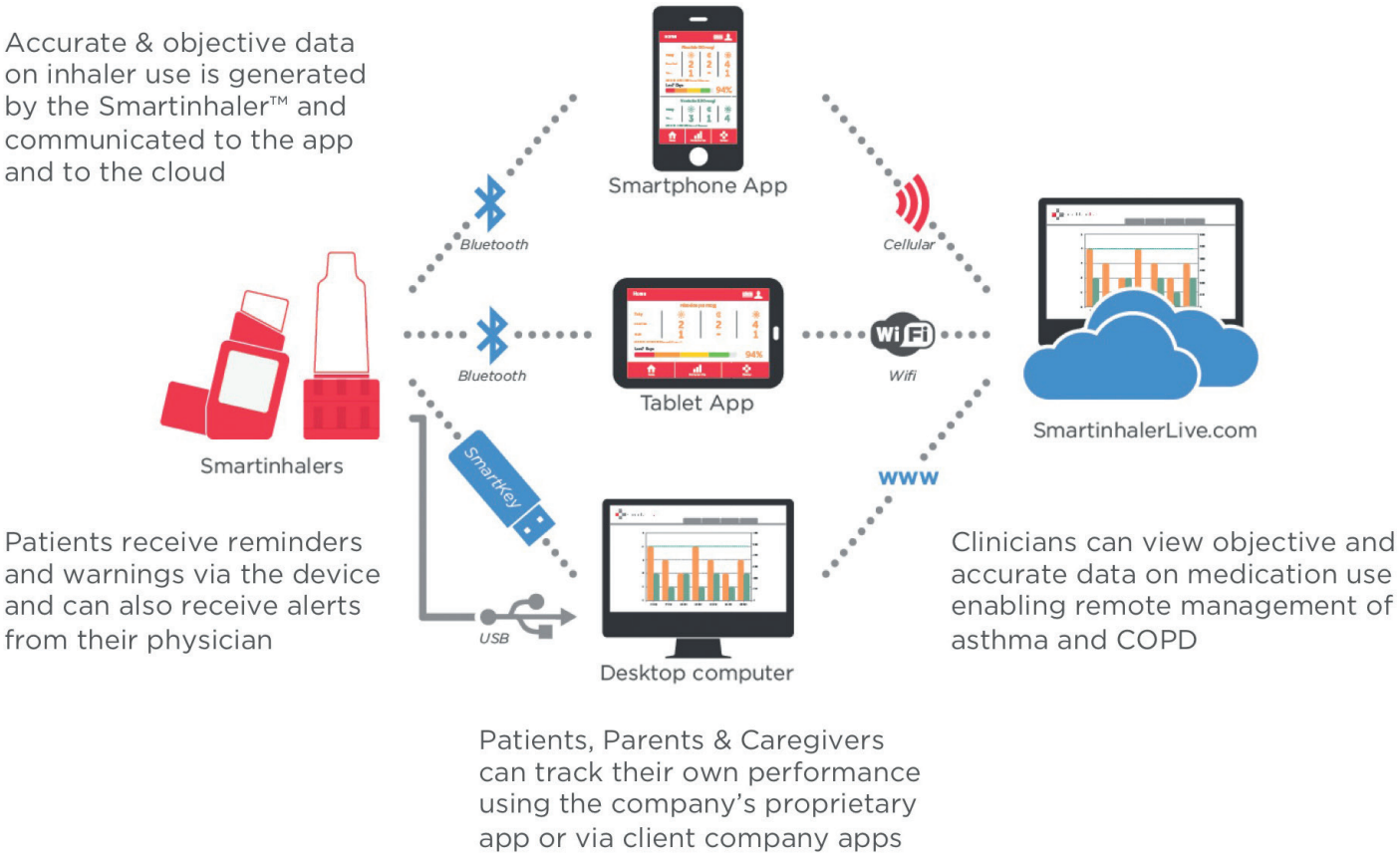


Figure 3: How the Adherium Smartinhaler™ platform operates.

CLINICAL OUTCOMES FROM DIGITAL INTERVENTION

Adherium's Smartinhaler™ platform features one of the world's largest ranges of sophisticated adherence devices for prescription asthma and COPD medicines, with the most robust peer-reviewed evidence base (Figure 4).

A total of 27 clinical studies on Adherium Smartinhaler™ have been published in peer-reviewed journal articles, and over 48 publications reference Smartinhaler™ technology. Right now, more than 60 clinical programmes are running in over 30 countries using Smartinhaler™.

> "Given the accumulating weight of experience and of clinical proof, the critical step in this field is going to market at scale."

Adherium's Smartinhaler™ has been proven to change patient behaviour, increasing the use of preventive inhaled medications, over and above changes generated through training from physicians and behavioural psychology techniques. Use of the Adherium system has been clinically proven to improve adherence by up to 180% and has been shown to reduce use of rescue medications and to reduce occurrence of severe exacerbations.

For example:

- Interim data from a 12-month study in children[6] has demonstrated that use of the Smartinhaler™ substantially increases adherence and significantly reduces the number of oral steroid courses required over the period. The interim data shows at 12 months a 144% increase in adherence in the Smartinhaler™ group *versus* control arm, a 37% reduction in the number of oral steroid courses required in the 12 months from 2.7 to 1.7 and increased lung function as measured by FEV1 (mean forced expiratory volume in 1 second % predicted), 87% in the control arm *versus* 100% with Smartinhaler™.
- A six-month study in 220 school-aged children who presented to the emergency department with an asthma exacerbation[7] showed that adherence to preventer medication increased by 180% in the group receiving reminders from Smartinhaler™. Use of rescue/reliever medication was reduced by 45%. Parent-reported exacerbations occurred in 7% of children in the Smartinhaler™ group at the two-month mark compared to 26% in the control group.
- Another six-month study with Smartinhaler™, in primary care with 143 patients aged 14 to 65[8] demonstrated an increase in adherence to preventer medication by 59% and a reduction in severe exacerbations by 61% (11% of patients in the Smartinhaler™ group *versus* 28% in the control group) (Figure 5).

MAKING THE TRANSITION FROM STUDIES AND PROGRAMMES TO REAL-WORLD SCALE-UP

Given the accumulating weight of experience and of clinical proof, the critical step in this field is going to market at scale. In July 2015, AstraZeneca and Adherium entered into a ten-year commercial product development and supply agreement. Adherium will supply innovative new devices and sensors that AstraZeneca will incorporate within

Figure 4: The Adherium product range.

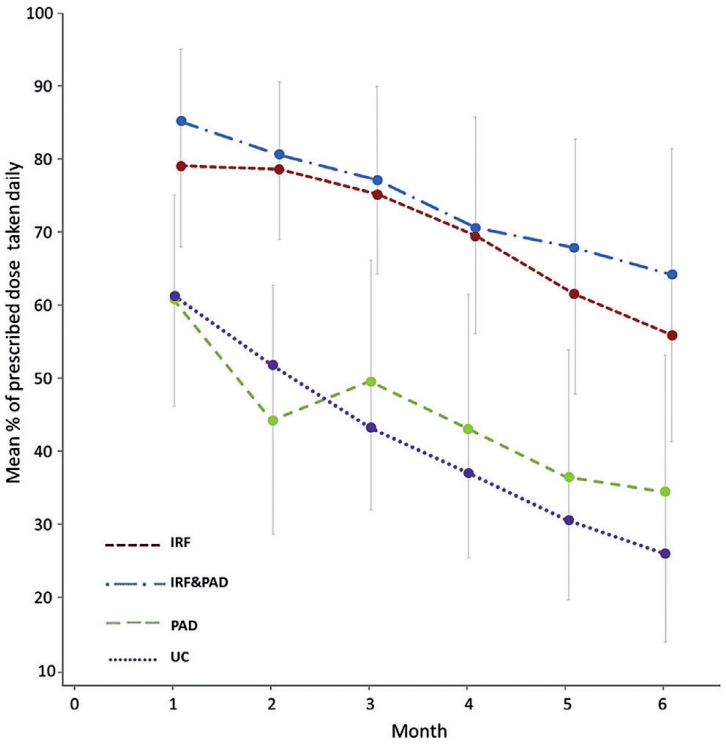
global patient support programmes for patients with COPD and asthma.

AstraZeneca had already successfully used Adherium technology in clinical evaluations and clinical trials, and piloted its use in programmes to support patients in the management of their conditions. This partnership validates the commercial importance of the Adherium technology in the global digital health market.

Bringing a workable and meaningful solution to the market is critical. With Adherium's "track and remind" solution, which has been robustly demonstrated and proven to have clinical impact, there is a proven intervention that is simple enough to be implemented and scaled. There will be many developments coming down the line, from incremental (miniaturisation, internalisation or integration, battery life etc) to additive (insight and intervention algorithms developed from big data), but there is also a lot to be both gained and learned from implementing the current solution.

As pharma and health technology companies implement and scale their digital health products, services and supporting infrastructure, they will have to adapt to take on new capabilities and organisation structures. While this may be difficult (change always is), they will be better placed to execute subsequent incremental innovations within their adapted organisations and business models.

They will also be best placed to unlock additive innovation, for example by being first to have the high-quality, huge data sets needed to move into big data insights and analytics, and to move to new models with risk and gain sharing, and payment by outcomes. The stakes are raised when moving to scale but so too are the opportunities and rewards.



IRF = inhaler reminders and feedback

PAD = personalised adherence discussions

UC = usual care.

Figure 5: The adherence advantage of Adherium Smartinhaler™ is maintained over time.[8] (Source: Foster et al, "Inhaler reminders improve adherence with controller treatment in primary care patients with asthma". J Allergy Clin Immunol, 2014, Vol 134(6), pp 1260-1268. Copyright © 2014 Elsevier. Reproduced with kind permission.)

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Adherium's Smartinhaler™ is proven to:

- Increase medication adherence by 180%, and reduce rescue medication use by 45% in children with asthma[1].
- Increase medication adherence by 59%, and reduce the risk of severe exacerbations by 61% in adults with asthma[2].

[1] *Chan, Amy HY, et al. "The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial." The Lancet Respiratory Medicine 3.3 (2015): 210-219.*

[2] *Foster, Juliet M., et al. "Inhaler reminders improve adherence with controller treatment in primary care patients with asthma." Journal of Allergy and Clinical Immunology 134.6 (2014): 1260-1268.*

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COMPANY PROFILE: SHL GROUP – CONNECTIVITY SOLUTIONS

SHL GROUP

SHL Group, the world's largest privately-owned designer, developer and manufacturer of advanced drug delivery systems, has been recently venturing into the field of connected devices. To identify and develop the most innovative solutions, we have been scouting for the latest technologies and concepts in the field. This led to the creation of our connectivity programme, Alubena®, focusing on connected devices such as Molly® C auto injector with the Recording Unit (see Figure 1) and their application to value creation for healthcare stakeholders.

Molly® C is a disposable auto injector, based on the well-proven Molly® platform; adding the Recording Unit allows it to connect to the patient's smartphone or other mobile device and transfer information about the injection. The information can be further shared with different stakeholders, including healthcare providers, pharma companies, payers and interested parties via secure cloud. The data collected can be analysed and used to improve patient's quality of life, further the knowledge about the disease and ensure the effectiveness of treatment for the outcome-based healthcare.

Molly® C and Recording Unit are just one example of SHL's work in this area. Another focal point is miniaturised integrated disposable electronics. The idea behind it is to embed the electronics into auto injectors in a way that allows the same operational usage as a non-connected device. The purpose is to make it suitable for patients with cognitive and physical disabilities that prevent them from using the Recording Unit. In such a disposable device, sensors are part of the electronics which detects injector functions, e.g. movement of an activation button. The information is transmitted to a mobile device and later the auto injector is disposed of in an environmentally acceptable way.

In parallel with the Alubena® programme, SHL is also working with various partners, including the recently established joint venture, SHL Connect, to support our connectivity capabilities and work on solutions in the field of smart packaging and training devices/accessories. The programmes complement each other to ensure that SHL can offer the widest range of connected services to our customers. These include:

DRUG DELIVERY DEVICES

Low adherence to medication therapy is a challenge in many aspects. It is not only a contributing factor to unnecessary suffering for both patients and their families, but it also results in large healthcare expenses that can be avoided as well as significant financial loss for the pharmaceutical industry.

A connected drug delivery device enables patient support programmes by providing real usage data. The data can be used to personalise the patient support and experience. The intent is to increase adherence to the prescribed therapy and increase patients' quality of life. Increased adherence will contribute to a healthy

"In parallel with the Alubena® programme, SHL Connect, a joint-venture between SHL Group and ConnectMeSmart GmbH, has been established to support our connectivity capabilities."

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Figure 1: Molly® C and Recording Unit.

outcome which will benefit all parties involved.

SHL's connected drug delivery systems are suitable for various therapy areas. The abovementioned Molly® C and RU concept, for instance, can be customised for specific user needs and different injector platforms.

"Molly® C and Recording Unit are just one example of SHL's work in this area. Another focal point is miniaturised integrated disposable electronics."

TRAINING & INSTRUCTIONS

SHL is developing intuitive training systems that provide a controlled, repeatable method for teaching and learning. The training method is multi-lingual and uses a unique graphical interface for superior user experience. Enhancing the learning process creates user confidence which will improve adherence.

SUPPLY CHAIN

Therapy outcome relies on drug efficacy and safety. To address these factors, SHL is working on environmental recording solutions for pharma applications which help ensure that the product has been continuously handled within specifications. Our environmental recording solutions can be employed throughout the supply chain right up to the last mile to the patient.

Molly® C and Recording Unit were the topic of our recent feature article, "Embracing the Future: Connected Drug Delivery Solutions" which appeared in ONdrugDelivery, May 2016, Issue 67, pp 6-8.

SHL GROUP

www.shl-group.com

Connectivity Solutions

- ✓ Drug Delivery Devices
- ✓ Training and Instruction
- ✓ Supply Chain

IS YOUR WIRELESS CONNECTED DEVICE SECURE?

There are many advantages of using wireless connected devices but the modalities used are open to cybersecurity threats. In this article, Jamie Kendall, Software Engineer at Key Tech uses an example of a wireless system architecture to explain the three common cybersecurity vulnerabilities and highlights the importance of proper implementation early on in the design process to mitigate these risks.

Wireless connected systems are clearly the future of drug delivery. They allow for valuable advances in the complete care of patients, including patient compliance monitoring, improved therapy and real-time delivery diagnostics.

However, it is important to understand the current state of wireless cybersecurity before developing a connected drug delivery device system. Threats to cyber security can pose a serious risk in healthcare. Beyond fictional examples from television shows, security researchers have demonstrated in real life that attackers could remotely interrupt care, such as blocking an insulin pump or tampering with a pacemaker. Hospitals themselves have to seek to prevent attacks. The recent MedStar Health computer network attack brought a large-scale hospital's network operations to a halt.

Before examining the risks to security, we will look at the wireless modalities available.

BLUETOOTH / BLUETOOTH LOW ENERGY

While becoming extremely popular recently, Bluetooth development began in the late 1980's. Bluetooth Low Energy (LE) was first introduced in the Bluetooth specification in 2010 to target smaller and lower power devices, specifically including medical devices. Both Bluetooth and Bluetooth LE have built-in security mechanisms that protect the integrity of transmitted data. Bluetooth protocol security has evolved since its inception, with versions above 2.1 supporting multiple methods for secure encryption key exchange. Bluetooth LE was added in version 4.0 and allows for a Bluetooth connection that is slower but uses less power to operate and has similar key exchange methods as Bluetooth. A PIN is typically a short numeric code that is then converted into an encryption key of a much longer length, usually 128 bits. The most familiar method of key exchange or pairing is the PIN exchange.

> "Security researchers have demonstrated in real life that attackers could remotely interrupt care, such as blocking an insulin pump or tampering with a pacemaker."

However, a simple or even static PIN used in an embedded connected device could be brute force cracked. Even some of the latest key exchange methods cannot prevent an attacker from performing a "man-in-the-middle" attack during the key exchange portion of communication. This means that a potential attacker in proximity to the connected device and its host could pretend to be both devices and stand in the middle of communication, intercepting keys and all traffic.

WI-FI

Wireless networks, or Wi-Fi, have been around since the late 1990s. For security, the first encrypted algorithm used to secure communication was called Wired Equivalent Privacy (WEP). WEP quickly proved that it had massive security issues. While the details of the failure are not important to this discussion, the bottom line is that an attack could reveal the encryption key and decrypt all traffic without any physical manipulation of the wireless system. In addition, most networks only require the encryption key to connect, which would allow complete

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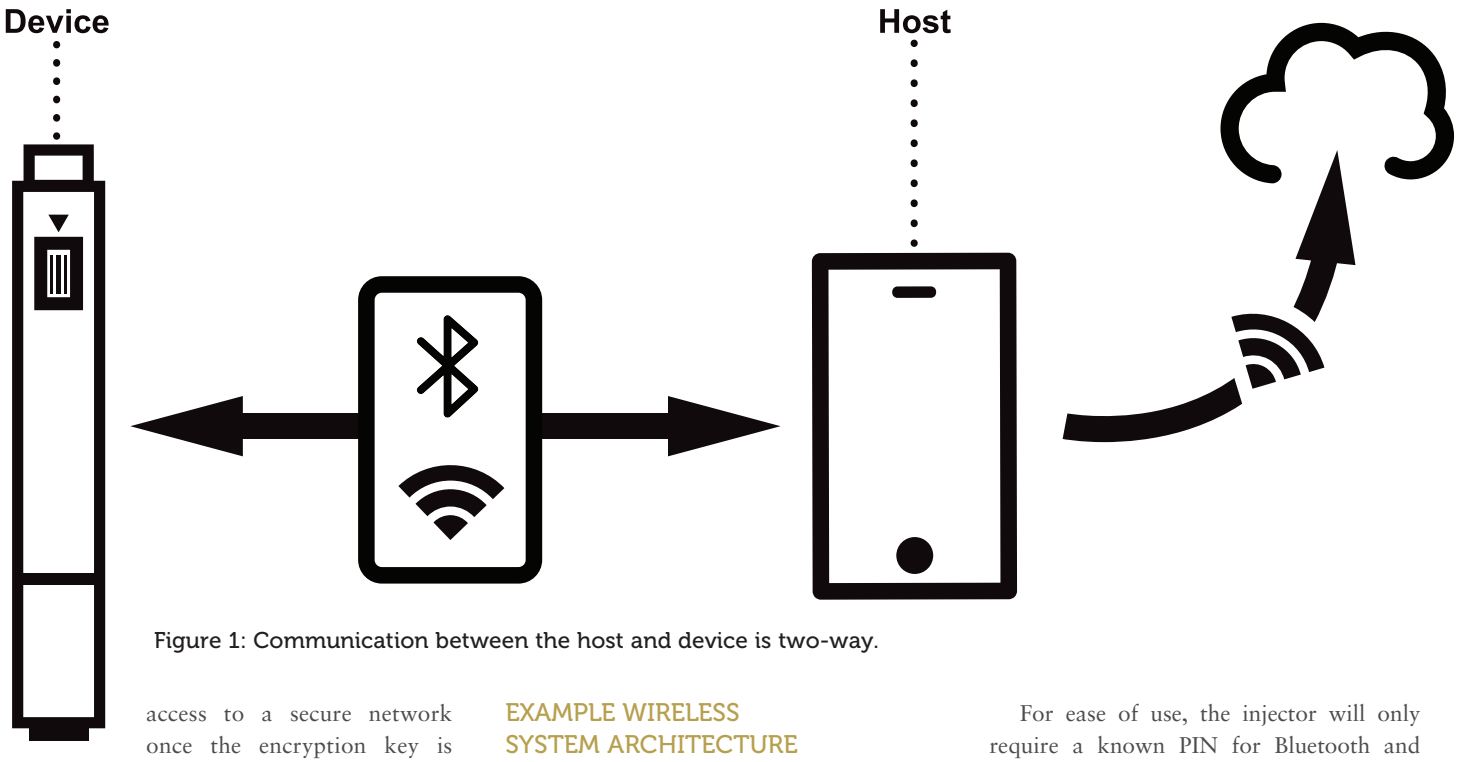

Figure 1: Communication between the host and device is two-way.

access to a secure network once the encryption key is compromised.

Newer encryption algorithms such as WPA/WPA2 are now available, but even these have weaknesses. WPA and WPA2 use AES (Advanced Encryption Standard), which is significantly better suited for Wi-Fi and doesn't have the same failings of WEP. However, for WPA key generation, most devices rely on a passphrase to generate a shared AES key. This means a plaintext passphrase is converted to a 256-bit key, using a known algorithm shared by almost all manufacturers. This step, in itself, is the biggest vulnerability, as this step allows for certain styles of attacks, to be discussed later.

EXAMPLE WIRELESS SYSTEM ARCHITECTURE

We will now explore a typical drug delivery auto injector system that uses Bluetooth or Wi-Fi communication methods to show the potential vulnerabilities in relatable scenarios.

The auto injector can be configured at the factory to either connect via Bluetooth or Wi-Fi to an application on the patient's tablet (Figure 1). In this situation, communication will be two-way – from the device to host and host to device. This will allow the tablet application to send injection results originated from the injector to a central system, as well as to set the dose that the injector will deliver remotely.

For ease of use, the injector will only require a known PIN for Bluetooth and a WPA2 passphrase when connecting in order to support a larger range of mobile devices. The pairing of the injector will remain as long as the device is used. Only on connection of a new device will a new PIN pairing procedure or passphrase be required.

This system has three common cybersecurity vulnerabilities.

Breaking Encryption

To make the auto injector system user friendly, it uses a short PIN for connection to a smart device. Unfortunately the short PIN allows for attackers using readily available and downloadable open-source

tools to try all possible PIN combinations to break the encrypted link and inspect traffic. These tools are typically used by malicious users hoping to intercept Bluetooth traffic in public places. These tools can also be aimed at a connected delivery device to capture the Bluetooth traffic for cracking offline. Passive Bluetooth collection tools also record the address of the devices and can use them as part of a cloning attack.

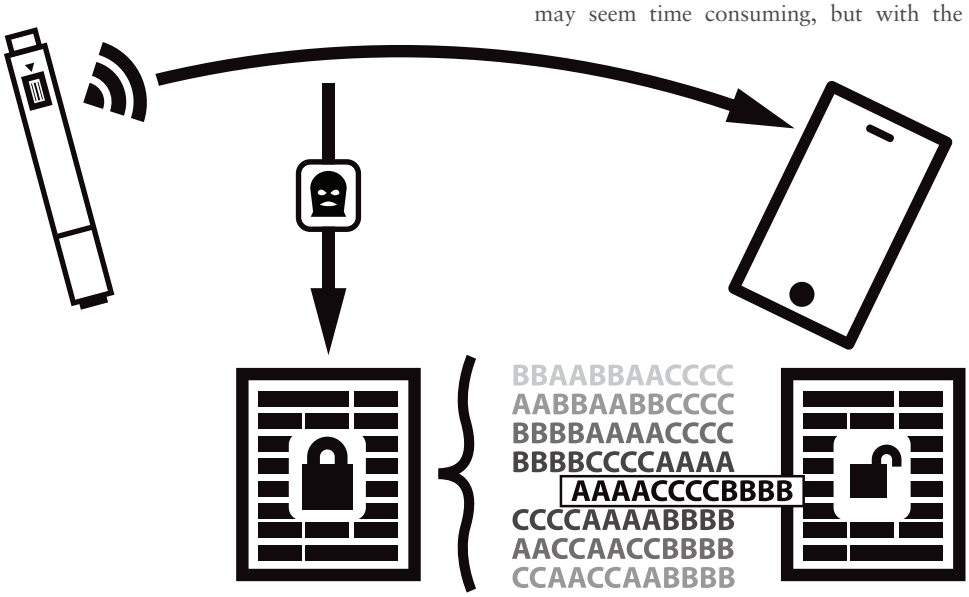

Figure 2: Using a brute force approach.

> "Careful selection and analysis of the current Wi-Fi and Bluetooth modules, as well as device hardware and software must take place early in design to prevent as much vulnerability as possible."

The Wi-Fi enabled connection can suffer a similar fate if we assume a WPA2 Wi-Fi network for data transfer. During initial connection, the host acting as a Wi-Fi Access Point manages a four-way handshake to establish a shared key, often created based on a user-provided passphrase. Capturing the information exchanged during the handshake allows an attacker to try all possible passphrase combinations.

If a simple word or short phrase was used for the passphrase, a dictionary can be used to create the pool of potential passphrase combinations and could crack the encryption relatively rapidly. Alternatively, a brute force approach can be taken for keys that are based on random numbers and characters (Figure 2). These approaches may seem time consuming, but with the advancement of dedicated hardware and cloud-based distributed cracking systems, this process can actually be performed rather quickly.

In both scenarios, broken encryption can have serious consequences. If no additional data encryption is used, all data passed between the connected delivery device and the host can be accessed by the attacker, and the device communication protocol could be reverse engineered. This would allow the attacker insight into system control as well as the potential access to private patient data, dose information and more.

The main message here is knowing that tools and attacks exist and should be factored into the system design to mitigate risk. When selecting a wireless protocol, the key exchange must be evaluated and carefully considered to reduce the likelihood of an attack like this. Longer PIN values and non-dictionary word passphrases would help mitigate the risk in general. Basing these values on the connected device's serial number, instead of a single standard key, could also help reduce the risk. It is possible to use a key generated without a passphrase to avoid the issues mentioned, but this would require more work for the user and could limit device support. If possible, using a key shared by the manufacturer with no user interaction would be best, but may not be practical for some situations.

Device Cloning

Once encryption is broken, knowing the security key (based on a passphrase or a PIN) can lead to the next level attack with more serious consequences: device cloning. Device cloning is when the attacker uses the established key and known device address to act as an imposter in the communication architecture (Figure 3). By using the key and device address, false communication could be sent to either the host or device. From the device side, fake or incorrect dosage information could be reported to the controlling application, viewed incorrectly by users, and thus impact therapy. In the reverse and more concerning situation, device control or the adjustment of delivery parameters in the app could potentially cause immediate harm to a patient. This type of attack can be performed with common tools available today.

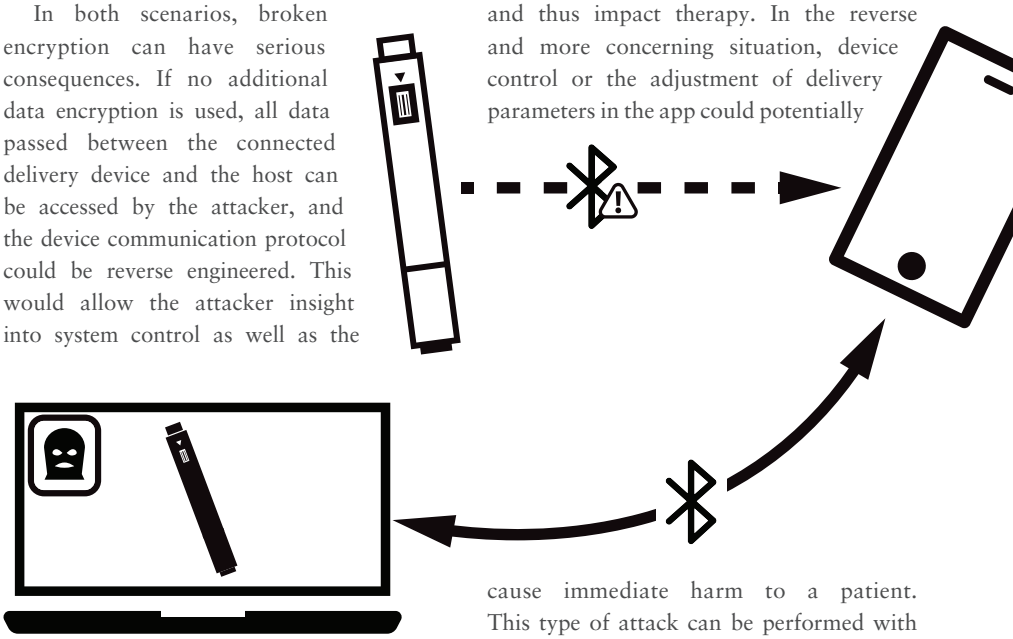

Figure 3: Device cloning.

The most efficient way to mitigate this threat would be to require additional authentication in the device level communication protocol. A custom application layer encryption, separate from the wireless encryption, would be one way to mitigate this risk, as well as potentially adding a cipher-based digital signature to all application packets to positively identify the sender.

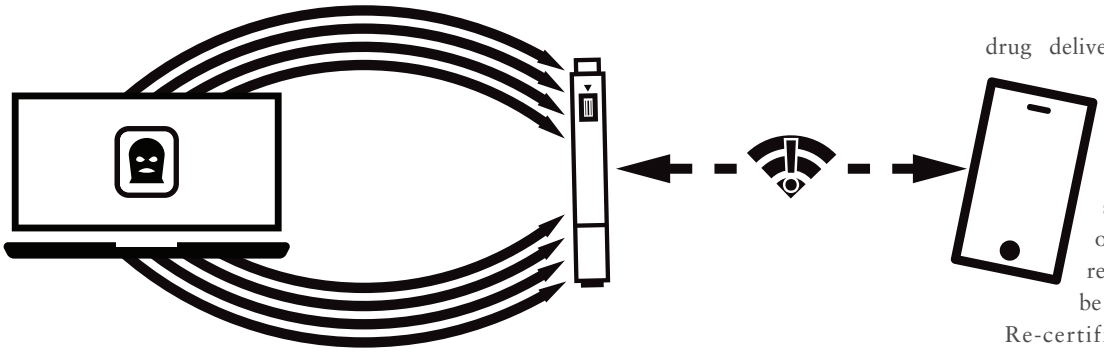

Figure 4: Denial of service blocks all legitimate communication.

Denial of Service

Another potential security risk with both example architecture configurations is the denial of service (DoS) attack. A DoS attack can take many forms, with the bottom line being reduced or non-existent communication on the device subject to attack.

In a Wi-Fi-based architecture, a de-authentication attack could effectively force the device to attempt to reconnect continuously. In the Wi-Fi protocol, a provision exists to notify clients that they have been removed from a Wi-Fi network by using the de-authentication frame. A DoS attack can take advantage of the de-authentication mechanism by broadcasting the packet with forged device addresses, causing the target device or host to attempt to reconnect repeatedly. This is done at a high enough frequency that all legitimate communication is blocked (Figure 4).

This poses clear risks for a connected delivery device. Dosage information and potentially critical or vital delivery factors could be missed. While this type of attack is hard to mitigate, a custom embedded Wi-Fi implementation stack could be modified in order to detect and/or ignore rapid de-authentication frames. This reiterates the point that connected devices need to be designed with support for the lost connection state, whether it is due to an attack or just communication failure.

SPECIAL CONSIDERATIONS FOR DRUG DELIVERY DEVICE DESIGN

Microcontrollers selected for drug delivery applications must have the processing power to handle potential security mitigations both now and in the future. The selection of a Wi-Fi or Bluetooth implementation module must be vetted for these security concerns and efficiency.

In the security world, rapid updates are usually the first line of defence against future attacks. With connected drug delivery devices, remote updates may not be feasible and could be difficult to implement. In addition to the logistics involved in rolling out new software for thousands of devices, there are also regulatory concerns that need to be addressed with a new release.

Re-certification or careful co-ordination may be required to push out a rapid update. Careful selection and analysis of the current Wi-Fi and Bluetooth modules, as well as device hardware and software, must take place early in design to prevent as much vulnerability as possible.

CONCLUSION

Wireless communication using Bluetooth, Bluetooth LE and Wi-Fi communication are all convenient and effective ways to get a drug delivery device connected to the outside world. With proper implementation and thought, the security issues discussed in this article can be mitigated. Some of the situations discussed in this article are worst-case scenarios or a combination of security concerns and potentially bad practices, but they are definitely possible using tools available today. All connected devices are potential targets, and the proximity restrictions of these connected devices should not limit the concern for advanced wireless security implementation.

Balda MEDICAL takes care

SMART PILL DISPENSER – A NEW TOOL FOR IMPROVING PATIENT ADHERENCE

Non-adherence by patients to dosing regimens is a major problem and it is estimated that around 50% of people with chronic disease do not take their medications regularly. This has major costs not only financially but also in increased rates of complications and higher morbidity and mortality. Harnessing the power of smartphones can provide a method of ensuring that patients remember to take medication at the right time and dosage. Paul Wismer from Balda explains how their product, the Smart Drug Dispenser, can fulfill these requirements.

Many of us are familiar with the challenge and the statistics concerning patient's adherence. Adherence is the extent to which a patient acts in accordance with the prescribed interval (and dose) of a dosing regimen. Poor adherence is ubiquitous in medicine, and its ramifications are far from trivial.

There are even two types that can be differentiated. The term primary adherence refers to the filling of the very first prescription. In chronic diseases, such as diabetes, the rate of non-adherence is around 20%. Secondary adherence refers to following the prescribed regimen once the prescription is filled. Here only around 50% are taking their meds correctly. Factors such as number of events per day (once a day *versus* four per day) are important. The more a person has to take, the greater the chance of non-compliance.[1]

> "Non-adherence costs the US alone a staggering $300 billion per year in the form of emergency department use, hospitalisations and diagnostic tests."

Non-adherence costs the US alone a staggering US$300 billion (£205 billion) per year in the form of emergency department use, hospitalisations and diagnostic tests. As said, nearly 50% of patients with chronic diseases do not take their medications regularly. Furthermore, patients who are non-adherent to treatment are more likely to experience worsening medical conditions, unnecessary complications and overall higher rates of morbidity and mortality (Figure 1).[2]

New research conducted for a national multimedia educational campaign to raise awareness about the importance of medication adherence shows that there are clear benefits and opportunities linked to increased communication between people who take prescription medications and their healthcare professionals, as well as to the use of tools that make it easier to adhere to medications (Figure 2).[3]

But the question is: what concrete solutions are available to help combat this huge problem? Over the years, a number of "dispensing aids" as well as organisers and reminders have been developed. But a more holistic approach is needed to help improve adherence, specifically the secondary

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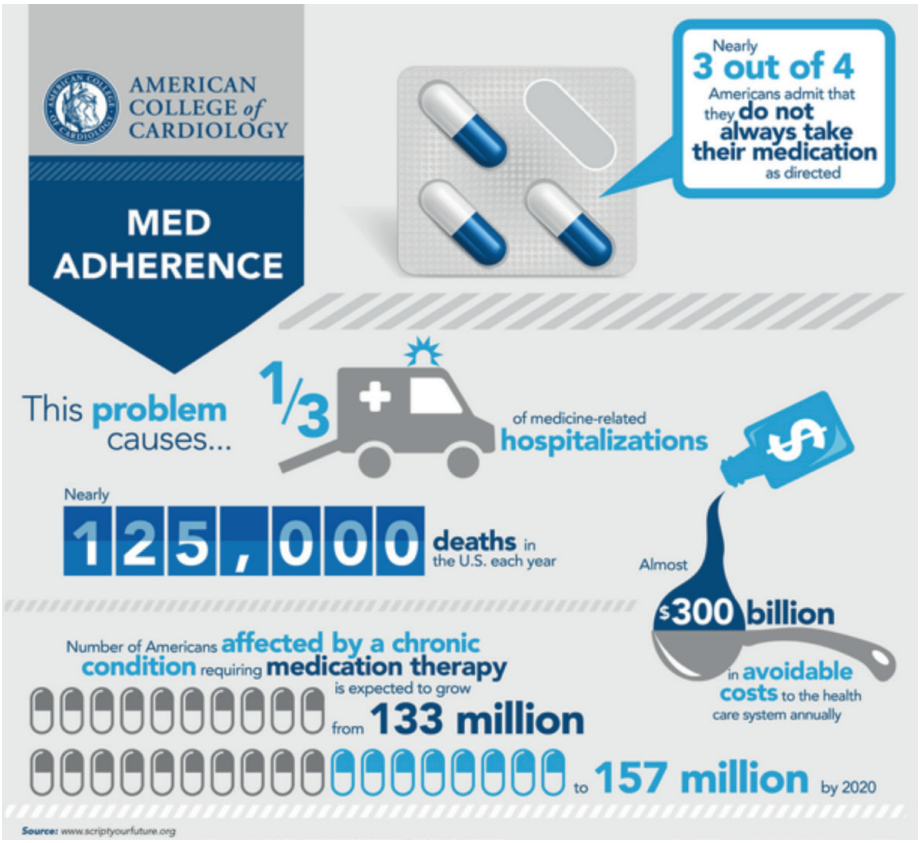

Figure 1: The cost of medical non-adherence (from www.scriptyourfuture.org).

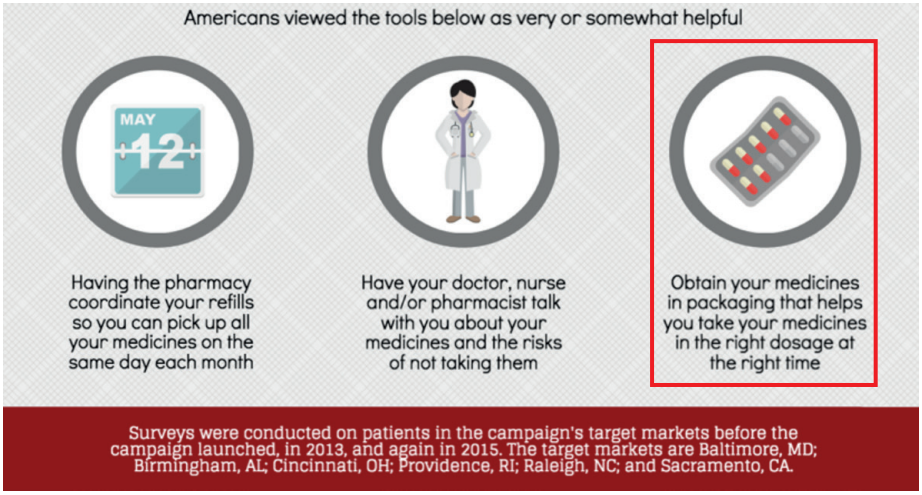

Figure 2: Packaging can be very helpful in improving compliance (from www.scriptyourfuture.org).

adherence (i.e. once the patient has obtained his/her first prescription).

THE SMART DRUG DISPENSER

We now live in a world full of smart phones and apps. Today there are 3.4 billion Smartphone subscriptions and Ericsson (Stockholm, Sweden) predicts this will grow to 6.4 billion by the year 2021.[4]

Why not use that computing and communication platform to help patients in their daily lives? This is the approach that has been taken by Balda Healthcare, which has teamed up with Mechatronic AG (Darnstadt, Germany) to develop the world's first "Smart Drug Dispenser" for pills.

Balda brings decades of experience with hand-held devices made of plastic and incorporating electronics. Mechatronic is an expert in designing electronics for medical products and designed the app in addition. This teamwork of expertise is now paying dividends. Using a minimum of electronics in the dispenser itself and communicating, via Bluetooth, bi-directionally with the smart phone/app, this system promises to provide adherence support.

Via the app, the number of pills and the time when the medication is to be taken is entered in a user-friendly way (Figure 3). This can be done by the physician or a family member or the patients themselves. The device, which easily fits in the palm of your hand, stores the dosage regimen and dispenses the tablets via the push of a button. Alone, it can give its own optical and even acoustic signals, if deemed necessary. The associated smartphone and app, however, would be the main source of user reminders – via APP alerts and an acoustic signal – until the proper dose has been dispensed. Using the power of the smart phone, a text message or email could be sent to a care provider or family member if the patient fails to take his or her (correct) dosage.

The dispenser locks itself after the proper number of pills have been dispensed and, in general, is locked until the time for medication is reached. This prevents under- or over dosage. This could help prevent abuse of pain medication, for example. Balda believes these features could be a way to give family members peace of mind, knowing the dosage regimen can be followed.

Obviously, unlocking the power of the smartphone, both in computing and in communication, means there are additional features that could be added into the app, such as monitoring the number of pills remaining and helping with the logistics of re-ordering by communicating with the prescribing physician or pharmacy.

We have seen the scientific figures showing that this support is dearly needed. The Smart Drug Dispenser therefore makes an important contribution to therapy adherence and safety. Balda introduced it to the medical community for the first time at the CPhI in Madrid, in October of 2015. In the meantime the Smart Drug Dispenser, together with its development partner, Mechatronic, has received two innovation awards at two different shows in the past nine months. The first was at the Compamed show (which runs parallel to Medica) in Düsseldorf, in November 2015. The second was at the MedTec Europe in April (Figures 4 and 5).

Christoph Klaus, Head of the Business Unit, Balda Healthcare, has described the potential of the system: "An ageing population that is also tech-savvy has a need for modern solutions. The Smart Drug Dispenser is an exciting product that provides added value for patients, physicians,

Figure 3: The smart pill dispenser.

relatives and also health insurers." Thomas Ullmann from Mechatronic AG is also pleased with the result of the co-operation between the development service provider and the plastics specialist: "With the Smart Drug Dispenser, we have taken an innovative step in the direction of user-friendly operation whilst offering a high degree of user safety."

THE BENEFITS OF THE SMART DRUG DISPENSER

- Solving a great unmet need: medical adherence
- Feasible today (technology is available)
- Ethically relevant and could save lives
- Unburdening of family members/give them peace of mind
- Potentially large cost savings for society – global cost of non-compliance estimated up to $1 trillion!

Specifically for pharma companies:

- Help in clinical studies to track/insure compliance
- Differentiator from competition for serial production
- Increase customer loyalty and revenue in general.

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Figure 4: DeviceMed Award for innovation (left). Presented at Compamed /Medica, Nov 2015. Winner of the Exhibitor Innovation Competition MedTec Europe, April 2016 (right).

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CONNECTED HEALTH: THE FUTURE OF EFFECTIVE DRUG DELIVERY

The development of connected injection devices by West Pharmaceutical Services is already well advanced. In this article, Chris Evans, Vice-President, Innovation, and Nicolas Brandes, Director, Market Development EU/Asia-Pacific, both of West, set the company's movement into connected health in the context of trends in the pharmaceutical industry, such as the increased number of biologics coming through the pipeline and the need for patient-centric approaches, and describe the specific requirements those trends place on their injection device designs. They introduce their partnership with HealthPrize which brings in elements of gamification and reward programmes into therapy adherence software and, looking to the not so distant future, they describe in detail a number of specific benefits – to various stakeholders – that their connected delivery systems will bring.

Keeping up with new drugs in development and the technologies to support them requires a novel approach to drug delivery. One of the biggest challenges in the injectable drug market today is patient centricity. With more patients diagnosed with chronic conditions and tasked with self-care at home, it's becoming increasingly important for patients to be fully engaged and invested in their treatment regimens. Connected health – and its integration within drug delivery systems – is showing great promise for meeting the patient-centricity challenge head-on and thereby improving the user experience and helping drive adherence.

PUTTING PATIENTS FIRST

With a steady pipeline of biologics and biosimilars poised to come onto the market for the treatment of chronic conditions, we are experiencing the very beginning of the potential that exists for a new wave of drug delivery. Patients who must regularly self-administer medication – not to mention the providers and health insurance payers that are invested in these treatments – have eagerly awaited this shift to more user-friendly drug delivery systems that better align with how people live their everyday lives.

> "Our connected health collaboration incorporates the power of a smartphone app with the SmartDose integrated drug delivery system to improve and reward medication adherence."

Patients are demanding more autonomy in managing their own self-care at home whenever possible. However, as the use of biologic therapies is on the rise, it can be challenging for patients tasked with injecting high-volume doses to do so consistently and effectively. This is especially true for patients with chronic conditions such as diabetes, haemophilia, rheumatoid

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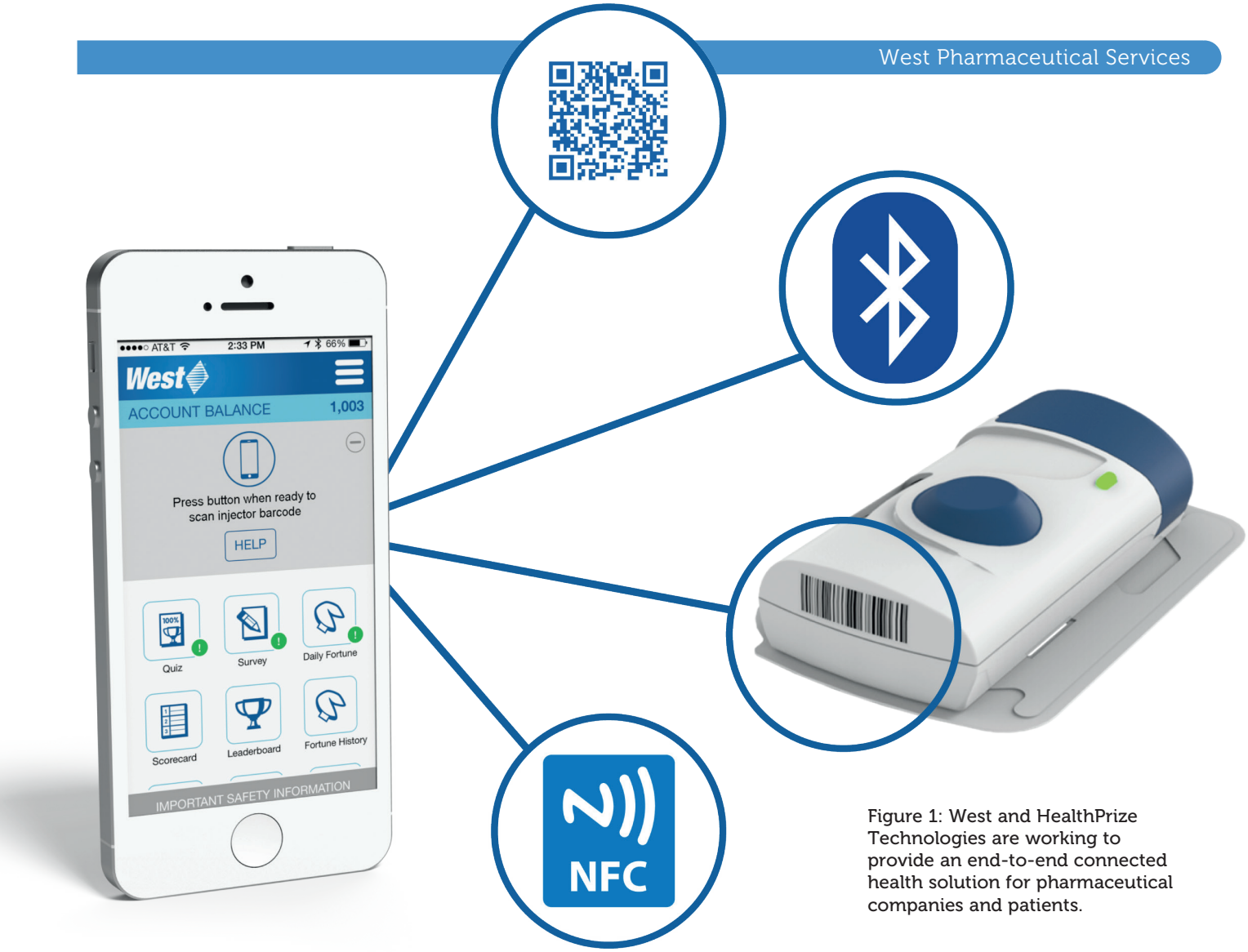

Figure 1: West and HealthPrize Technologies are working to provide an end-to-end connected health solution for pharmaceutical companies and patients.

arthritis and multiple sclerosis, which often require repeated injections for effective, long-term care.

While there are numerous auto injector devices on the market, pharmaceutical companies need innovative and responsive packaging partners that can keep up with the requirements demanded by advanced biologics. Some glass-sensitive biologics must be housed in polymers because of the risk of incompatibility, breakage or protein aggregation with glass. Other requirements are more suited to injectors that can control the delivery of large doses over time when the drug is too much for a single injection.

> "One way to increase patients' affinity for their self-injection system is to connect it to another device that they already use: their smartphone. Smartphones are powerful tools used by most of us every day."

West's SmartDose® Electronic Wearable Injector, incorporating a Daikyo Crystal Zenith® cyclic olefin polymer (COP) cartridge, is designed to enhance the experience of patients required to self-inject a larger volume biologic drug at home. This wearable injector adheres to the patient's body, usually the abdomen, and automatically injects a drug slowly over time via an electromechanical drive. By making it easy for patients to self-administer medication, the SmartDose system encourages patients to comply with their prescribed dosing regimen.

We recently partnered with HealthPrize Technologies, a leader in patient engagement and medication adherence solutions, to make the SmartDose injector even more patient centric. Our connected health collaboration incorporates the power of a smartphone app with the SmartDose integrated drug delivery system to improve and reward medication adherence with unique gamification technologies. In doing so, we have created a patient-friendly injector that allows for system configurations that not long ago seemed part of the distant future.

Putting all three together – the right containment materials, delivery systems and apps that track compliance to prescribed treatment regimens and reward patients in order to reinforce medication adherence – creates a powerful next-generation digital health ecosystem that can help solve some of the more significant issues that evolving healthcare models pose.

ADDRESSING USABILITY

Before bringing a connected health offering to life, it is important to understand the fundamentals of patient-centric design. One of the most successful elements in fulfilling the need for patient-centric design is human factors analysis, which benefits the patient by making injection systems more comfortable and user-friendly. More patients are using auto-injection systems to take medications at home that previously were delivered in a clinical setting. Increasingly, patients are taking biologics that require less-frequent, high-volume doses. In some cases, doses

only need to be delivered once a month, making it easy to forget these processes from month to month.

By taking a systematic, data-driven human factors approach to addressing usability earlier in the development of injectable drug delivery systems, it is possible to troubleshoot and eliminate or minimise the risk of potential user errors and help build successful outcomes for the end-user patient. Incorporating patient feedback earlier into the design process also assists in creating delivery systems that address factors such as reducing fear and discomfort during the injection process.

What does patient-centered design mean in practical terms? For West, it includes listening to patients to address their personal priorities. Often this involves talking to users three to five times before even prototyping a self-injection system to understand their needs and how best to meet them. It also means understanding how patients feel about their diagnoses, and conceptualising how to make a drug delivery system that will improve their outlook, as well as finding out what features and design factors will improve medication adherence.

We also continually validate and improve our designs to ensure that data-driven research is driving our approach to designing patient-friendly injectors. Armed with this knowledge, we can create delivery systems that patients are more likely to use correctly the first time and every time.

PUTTING QUALITY INTO DESIGN

In addition to considering human factors testing and analysis, the selection of components that go into a drug delivery system is patient-critical: packaging components must be of the highest quality in order to help the injector function safely and effectively. Incorporating scientific Quality by Design (QbD) principles into both the design and manufacture of packaging components can lead to greater understanding of the impact that material attributes and process parameters have on the critical quality attributes. It also enables greater control over sources of variability in manufacturing.

Regulatory agencies set high expectations for pharmaceutical and biotechnology manufacturers and hold them accountable for assuring all of the parts of integrated drug delivery systems are of the highest quality. The use of components within a self-injection system based on a holistic QbD process assures a well-understood product that has been developed to protect patient safety and minimise risk for the pharmaceutical manufacturer. And, most importantly, it helps put parameters in place to ensure the injectable medication contained within a delivery system can be used safely and effectively.

West developed the components for prefillable systems with QbD in mind, addressing the needs for today's biologics. One example is the West NovaPure® brand of elastomeric components. NovaPure components, such as stoppers and plungers, were created through QbD processes that have been shown to optimise breakloose and extrusion performance, provide low part-to-part variability and particulate specification while ensuring high cosmetic quality. When combined with West FluroTec® barrier film, the components help improve auto-injector performance through dimensional consistency.

> "Connected health programmes such as HealthPrize and other systems that "gamify" treatment regimens – and allow doctors and nurses to monitor patient data and medication adherence – show promise in giving patients better reasons for caring for themselves."

This data-driven component of container development helps ensure a biologic reaches the market in a delivery system that not only helps to protect the drug product's quality and efficacy, but will also help maintain reliable drug delivery throughout the drug product lifecycle.

CONNECTED HEALTH

The quality of a delivery system is critically important for patients. However, a patient's top concern is often usability; it is important to have a drug delivery system that is easy to use. Auto injectors that are designed with this patient-first approach have the ability to help improve medication adherence. When a self-injection system is comfortable, reliable and familiar, a patient is more likely to use it as prescribed, which can lead to improved outcomes, positively impacting patients, providers and pharmaceutical companies.

One way to increase patients' affinity for their self-injection system is to connect it to another device that they already use: their smartphone. Smartphones are powerful tools used by most of us every day. They help us remember the grocery list, who won last week's sporting event, who recorded a popular song or acted in a favourite film and keep us in touch with family and friends in ways we never could before. In much the same way, smartphones and intuitive apps can also be used to make information about medications and step-by-step instructions on how to administer them easily accessible in patients' daily lives.

When setting out to design the next generation of drug delivery systems, the West team understood the vast potential of smartphone apps for helping to improve medication adherence. But we also knew we needed to find a software partner to accelerate our plans for integrating a connected health app with our self-injection systems. We chose HealthPrize, which created a dynamic software-as-a-service platform that engages and educates patients and records when they take their medication. In the future, the platform may also potentially provide the ability to track more details about patient behaviour, as well as automate the reporting process through sensors in the injector.

Leveraging gamification, the HealthPrize platform rewards patients for medication adherence. As a concept, gamification has made inroads in online marketing by applying elements of game playing, such as scoring points, competing with others, setting a hierarchy of rules and, of course, reaping rewards for success. But it is showing promise in other sectors as well, including fitness and healthcare, and for helping patients find a new way to meet the daily challenges of chronic disease management.

Connected health programmes such as HealthPrize and other systems that "gamify" treatment regimens – and allow doctors and nurses to monitor patient data and medication adherence – show promise in giving patients better reasons for caring for themselves, in both incentive and accountability.

Such technology options are a value-add for pharmaceutical companies and payers as well. By pairing their injectable drugs with innovative and engaging patient-focused delivery systems that track when a dose is delivered, drug makers and payers alike can have greater confidence that treatments are being taken as prescribed.

Forward-thinking companies are now also looking at the potential for smartphone apps to improve patient education and experience around self-injection systems. By using an app to guide patients in training, they don't have to remember everything outlined to them at the doctor's visit, when they might have many other things on their mind. Additionally, having the opportunity to reward patients for documented training, as well as to provide prompts and reminders around additional resources, has great potential for the safe, effective use of self-injection systems.

LOOKING TO THE FUTURE

With drug delivery systems, one size may not fit all patients, at all points, in different stages of different diseases. But learning how patient attitudes towards diagnosis evolve, how they view and use their drug delivery system, and how their needs change as they progress through various stages of the patient journey will lead to better understanding of how to keep them from going off their critical medications… and what reasons they have for doing so.

The pharma industry is conservative, but connected health's return on investment is beginning to show better outcomes, spurring the movement to build a digital health ecosystem around injectable drug delivery. In the future, data around medication adherence will be effectively tracked in real-time, including what medication was administered, where, when and how much was delivered. This critical intelligence will be reported back to providers and pharma companies.

> "In the future, data around medication adherence will be effectively tracked in real-time, including what medication was administered, where, when and how much was delivered."

There will be reminders and messaging when a patient misses a dose of a needed therapy and, when needed, an appointment will be initiated with a healthcare professional to reassess their treatment plan. That might sound like a great leap patients will have to take. But, in the end, we can all benefit from investing in better connected systems in the pursuit of healthier outcomes.

Additionally, by focusing on value-added offerings, along with the right primary packaging for injectable biotech drugs early in the drug development process, drug makers can better differentiate their products with unique packaging and delivery systems that may help aid patient compliance, and ultimately, outcomes.

The greatest benefit, however, is to patients. Patients living with chronic conditions who must inject themselves daily want their routines simplified and straightforward. Having a sensor detect when a dose is taken, logging the details so the patient doesn't have to do it manually, and sending confirmation to a care provider is the kind of simplified process likely to be welcomed among people whose lives have already been complicated by living with a chronic disease. The lesson today's technology companies are learning, over and over, is very clear: provide clear benefits to the end-user. Give patients value that will enrich their health, comfort and care quality. This is the promise and opportunity of connected health.

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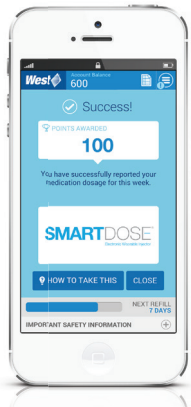
The SmartDose® electronic wearable injector combined with the HealthPrize adherence program makes for a powerful combination. The SmartDose injector helps your patients leave the treatment center behind, making self-administration at home simple and easy. And while at home, HealthPrize helps your patients stay on track with their therapeutic routine, through rewards-based patient education and adherence tracking.



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West seeks partners for its SmartDose electronic wearable injector technology platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company. The SmartDose system, HealthPrize platform integration is for conceptual purposes only.

Medicom
Innovation Partner
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THE DRUG DELIVERY DEVICE AND CONNECTIVITY CHALLENGE

Pharma organisations seeking to ensure a premium patient experience are leveraging smart, connected medicine delivery technologies and connected health solutions that enable patients to adhere to their prescribed medicines and to evidence outcomes. In this article, Neil Williams, Head of Connected Health at Medicom Innovation Partner, offers insights into the challenges and experiences of developing a complete connected system including injection device, app, cloud storage, integration engine and dashboarding tool, and what to look for in a partner, to help deliver connected health devices, apps and a strategic platform.

Patients are engaging in digital transactions with their healthcare providers, payers and social community. There are many opportunities and challenges, which need to be considered by Pharma, as the health industry refocuses towards revenue models based on results rather than activity.

> "Without question, the patient should always be in control of how their data is utilised even if it were to be anonymised."

THE FINANCIAL POTENTIAL OF DIGITAL HEALTH SOLUTIONS

It is reported that improving digital health products and services could liberate US$300-450 billion (£206-309 billion) in the US. Pharma can play its part here and directly benefit. Increasingly healthcare payers and providers are focusing on outcomes measures and linking outcomes to costs. Pharma can leverage "real world" data to prove adherence delivers enhanced results; this data can be leveraged to help change prescribing behaviours, improve positioning within formularies, retain patients and bring new patients.

Connected services can also bring significant insight to Pharma. For example, if a disease-specific app was launched it would be possible to know where your medicine is densely used and where it is lightly used. You would be able to know which patients might be interested in study participation and be able to cohort patient groups. Of the top performing health apps, 68% include social networking; this is a rich source of data that can help pharma better understand patients' daily challenges and likes.

Number of apps across Apple AppStore and Google Play	Percentage of apps with medication reminders	Percentage of apps with data sharing	Percentage of apps with data export	Percentage of top performing apps with social media
~ 90,000	2%	2%	9%	68%

Table 1: Some mHealth app statistics.

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Without question, the patient should always be in control of how their data is utilised even if it were to be anonymised. Complying with standards such as HIPAA, information security and governance are mission-critical requirements of any connected health service.

MEETING STAKEHOLDER REQUIREMENTS

There are over 90,000 health apps across the Google Play and Apple App Store; many of these are simple health diaries, dieting aids and connected wellness apps that link to activity trackers, blood pressure, scales etc. All too often these apps are poorly aligned to patient cohort and market requirements. For example, only 2% of published health apps have a medicine reminder and or a data export function despite these features being commonly requested within focus groups (Table 1). For an app and connected health solution to stand out and deliver real-world benefit to a patient, the entire connected health strategy needs to be developed and aligned to stakeholder requirements.

It is necessary to work closely with patients and clinicians to really understand their needs, and use proven processes to test concepts and define and produce an optimal solution. It's also important to consider the caregivers, case managers and wider support systems around the patient to ensure that the delivered device and software is purposeful and valued.

THE REGULATORY AND PRIVACY CHALLENGE

There are significant privacy challenges in the development of a connected health solution. The development needs to be mindful of the likely regulatory scenario and the possibility that the app and cloud platform may be considered to be part of a system/combination product by the regulatory authorities. Different markets have variable privacy standards, hosting requirements, treatment protocols etc and it is vital that the selected partner understands how to address these.

Understanding the regulatory processes and being accountable for both device and software compliance as the registered manufacturer of on-market products brings a burden of responsibility that challenges most software designers.

While it is necessary to be vigilant regarding privacy, it is also important to be aware that these challenges have been addressed in the healthcare IT industry for many years. The development partner must understand how to ensure patient data is safe, how to put patients in control of their data and data sharing, and how to do this in a regulated medical device environment.

It is also important to consider the medico-legal issues surrounding patient data and what implications this can have for a pharma company hosting or processing data on behalf of a patient.

> "A true connected health platform needs to support the requirements of all stakeholders fully, and it needs to be extensible such that a pharma company can add multiple disease specific apps and services to a common infrastructure and clinical database."

CREATING A TRULY-CONNECTED HEALTH APP

A truly connected app needs to be built on a connected health platform that allows integration and, with the patient's permission, sharing of health data so that powerful insights can be gained, outcomes optimised and all stakeholders able to derive value from patient and device data.

An app needs to deliver valuable services and insights to patients so that it becomes a trusted part of their daily life, and facilitate gathering of data which can be insightful to patients, providers, payers and pharma. For example, medication expiration and usage tracking and re-ordering adds convenience for the patient and also helps pharma understand use patterns, track and trace, geographical prescribing variations and much more. Such data also helps clinicians and case managers understand patient adherence and correlate this to clinical outcomes and other lifestyle factors.

OUTCOME IS THE NEW INCOME

Insights about adherence are already being requested by pharmacy benefits managers, and the market is increasingly being driven to an outcomes-based revenue model. Proving the value of a medicine and having an engaged patient population could not only help patients achieve optimal outcomes but could also drive discussions about formulary position improvements.

Apps need to work seamlessly and securely even when the mobile device isn't connected to the internet, images a patient takes should not be accessible in their devices photos app, and if the patient wants to remove the app, all the associated data needs to also be removed from the mobile device. From the patient's perspective, the app needs to "just work" at any time and any place. A significant amount of upfront work and prototyping the user experience, design, workflows and consideration of human factors needs to be undertaken early in a project, to ensure that patients receive a solution that is valued and where necessary regulated.

THE CONNECTED HEALTH PLATFORM

To realise the value of patient self-generated data fully, it needs to be appropriately managed and shared. A simple medicine diary will only create insights about adherence for the patient to look at and perhaps share at an occasional consultation. The opportunity to integrate and share data across stakeholders brings significant insights about behaviours and outcomes. Data needs to be liberated and should not be contained in a silo. This is a challenge that pharma can help address while also addressing internal needs of on-boarding new patients, adherence and creating engagement between health professionals, patients, payers and pharma.

A true connected health platform needs to support the requirements of all stakeholders fully, and it needs to be extensible such that a pharma company can add multiple disease specific apps and services to a common infrastructure and clinical database. A platform should also be engineered to ensure that privacy and regulatory requirements are implemented. Note that these vary from market to

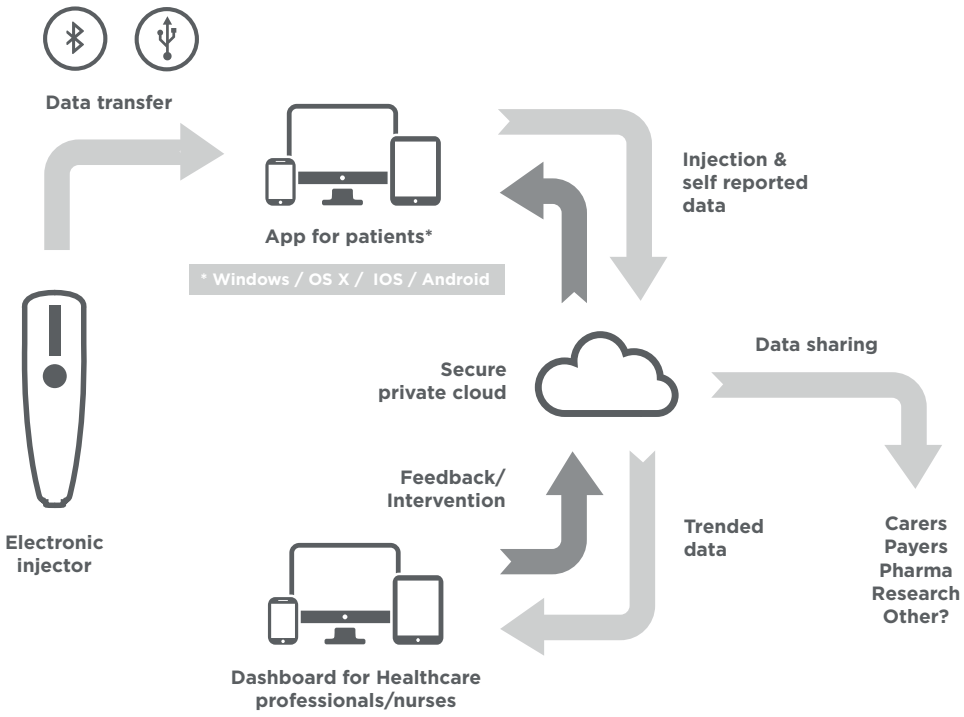

Figure 1: The complete connected system architecture.

market, which requires global experience of health data and privacy requirements. Additionally, the incorporation of clinical coding (ICD10, for example) allows a platform to be leveraged for global comparators, scientific research and integration to health provider and payer systems.

The requirements of pharma are different to those of provider organisations. A commercial case-management solution that looks at cohorts and risk stratification is a valuable tool. However, it doesn't specifically address the patient, healthcare professionals and pharma – "one size fits all" is not the most effective solution to patient cohort needs and stakeholder engagement.

MEDICOM'S APPROACH TO CONNECTED HEALTH SOLUTIONS.

Delivering a truly connected, potentially regulated, health solution is complex and requires expertise and experience (Figure 1). Medicom has extensive experience of smart, connected, medicine delivery devices and how best to leverage these technologies to create value-driven device and connected health strategies. Working for pharma clients, Medicom defines disease- and molecule-specific drug delivery strategies, tests concept feasibility, and designs and manufacture advanced connected medicine delivery devices, apps and cloud platforms. Through ongoing internal development programs and access to intellectual property, Medicom has a portfolio of technologies that may be applied to accelerate time to market.

Medicom is bringing its third-generation connected health platform to market for its pharma clients to leverage in conjunction with connected health apps and regulated connected devices, enabling connectivity across the health ecosystem. This platform solution is tailored to each pharma client's requirements, and is typically hosted in a private cloud. Each pharma client can have a single, private cloud instantiation across the entire company portfolio, capable of being tailored to address multiple disease areas, multiple branded apps, portals and integrations while also providing a single source for advanced analytics and machine-based learning.

CONCLUSIONS

- Connected drug delivery devices and systems are entering the pharma landscape.
- Seek a platform approach that can be specifically tailored to your initial needs yet is extensible across your business as your connected health strategy and areas of disease focus evolve.
- Ensure that the designed user experience is fully oriented towards researched and evidenced patient, healthcare professional and other stakeholder needs for each disease area.
- Leverage partners with proven connected health experience in both drug delivery devices and software; in the case of combination products it is complex to separate solution components and manufacturer responsibilities.
- Consider that your app, platform and connected drug delivery device can be regulated.
- Begin with the end in mind; while your initial ventures into connected health may be modest, ensure that you choose a partner and platform technology that can support your longer-term vision and advancing market expectations.

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 for the high-value rare disease and orphan drug market. Medicom Innovation Partner was established as a technology venture of Bang & Olufsen A/S back 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 is 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 specialty 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, specialty inhalation drug delivery devices, single use surgical devices and consumable diagnostic components.

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

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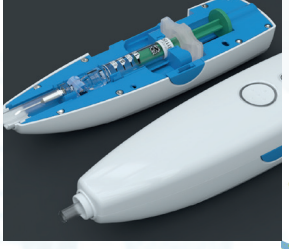

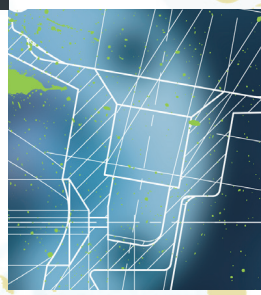

Devices
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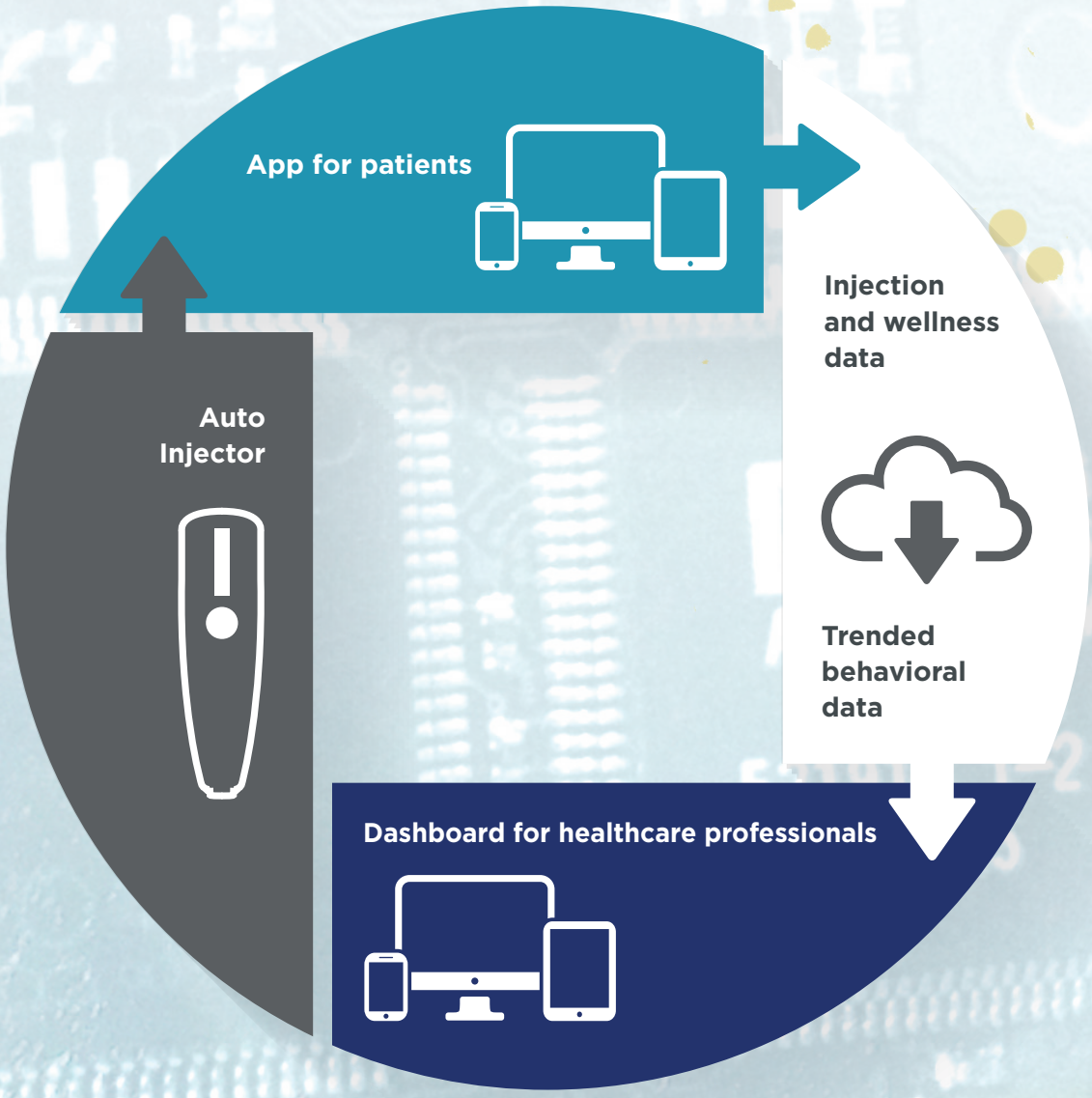
Connected Health Service Solutions



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SIMON MICHEL

CHIEF EXECUTIVE OFFICER, YPSOMED

In this exclusive in-depth interview with ONdrugDelivery Magazine, Simon Michel, Ypsomed Chief Executive Officer, talks about his vision for how the connected world of drug delivery devices will evolve, and Ypsomed's central role within it. Mr Michel comes across as a CEO tackling this topic not at a distance, but one who is fully involved, has a true grasp of how connectivity can improve healthcare, has a detailed knowledge from the level of the broadest, biggest global issues to be considered, right down to the detailed technical level. This top-to-bottom understanding gives him a clear vision of the route through, the steps the industry needs to take, to make it happen.

Q Ypsomed reported its 2015/16 annual results in May with continued growth of 10%. How was this achieved?

A Ypsomed's results across both of its divisions, the retail arm, mylife Diabetescare, and on the YDS (Ypsomed Delivery Systems) business-to-business side, were strong and in terms of revenue their contribution is now roughly equal, fifty-fifty. Business has actually been picking up in both areas and the top-line growth of 10% is going to accelerate in the coming years. We calculate, with an annual growth of 12-15% year-on-year as a realistic forecast, revenue of CHF500 million (£363 million) in 2019.

> "The power must come from the smart phone or other device that sends the power to the pen and the pen then sends back data. In other words, we have to work with NFC but its range at present is only a couple of centimetres. We need NFC that works at a range of 2-5 metres, and this standard doesn't exist yet."

On the B2C (business-to-customer) diabetes side, it is the insulin pump market that is growing faster than expected. For example in countries like the UK, and others in Europe, children are put directly onto a pump, they are no longer given a pen, and with the OmniPod Patch Pump we have a great product in our hands. On the B2B (business-to-business) side which develops the pens and autoinjectors, there are strong global trends such as the increasing incidence of diabetes, the emergence of biosimilars and the increasing numbers of drugs coming through that have to be injected. We are in these areas and we are a market leader.

Q Would it be correct to say that this growth has been through increasing revenue streams rather than through acquisitions and the like? It seems to be a strategy that works.

A Yes. This is pure organic growth, and it will stay purely organic growth for the forseeable future. We have done our homework. When you look back in our history, we were at one time the sole provider of insulin pens to Sanofi and today, we are talking with dozens of pharma companies and Sanofi is still a very good client for SoloStar pen components.

Q Ypsomed's platform strategy for delivery systems is paying off. What is the focus moving forward?

A Ypsomed has really changed the rules. I would even say we have changed the rules in the market. Ten years ago we introduced the first real pen platform concept. Before that, companies like Ypsomed sold projects so, for example, if a customer came to us, we would sit down together, our engineers would begin to draw first concepts of a pen and four years later there was a product ready for clinic. Today this has changed dramatically. It's no longer four years – it takes a matter of months. So we have accelerated these timelines massively by developing platforms, by engineering them, by patent protecting them and, this is key, we also industrialise them.

If a pharma company comes to us today we have injector platforms ready, fully industrialised – you can really buy them off the shelf. The adaptations required for the autoinjectors and disposable pens are relatively minor compared to ten years ago. Worldwide we are conducting over 50 projects in parallel and this is not the ceiling. This world is changing so rapidly now.

Q How does being active in the diabetes care business support activities for the delivery systems business?

A That, of course, presents a really good opportunity. We currently serve around 30,000 OmniPod patients and we are adding around 800 per month.

At Disetronic, Ypsomed's predecessor company (now part of Roche) my father

(Willy Michel) invented the first insulin pump, next to Alfred Mann, 30 years ago. They were head-to-head, competing. Al Mann sold his pumps to Medtronic and we sold ours to Roche Diabetes Care. There's a lot of history here and contact with patients. We have kept this direct contact over the years.

We now have 15 sales subsidiaries and 350 reps in the field, daily contact with patients and a hotline with 40 people manning it. It's a very strong patient interaction on the B2C side, and this interaction has clear benefits on the B2B side too. We do focus groups, we test new concepts with patients. There is really a strong crossover internally between the B2C and B2B sides of our business, around knowledge building and really knowing the patient.

There is also of course strong interaction and constant communication between the two sides of the business "on the ground". Here at Ypsomed in Burgdorf, we are 500 people, including 150 engineers, 100 people in product management, and the B2B and B2C teams are located very close to one another within the building.

Q How do you see connected devices making an impact in the market for self-injection systems?

A Let me give you an example of how connectivity is already changing the world. For two or three years now, my sons have been using the Oral B 6000 toothbrush, which is Bluetooth integrated and I can check their usage on my mobile phone via the app. As soon as you think about this example, you quickly realise that there are many, many even more intelligent ways to use connectivity technology. You realise that autoinjectors must be smart.

Personally, my affinity and familiarity with telecommunications and data is very high. In a previous role I worked in this sector while we were introducing 3G mobile networks in Switzerland.

I would just be a bit careful on the expectations in the market. When I look at the history of devices, the 1980s was the decade of the re-usable pens, the 1990s was the decade of disposable pens and the focus was definitely on the function back then. Then in the 2000s, the focus was on cost and we saw the first large-volume, fully automated 50, 70 and 100 million-unit pen lines as we operate today. This decade is the decade of usability. We have been talking about usability for more than ten years but in reality these devices are hitting the market now. So thinking about smart devices and connectivity, I would talk about the next decade; the 2020s will be the decade of adherence and smart devices. These things take time. The industry is extremely slow moving, especially in the world of combination products. You cannot quickly change a disposable product just like that.

We also have to look at the standard on the tech side. At the moment we are extremely limited. We talk about low energy Bluetooth and NFC (near field communication) but low energy Bluetooth in most cases is too expensive at the moment to put into a disposable device so we talk about re-usable solutions.

The industry focus is on disposable pens but there is very limited room in the budget to put in Bluetooth connectivity and power source – it's over one dollar per device.

Also, it's not really acceptable that a disposable pen has its own electrical power. The power must come from the smart phone or other device that sends the power to the pen and the pen then sends back data. In other words, we have to work with NFC but its range at present is only a couple of centimetres.

The normal distance between a person and their mobile phone is in the 1.5-metre range. It is usually either on their body in a pocket or worn, or nearby on a desk or table. NFC on an autoinjector, as it is now with such a short range, is an intermediate solution. It gives added value for some therapies if you can really train the user to hold the autoinjector to the phone for data transfer but this is an active process, not passive.

So, on the one hand, we have to wait for the tech to emerge for communication. On the other hand, companies like Ypsomed have work to do on solutions to record the information on disposable devices: how much was injected, at what speed, at what time. This is an electronic and mechanical engineering job.

I would like to touch on another topic which we believe is a kind of dilemma in the industry, which we still have to solve, the different parties have to find their roles. There is no doubt about it, pens and autoinjectors must become smart in order to enhance adherence. There, we are all clear. But if you look in the industry, who is going to build the infrastructure (Figure 2)? Payers for example, have very little motivation to invest here because most payers (not all but most) really have a quarterly financial focus and there is very little incentive for programmes to look at the health status of patients ten years down the road. Also there are no global insurance companies. Most of them are local focusing on one or a few countries, so they have limited interest in investing in global cloud solutions.

Then looking at pharma, big pharma, in the whole of their history, they have avoided owning patient data. Now suddenly they are faced with a need to change this, to build up knowledge bases and interact with patients. Pharma companies are not yet sure they want to do it, they don't have cloud teams – IT teams to talk about integrating the cloud into customer care, for example, do not exist. There are existing third-party cloud providers out there but at the moment they are very much patient focused – they are not yet payer or pharma focused. Finally, looking at doctors, there is still reluctance in the medical professional community to go online and transmit patient data via the cloud. The question is: will the device manufacturers be the ones who will jump into this role of building the infrastructure?

At the moment, Ypsomed is analysing intensively whether we should offer OEM cloud services, a pay-per-user cloud service where a pharma company can hook up, it's fully secure, we transfer the data from all our autoinjectors, via the mobile phones of the patients, into the cloud and the data will land where pharma can use it.

Figure 1: Leveraging YpsoMate, the two-step autoinjector platform, YpsoMate Smart features NFC-based connectivity and built-in low-cost sensors to identify use status.

This might be for Phase IV study data, or for routing to doctors to inform them whether the patient has taken a shot or not. This is a real dilemma – the industry still does not know yet who will be in the cloud-provider role. We are quite sure that the device manufacturers have to play a part.

Q Which device types and geographical areas have the greatest potential for connectivity?

A Geographically, this is global, the whole world. But to be more specific, the number one area in terms of potential is the US because they have the biggest budgets around for drug and device development. You can even think about business models that are offered by newcomers, who want to offer integrated solutions in the field of diabetes and they can do it because there is money around. There is venture capital around for new companies and there is also money around in the system to pay for cloud solutions and connected services.

In terms of which types reach the market as connected devices first, I believe it's a head-to-head race between the first insulin pen and the first autoinjector.

At the moment, Ypsomed is working in both areas in but remember, as I mentioned just now, there will be intermediate solutions and the industry will still have to wait for the ultimate architecture for the way it works. It is still not there because the communication technology needed is the missing piece. Security is another hurdle which governments, healthcare systems and pharma are confronted with.

Q You announced a new wearable injector YpsoDose in your annual report. Will this device also be connected?

A In the LVI field you have a number of players who have brought projects forward and Ypsomed is now working actively in this major new device class to compliment pens and autoinjectors.

So our device, YpsoDose (see Figure 3), is fully disposable, electromechanical, it has an auto-insertion needle mechanism, it has a glass container, prefilled with a sterile fluid path, and it is for 5 mL. We believe that there will be a need to develop a range of devices to cover the range of customers' volume requirements. We'll be presenting the first YpsoDose product at the PDA Universe of Prefilled Syringes & Injection Devices conference in California later this year.

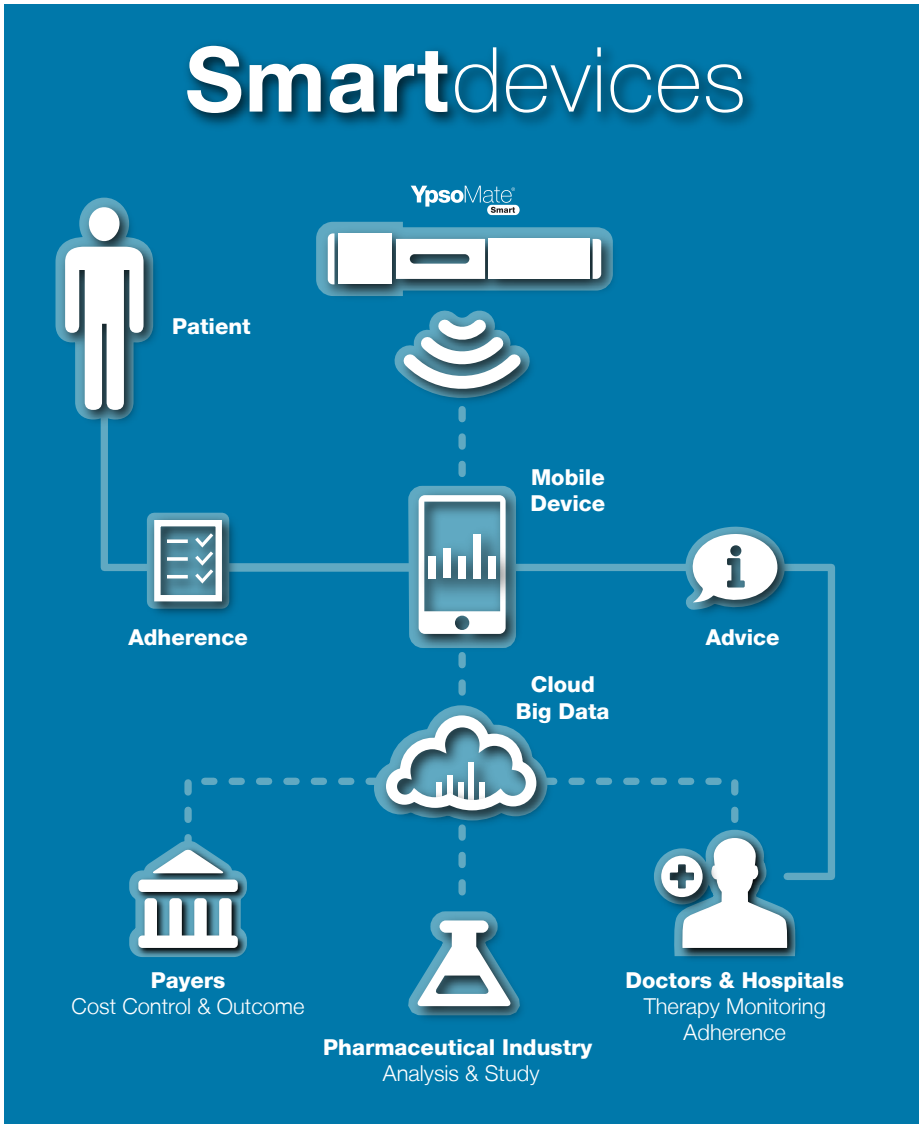

Figure 2: Typical architecture of how smart devices integrate into the complex healthcare environment.

The communication, connectivity, is of course an important element for YpsoDose. In the pump world, it is much easier to integrate communication technology into the device. Take our insulin pump, for example. It is called YpsoPump, and it is being launched imminently in 18 markets in 18 months. It's half the size of the Medtronic pump, has a touch screen, no letters, symbols only. It's a prefilled solution so it avoids cumbersome manual filling of insulin. In this pump, weighing 83 grams, there is of course a Bluetooth module integrated because in a pump there is enough budget to build in a really smart, robust and stable module, and there is space.

So for YpsoDose, it is optional to have the connectivity module inside. Whether or not it is included for specific products will depend on whether it really adds value to have the information about whether the patient has injected or not sent to the doctor or nurse. It depends on the therapy. If it is for a patient taking shots after chemotherapy then yes, the nurse wants to know. But for other diseases it is not useful that the doctor or nurse knows every day and every week whether or not the shots have been taken. It can be checked in a quarterly review. So it's really indication dependent but yes, of course YpsoDose has connected capability just as our YpsoPump does.

Q How do you see the future of self-injection systems moving forward?

A Earlier in the discussion I mentioned the different decades and different focuses and stages of development from the 1990s through to the 2020s. It is clear now in the industry that the next decade is about adherence. We have to achieve a situation where shots are taken. You know 70% of

Americans are not taking their insulin shots outside of home for various reasons – they might be ashamed, they might forget it, they might not care enough. This is traumatic.

The new products coming through are so user friendly they can be handled easily without a manual, without instructions – we have achieved that. So the next step is to motivate the patient. This can be achieved in several ways. One way is to automate, which, in the insulin world, is the discussion about closed-loop or semi-closed or smart loop systems. Also, looking at the longer term, on the sensor side, we are getting better and better with continuous sensing, which gives good enough data to, for example, at least to shut down the pump at night during a hypo, or to give more insulin during the hyper in the morning hours. There are some elements emerging here where automation is a way to achieve better adherence.

Then also of course, connectivity, the smart element, can be used to trigger the enhancement of the therapy. Parents will be able to see whether their child is taking their shots at school, and be able to send them a message or call them saying please take it. Eventually, and this is my hope, payers will be able to call up patients and remind them. In the US, for example, insurance companies might call a patient and tell them that they have not taken their shots and that they need to take them in order to remain in the plan.

Information being used to enhance adherence is the future, and for this we need to have the connected delivery systems available.

A crucial advantage Ypsomed has here is our true understanding of patients and our ability to learn important lessons from our B2C side and apply them in our B2B side, to be able to transfer elements from our diabetes business, where we are in close contact with patients constantly, to our delivery systems business.

The subject we touched upon earlier, of which players are going to be the ones to provide the cloud is also a very important one, I believe, for the future of the injection devices industry. I would really like to motivate the pharma industry to think about their role, about who plays what role. We talk to more than 100 pharma companies. Very, very few of them, less than a handful, have decided whether they want to be the one to have their own cloud. My wish is that out there in the industry there will be independent players to build the cloud. No-one is stepping forward and without the cloud we cannot progress. It is not simple to implement safe, secure worldwide data provision. You have to localise data. In some countries because of data protection laws you have to store data locally in national servers.

Somebody has to take up the job and to put the upfront investment into the cloud development. Without this we can talk about smart devices for a long time but it will not be safe to send the information via any normal protocol to some unknown server somewhere.

Figure 3: The YpsoDose large volume injector is is fully disposable, has an auto-insertion mechanism, has a glass container, prefilled with a sterile drug path, and it is for 5 mL but can be expanded up to larger volumes.

ABOUT...

Simon Michel, Chief Executive Officer of Ypsomed Holding AG and the Ypsomed Group, has been with Ypsomed since October 2006, member of management since 2008, and responsible for Marketing & Sales.

From 2003 until 2006, Mr Michel worked for Orange Communications AG in Zurich and Lausanne, where he was responsible for, among other things, the introduction and marketing of UMTS.

Mr Michel studied economics at the University of St Gallen, Switzerland, and completed a Masters with a focus on media and communications management. Since 2006, he has been a member of the Board of Directors of Sphinx Werkzeuge AG and since 2008 a board member of the Burgdorf-Emmental Trade and Industry Association. Since 2015, he has been a member of the Board of Directors of the Solothurn Chamber of Commerce, Chairman of the Industry Commission and a member of the Board of Directors of FASMED, the Federation of Swiss Medical Devices Trade and Industry Associations, as well as a member of further boards of trustees and advisory boards.

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ONdrugDELIVERY

ONdrugDelivery 2016/17 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
July 2016	Novel Oral Delivery Systems	June 13th
September 2016	Wearable / High Volume Injectors	August 1st
October 2016	Prefilled Syringes	August 29th
November 2016	Pulmonary & Nasal Delivery	September 26th
January 2017	Ophthalmic Drug Delivery	November 21st
February 2017	Prefilled Syringes	December 19th
March 2017	Skin Drug Delivery: Dermal, Transdermal & Microneedles	January 23rd
April 2017	Pulmonary & Nasal Drug Delivery	February 27th
May 2017	Injectable Drug Delivery: Devices Focus	March 27th
June 2017	Connected Drug Delivery Systems	April 24th
July 2017	Novel Oral Delivery Systems	May 29th