CONNECTING DRUG DELIVERY

ON drugDELIVERY

OUTSTANDING ISSUE SPONSOR

BIOCORP

BD

enable injections

flex

H&T PRESSPART

Medicom Innovation Partner
a Phillips-Medisize Company

NYPRO
A JABIL COMPANY

SHL GROUP

SONCEBOZ

YPSOMED
SELFCARE SOLUTIONS

JUNE 23RD 2017 • ISSUE Nº 76

PODD

MARRIOTT COPLEY PLACE, BOSTON, MA
OCTOBER 19-20, 2017

7TH ANNUAL

PARTNERSHIP OPPORTUNITIES IN DRUG DELIVERY

15% Off Registration

for ONdrugDelivery Readers

Coupon Code ODD

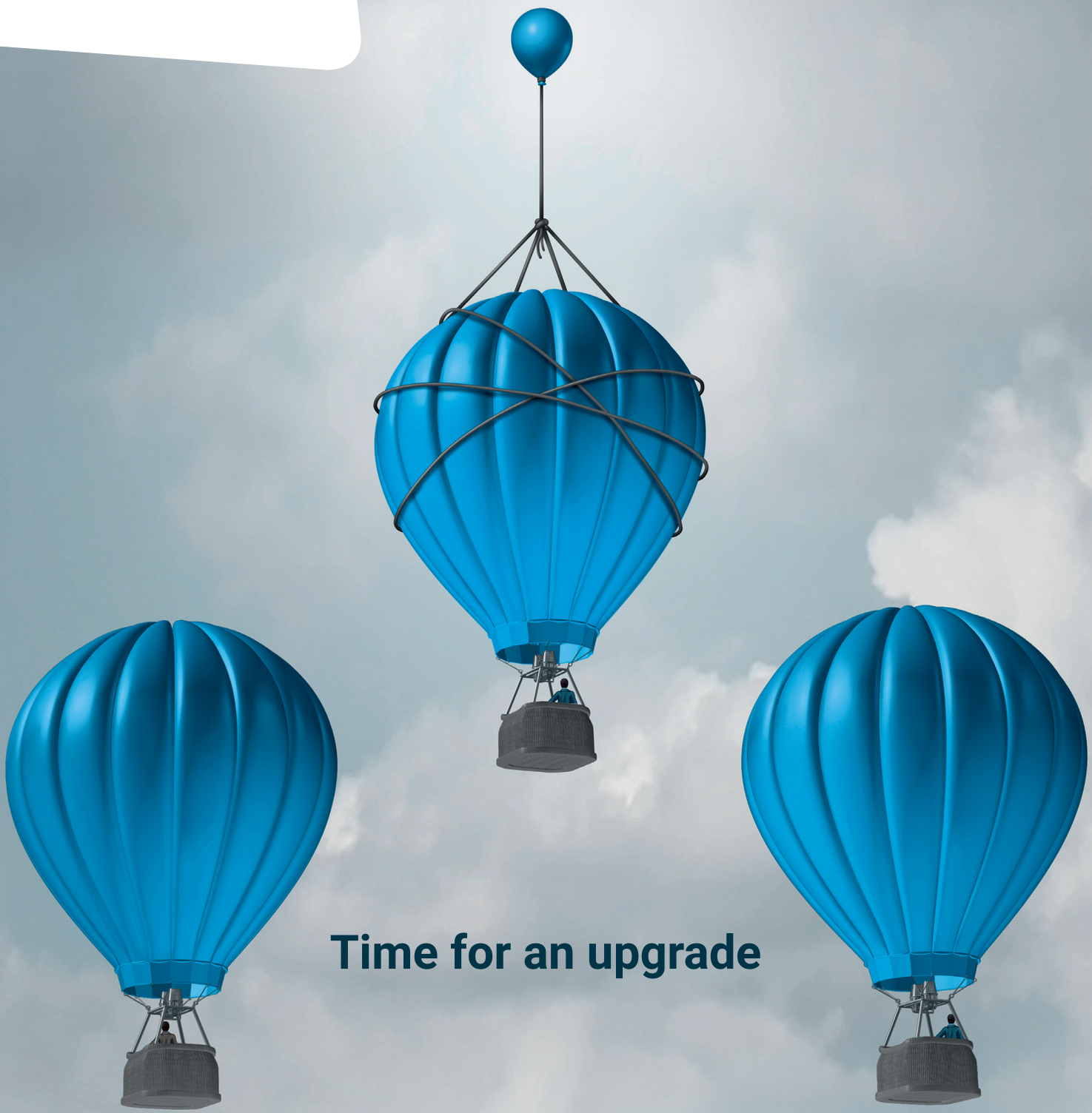
Register now at
www.theconferenceforum.org

Organized by
THEconferenceFORUM

Executive Sponsors
3M
BD
Advancing the world of health

BIOCORP

Design • Develop • Manufacture Medical Devices



Time for an upgrade

Give your existing device the benefit of connectivity.

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

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

ONdrugDelivery Issue Nº 76, June 23rd, 2017

CONNECTING DRUG DELIVERY

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

12 MONTH EDITORIAL CALENDAR

Jul	Novel Oral Delivery Systems
Sep	Wearable Injectors
Oct	Prefilled Syringes
Nov	Pulmonary & Nasal Delivery
Jan '18	Ophthalmic Delivery
Feb	Prefilled Syringes
Mar	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Devices Focus
Jun	Connecting Drug Delivery

SUBSCRIPTIONS:

9-10 issues of ONdrugDelivery Magazine published per year, in PRINT & PDF.
PDF subscription is always completely **free**.
PRINT subscription costs **£189/year**.
Print subscription includes delivery of a printed copy of each issue to one address anywhere in the world.
E: subscriptions@ondrugdelivery.com

EDITORIAL AND ADVERTISING:

Contact: Guy Furness, Proprietor & Publisher
T: +44 (0) 1273 47 28 28
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

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

ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd. Registered Office: The Candlemakers, West Street, Lewes, East Sussex, BN7 2NZ, United Kingdom.

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

ONdrugDELIVERY

NEW TECHNOLOGIES FOR LOW-COST CONNECTED DRUG DELIVERY DEVICES

Here, Charley Henderson, PhD, Applied Scientist and Electronic Engineer at PA Consulting Group, provides an overview of the various wireless connectivity options that are now available for devices and looks at how the corresponding electronic system costs can be reduced to drive widespread adoption.

The current high activity in reporting the development of connected drug delivery devices suggests it is a fast growing trend. Yet, whilst inhalers and auto-injectors are emerging that have electronics, sensors and communications built in to monitor how patients use them, we are far from these items being prolific in the market. This is true across multiple sectors. As designers of new products, we see a growing aspiration to connect ever more categories of device.

One of the key challenges for widespread adoption in drug delivery applications remains the cost effective integration of simple to use electronic communications systems. This is because delivery devices are currently simple, mechanical and made at low cost in extremely high volumes.

In terms of cost, electronic hardware does not come for free. The price of even simple wireless modules can exceed that of the mechanical parts of an inhaler or auto-injector by an order of magnitude. This is a significant challenge for the business case, and may require different business models to realise the value.

Secondly, a standard printed circuit board assembly does not naturally integrate into an existing device design as a retrofit; and add-on housings add bulk and cost.

Lastly, connecting to any existing wireless network generally involves pairing processes, passwords, apps and/or subscriptions. These may detract from the reliability and usability of the system for the patient.

New Technologies Address the Challenges

The good news is that there are new technologies emerging. We are frequently challenged to develop novel connectivity solutions for medical, consumer and industrial products alike. Whilst every product has unique requirements and the solution needs to be customised, in this article we describe some of the key enabling technologies we envisage for future drug delivery applications.

MAKING CONNECTING EASIER

Whilst it may seem obvious, wireless communications require two ends to the link. One side needs to be on the device which sends and/or receives the information. The second matching side of the link needs to bridge the data into the cloud where the data can be stored and presented back to engage patients, caregivers and other stakeholders.

There are clear cost benefits to using infrastructure that already exists as the second side of the link; rather than making and servicing a separate hub. And this second side of the link is now available almost universally to consumers through smartphones and telecommunications networks.

However, this reduces the solution space to the standards supported by these existing devices. Namely near field communication (NFC), Bluetooth and cellular, of which Bluetooth is currently the leading choice in drug delivery.

The issue is that none of these technologies were necessarily developed for the connected device applications we are considering, and this poses some practical issues. The trade-off is illustrated in Figure 1.

> "One of the key challenges for widespread adoption in drug delivery applications remains the integration of electronic communications systems into the devices."

Dr Charley Henderson
Applied Scientist and Electronic Engineer
T: +41 61 277 22 00
E: Charley.henderson@paconsulting.com

PA Consulting Group
Aeschenvorstadt 71
4051 Basel
Switzerland

www.paconsulting.com/technology-and-innovation

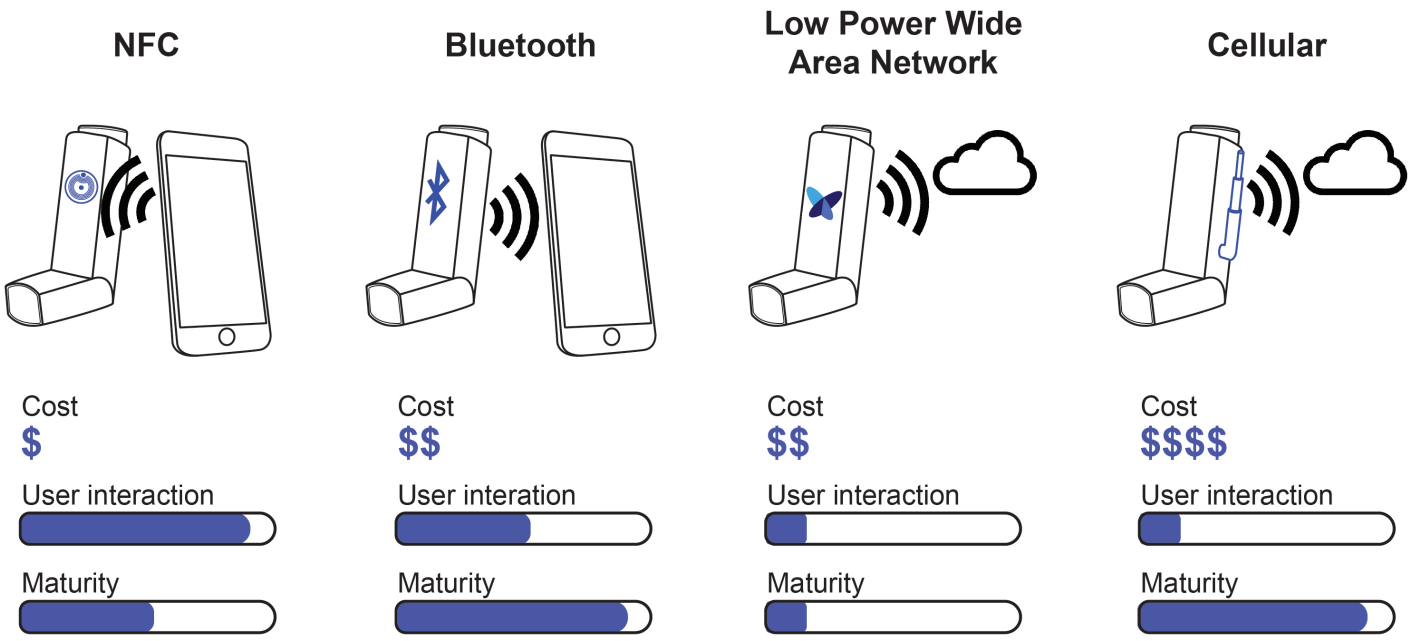


Figure 1: Wireless connectivity options.

Near Field Communications

NFC connects two devices over a very short distance, of the order of about 1 cm, using coil antennas. The key advantage is that one side of the link can be extremely simple and low cost because the other side of the link, or reader, provides the power supply and reference oscillator. The simplest example is a passive HF RFID tag that returns a pre-programmed number, and this is one of the only electronic systems that is truly cost optimised for disposable applications. However, sending back data from a sensor or other electronic system on a drug delivery device can equally be done, and single NFC chip solutions are emerging to do this.

Practical usability issues remain. Firstly users will always need to read data from the device by holding their smartphone close to it, having installed an app. The interaction is similar to contactless payment and in the best applications may form an integral part of the patient engagement. However, as such, it requires patient compliance to work, so is unlikely to cover all incidences of non adherence. Furthermore, NFC is not yet available for this type of application on all smartphones, although this is likely to change.

Bluetooth

Bluetooth is one of many short-range digital RF communications standards that operate over ranges of 10-100 m, and has the benefit of being readily available on smartphones. This makes it a leading candidate for connected health solutions that use smartphones to engage patients. Whilst component costs are greater than for NFC, this is in part because component solutions have not been optimised for low-cost, simple, disposable devices.

Ongoing patient action is still required to make it work. At the present time, using Bluetooth to communicate with a drug delivery device is likely to require the user to install an app on the corresponding phone, and to keep it in range with this app and the Bluetooth function running when the device needs to communicate.

At this point, it is worth ruling out WiFi for low-cost applications. As a widely available short-range network, it doesn't have the restriction of needing to keep apps running on a phone. However, it is a complex protocol optimised for high bandwidth – this means it is fundamentally inconsistent with a small, low-power, disposable device in terms of hardware cost, power and size.

The middle ground, however, may be the integration of Bluetooth into WiFi routers. This technically may not be a big step as the two standards use the same frequency. This would address the challenge for many Internet of Things (IoT) applications, and dedicated Bluetooth routers are already emerging.

Cellular

Using a cellular network has the advantage that, in principle, a product can be supplied that communicates reliably, without any action or infrastructure required of the user. Cellular networks are commonplace, and commoditised modules are available for around US$5, though a substantive power source and network subscription is also required – making it impractical for most disposable drug delivery devices.

> "Innovative approaches here include using the microphone and processing capability of the smartphone to listen for specific sounds that a drug delivery device is engineered to make."

Low Power Wide Area Networks

There are a number of new players looking to develop public networks specifically designed for large numbers of low-power, low-cost devices that send small amounts of data. This, in principle, could be ideal for connected drug delivery device applications.

There are several network services emerging at various stages of development, including SigFox, LoRa and narrowband IoT solutions from cellular providers. None yet have universal coverage, but it is definitely one to watch for future product iterations. This is particularly true if, as seems possible, the device end hardware could be comparable in cost and size to a current Bluetooth solution.

Figure 2: NEXThaler®: example of device connected to smartphone via non-electronic, audio communication. The app was developed by PA Consulting Group.

Acoustic or Visual Communications Using Smartphones

There are non-electronic means to connect devices with smartphones. Innovative approaches here include using the microphone and processing capability of the smartphone to listen for specific sounds that a drug delivery device is engineered to make. This is particularly applicable to inhalers. Figure 2 shows an example app we have developed, where the inspiratory flow profile from a specific inhaler is monitored acoustically.

Furthermore, the smartphone camera can be used to image and verify use of devices with mechanical visual indicators.

None of these solutions are more reliable, robust, or easier to use than the wireless approaches. But they are potentially useful for low-cost applications in the short term.

ALTERNATIVE INTEGRATION OPTIONS TO RIGID BOARDS

Conventional electronics assembles the main communications components onto a rigid, fibreglass, printed circuit board (PCB)-based module. This needs to connect with the mechanism so that it can, at a very minimum, detect actuation of the device. Integration into a device is the most effective way to achieve this. However, this adds bulk and assembly time/complexity at best. In the case of existing products, this typically requires either re-design or the addition of a costly add-on assembly from which sensing is non-trivial. Furthermore, all this has to be achieved without impacting performance of the device/system.

There are, however, alternatives that may both make integration more straightforward from a design perspective, and reduce overall costs (Figure 3).

Smart Label on a Flexible Substrate

Electronic systems can be assembled onto flexible substrates, which could, in principle, be applied to the inside or outside of the device casework in the form of an adhesive sticker, removing the need for significant internal feature design and assembly steps. The simplest existing example of a mature product that does this is an RFID tag sticker.

Flexible circuit assemblies are an established technology, using polyamide substrates that can withstand the high temperatures of the soldering process. Lower cost approaches using printed electronics are also on the horizon.

The simplest sensor in this case is an electrical track in the label that gets broken by a binary event (e.g. removing the cap), causing the event to be detected by the system. However, integration of switches or other sensors is also possible.

Moulded Interconnect Device (MID)

The integration of conducting tracks onto the surface of injection-moulded plastic parts is a relatively established technology, for applications such as mobile phone antennas or automotive switches. Advantages include removing the need to run wires or integrate metal parts to make switches, and ultimately the opportunity to make the existing substrate the circuit carrier, and place components directly, thus removing the PCB.

Given that many simple drug delivery devices are made from injection-moulded plastic parts, MID technology may be one route to integrate the sensing system with the rest of the device, without the need for PCBs and wiring.

COST OF CONVENTIONAL PCB-BASED ELECTRONICS

Conventional architectures and PCB-based electronics assembly approaches are unlikely to enable drug delivery device connectivity solutions for significantly less than the order of several dollars. Indeed, $5 for an assembled product is low cost for the electronics industry, and we don't think this is going to change easily.

Conventional printed circuit board and component-based electronics have evolved to become a standardised,

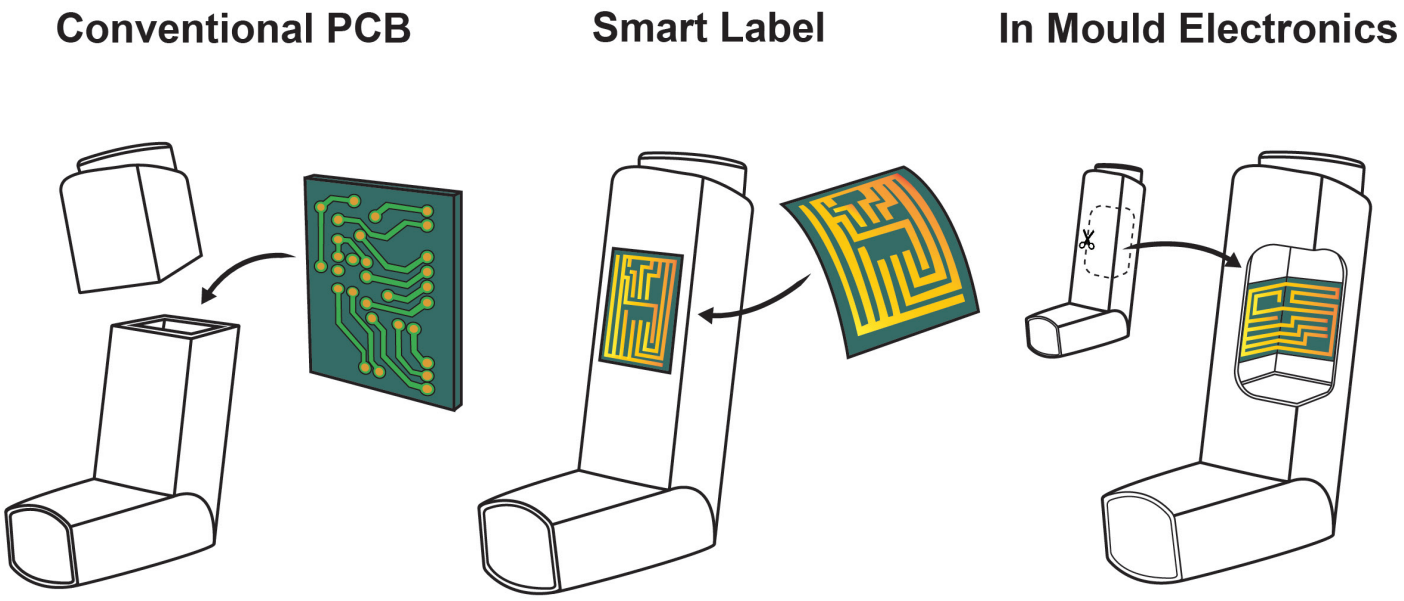


Figure 3: Approaches to the integration of electronics within devices.

sophisticated, automated and reliable means to mass-manufacture a diverse range of electronic systems. However, to achieve this, any product manufactured through it has an extensive supply chain and a number of manufacturing steps.

A simplified list, for purposes of illustrating the number of different steps and processes which contribute towards the cost, is as follows:

- **Component manufacture:** Standard components are manufactured using a wide variety of sophisticated processes and materials. They are placed into reels, and sourced through a supply chain. A typical board design may include tens to hundreds of parts.
- **Board assembly:** The PCBs are screen printed with solder paste. A bespoke set of component reels are loaded into a pick and place machine, the design is programmed in, and the components placed on each PCB. It is then placed through an oven to solder the components down. The process may be repeated on two sides.
- **Test:** Manufacturing errors do occur, and a test process may include both optical inspection, and functional test through loading the board onto a "bed of nails" test fixture.
- **Box build:** Boards are assembled into caseworks, and manually connected with any external wires required, e.g. to sensors in locations that are not on the board and planar.

Historically, the cost of electronic products has reduced whilst function has increased. This, however, has been largely driven by reductions in the cost of integrated circuit components (chips), driven by Moore's Law (the observation that the number of transistors in a dense integrated circuit doubles approximately every two years). However, the chip cost in a simple connectivity solution is only a small component of the total cost. The rest are commodity parts and assembly steps which are unlikely to change.

Taking the example of assembling a Bluetooth transceiver into a device, an approximate build-up of the cost is shown in Figure 4. The vast majority of these costs are commodity components or assembly steps that are well optimised and unlikely to achieve significant further reductions. The vast majority of these parts are commodity components or assembly steps that are not seeing significant reductions.

We therefore believe that a step change in the means of manufacture and assembly is needed. Furthermore, we see opportunities to do this through printed and flexible electronics.

PRINTED & THIN FILM ELECTRONICS

We see technologies to assemble electronic systems on low cost flexible substrates, and the printing of some of the components, as key enabling technologies to significantly reduce the costs of simple disposable systems.

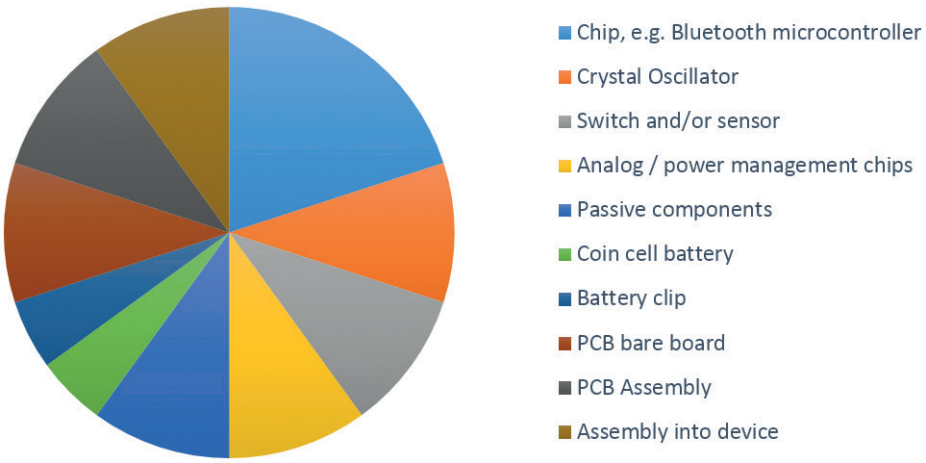


Figure 4: Approximate distribution of costs in a simple Bluetooth Low Energy (BTLE).

In this type of system, tracks are deposited or etched directly onto a low-cost substrate, and components mounted using low-temperature bonding techniques. In principle, this can be applied in a high-speed, roll-to-roll process. And, as the technology evolves, an ever greater proportion of components will be able to be printed.

For example, processes to print conductive tracks, passive components and batteries are increasingly well established; whilst technologies to print simple sensors, displays and transistors are demonstrated. Furthermore, where parts cannot be printed, they could in principle be integrated into a single custom chip (ASIC), minimising the component count.

This takes electronics much closer to printing and laminating technologies in terms of process.

Applying this to the cost breakdown for a wireless module in Figure 4, by removing or reducing costs for PCBs, clips, passive components and assembly, the total could be significantly reduced when extrapolated to high volumes – closer to $1 than $5 in principle.

The leading example of devices currently made in this type of process are HF and UHF RFID tags. These comprise a single, ultra-low-cost, silicon die mounted on a low-cost flexible substrate (e.g. PET), with printed or etched metallic tracks to form the antenna. They are made in high-speed processes, optimised for this specific type of product. The simplicity of the design, optimised process and low-cost materials enables them to retail for costs sometimes below $0.10 from commodity suppliers.

The principle of applying the same type of assembly process for more sophisticated systems has already been demonstrated. Examples include time temperature labels with printed tracks, batteries and displays. However, these have yet to make it into high volume, mass market, low-cost applications.

Scale-up of the volume manufacturing process to realise the cost benefits is still underway and needs market demand to drive investment. However, as a part of a product roadmap, this potentially offers device makers a route to significantly lower cost connected products in the longer term (Figure 5).

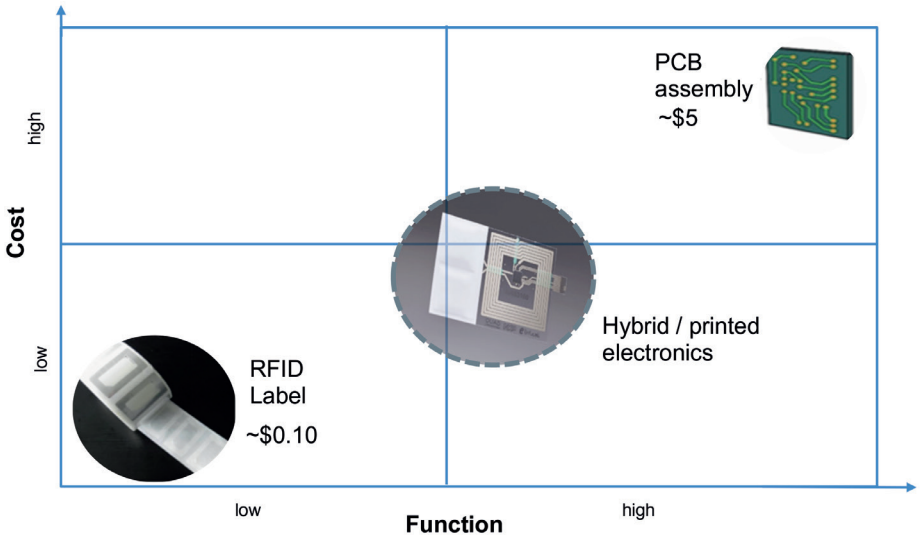


Figure 5: Cost versus function for different electronics assembly approaches. (Hybrid / printed electronics image (centre) Copyright © 2017 Quad Industries. Reproduced with kind permission.)

CONCLUSION

Smart connected drug delivery devices are starting to make it to the market, and for the immediate future these are likely to comprise the integration of Bluetooth and NFC modules at a cost of several dollars.

For the right application in which these connectivity and cost points are acceptable, this creates a useful platform technology upon which to build the complete solution, which includes the app and IT components; and together to demonstrate benefits such as improved patient adherence.

The proposition, however, becomes even stronger as there is a clear line of sight to much larger scale market applications, enabled by reduced costs, ease of integration into devices, and seamless communications. This is not unrealistic. Many of the new technologies to enable this are relatively advanced in development, but are awaiting scale-up.

PA therefore believes that the opportunity now exists for device makers to build this line of sight into their development roadmap. Through this, device architectures can take account of these technologies. Crucially, the strategic investment in specifying, designing and scaling up the new electronic subsystems, as well as building the necessary supplier relationships, can start now.

ABOUT THE COMPANY

PA Consulting Group is an independent firm of more than 2,600 people, operating globally from offices across the Americas, Europe, the Nordics and the Gulf. The company's areas of expertise include consumer and manufacturing, defence and security, energy and utilities, financial services, government, healthcare, life sciences, and transport, travel and logistics. PA combines industry knowledge with skills in management consulting, technology and innovation, which it believes allows it to challenge conventional thinking and deliver exceptional results that have a lasting impact on businesses, governments and communities worldwide.

ABOUT THE AUTHOR

Charley Henderson is an applied scientist and electronic engineer at PA Consulting Group, with a strong track record in creating and delivering technically demanding products for medical and consumer applications. He has a particular interest in low-cost and low-power connectivity solutions for IoT applications, drawing on significant experience developing sensors, wireless and embedded electronic systems. Henderson holds a PhD in Photonics, MEng in Electrical and Information Engineering, is a Chartered Engineer, and member of the Institution of Engineering and Technology (IET) and the Institute of Electrical and Electronics Engineers (IEEE).

ARNAUD GUILLET, BIOCORP

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

In this interview, Mr Guillet discusses Biocorp's existing connected device offering, how it delivers value for the company's pharmaceutical partners, the development of the accompanying software and data architecture, and how Biocorp has very significant opportunities to leverage its triple expertise in medical devices, electronics and software further.

Q Starting with some background on Biocorp's business, please could you broadly describe Biocorp's connectivity offering specifically in the context of Biocorp's overall business model and commercial strategy?

A Biocorp offers two types of connected solutions, integrated solutions and what we call add-ons.

Integrated solutions are actual drug delivery devices natively connected, developed from scratch, and their form, shape and process are like regular products on the market, but they incorporate electronics and can communicate treatment information in real time to a mobile app or data platform.

Add-ons are smart sensors that can be attached to regular devices on the market, turning them into connected products. Typically these require no modification to the existing devices and have no impact on the regulatory and industrial processes.

On the device side, our strategy is to develop mature technical products and then we customise these products based on our partners' needs and the specific requirements of each pathology. We handle the full development of the device from conception to final validation, and we manufacture and assemble the products in our facilities.

For the software side, we are highly flexible. Depending on the requirements of our partners, we can either undertake the development of the software ourselves, using our own architecture. Or we can connect our devices to existing data platforms or apps. In both cases, Biocorp's software teams are highly involved of course to ensure that, for example, data transfer, storage and access are secure, continuous and accurate.

> "You can boost usage further by working on interoperability with other successful digital platforms, which automatically maximises the benefits of connectivity."

We already have several development programs in motion using our proprietary technologies with major pharma and biotech companies.

Q Biocorp is developing connectivity technology across both the parenteral and respiratory areas. Please could you tell us about what you are doing in each of these two areas, what technologies are you developing?

A In the parenteral area we have two main products. The first is the Datapen® (Figure 1), a re-usable electromechanical pen that uses standard cartridges. In terms of usage, it's like a regular pen although we offer additional functionalities to guide the patient. All treatment information is recorded and automatically transmitted to a mobile app via Bluetooth. This brings additional benefits beyond connectivity. For instance, electromechanical injection allows highly accurate dose delivery and additional comfort and stability for the patient. Thanks to the screen, we can provide visual information to guide the patient and indicate the process step by step.

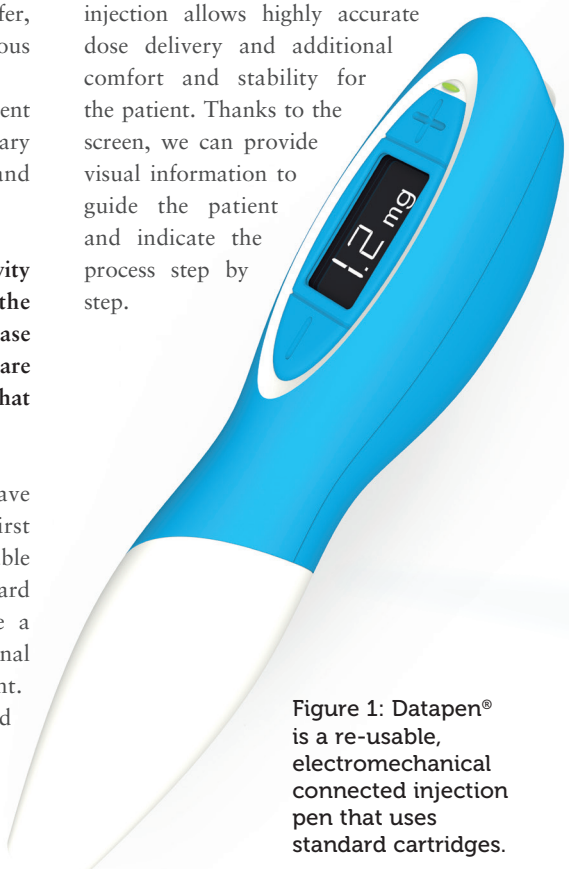


Figure 1: Datapen® is a re-usable, electromechanical connected injection pen that uses standard cartridges.

Our second parenteral product is the Easylog® (Figure 2). This is an add-on solution that quickly brings connectivity to regular pen injectors. It can be adapted to any pen injector on the market, whether disposable or re-usable. The patient attaches Easylog® to the pen and it automatically records each injection – the dose, time and date – and transfers that information in real time to the mobile app. It's really about automatic transferability, with very high accuracy levels. It's seamless and effortless for the patient, who can keep their existing device yet benefit instantly from connectivity features. It's also very easy to implement for pharma companies because it does not impact on existing devices and does not require any significant change for the regulatory and industrial process.

Easylog®, which can be customised to fit requirements, is already at an advanced stage of development thanks to several partnerships in different therapeutic areas.

On the inhalation side, we recently launched Inspair® (Figure 3) which is a smart sensor for inhalers that not only records each delivery of the dose, but also monitors hand-breath co-ordination for proper inhalation technique, and it also provides feedback to patients about their technique. Therefore it's designed not just as a treatment monitoring solution but as an education tool to highlight the importance of inhalation technique, which is a key factor when it comes to inhalers. Each inhalation curve and application of pressure on the canister (to actuate the dose) is recorded and displayed on a dedicated mobile app so the patient can check if their co-ordination was optimal.

Figure 2: Easylog® is an add-on solution that quickly brings connectivity to any regular pen injector, whether disposable or re-usable.

"Another very important point, sometimes forgotten, is about supporting adoption of digital tech by pharma, especially the with regard to the data. This is not their environment, they are not digital data companies. All of this real life data can be extremely valuable for pharma."

Figure 3: Inspair® is a smart sensor for inhalers that records each dose delivery, monitors hand-breath co-ordination and provides feedback to patients on technique.

Q **In the past, the drug delivery business had a tendency to become segmented into different classes of delivery system or different technologies that address specific routes of delivery, often with little interaction between the different sub-disciplines. Connectivity cuts across these divisions, with Biocorp – working in both parenterals and inhalables – representing a prime example. I wondered if you could talk a little about the similarities, and the differences, when it comes to connectivity technology for the parenteral and respiratory sectors?**

A Of course all connected devices are facing some very similar challenges. We're talking about improving treatment adherence and patient experience. This can only be achieved by designing solutions that easily integrate, facilitate treatment monitoring and help patients to use their device properly. This is why at Biocorp we have always developed our devices with this type of benefit in mind – accurate and automatic tracking solutions plus the guarantee of proper use of the device.

For all therapeutic areas you need to record every dose delivery together with the time and date. You need to set up reminders to avoid missing doses, and provide guidance to ensure full patient engagement. I think this is a key part of any connected offering, across all therapeutic areas.

But of course you also need to consider the different requirements from one pathology to another. This is why typically we have a platform and know-how about gathering information from existing devices and we are leveraging this platform for bioscience applications.

Parenteral and inhaled products have different requirements and so for each pathology we prioritise the functionalities that matter to patients and healthcare practitioners (HCPs). For example, in the injection field, accuracy of delivery and precision of information recorded is a key topic. This is why we designed the Easylog to record the exact dose delivered automatically. On the other hand, for inhalable drugs, rather than very precise

recording of the amount of drug delivered, the key challenge is more about inhalation technique and proper use of the device. So this is why Inspair™ records pressure on the canister, and the inhalation curve, to support patients in their use of their inhalers.

When it comes to connected solutions, you don't want the patient to be overwhelmed with information. You start from a common basis and then put in only the key functionalities that bring true value to the patient.

Q I have heard it said several times by people working in the industry that adding the communication tech itself to drug delivery devices is the "easy" part of creating a connectivity offering. To what extent do you agree with this? What do you think are the most challenging aspects, and how does Biocorp differentiate itself from others in the space as it meets those challenges?

A It's an interesting remark and I would say that I only partially agree, because of course there are many challenges beyond the communication tech itself, for instance software development, data and apps, patient adoption, pharma adoption as well. However, the communication tech itself can be challenging because it implies changing the initial device somehow, a device with which the patient is already familiar, which regulatory approval has been obtained, and for which an industrialisation process has been built.

It's quite challenging to add this communication tech with minimal impact on the patient (same user process, same number of steps etc). And you must not impact the regulatory pathway, nor the industrial process. So if we're talking about a connectivity integrated device, for example a re-usable pen injectors, you need to make this compatible with standard cartridges. It also needs to be as close as possible to the shape and process of existing devices. Similarly for add-ons, these must not affect the device usage and must not come into contact with the drug, and they must guarantee discreet and elegant integration. Once they are on the device, there must not be any additional use steps.

All of this has to be kept in mind when integrating the communication tech, and this is why Biocorp can leverage its 20 years of experience in the development and manufacture of medical devices. We're familiar with all these requirements. We are also pioneers in electronic and connected solutions and we know all of the criteria we need to meet to integrate the tech with the medical device.

Once you have successfully integrated the tech, then you have to take care of the software. There are essentially two aspects of the software, the data and the app. For the data you must guarantee 100% data security – this is crucial for patients, HCPs and regulators. Once the data leaves the device it must be encrypted and transferred to the data platform located in a certified data hosting server. No data should be stored on the smartphone and patients must be authenticated before accessing their information through the app. If pharma wants to access their patients' data, they must be anonymised and delivered in a statistical format.

For the app, you have to design an easy-to-use, highly visual and intuitive app with only the most valuable functionality for the patients. The design is really crucial for us, and we ultimately guarantee sustainable usage over time.

When these first two steps have been completed successfully – seamless communication tech integration with the delivery device, and the software and app with relevant content – you can foresee good patient adoption. Then you can boost usage further by working on interoperability with other successful digital platforms, which automatically maximises the benefits of connectivity.

Another very important point, sometimes forgotten, is about supporting adoption of digital tech by pharma, especially the with regard to the data. This is not their environment; they are not digital data companies. All of this real life data can be extremely valuable for pharma, but there are two challenges that you need to have in mind: access to data and capacity to exploit data. Pharma are not allowed to access personal data. Therefore, Biocorp has developed a data processing system to anonymise and deliver data to pharma companies in a statistical format, which is exploitable by pharma. We then work with

"Pharma are not allowed to access personal data. Therefore, Biocorp has developed a data processing system to anonymise and deliver data to pharma companies in a statistical format, which is exploitable by pharma. We then work with the pharma data teams on the best way to optimise the analysis and exploitation of the data. We make sure that they are using this goldmine of real life data."

the pharma data teams on the best way to optimise the analysis and exploitation of the data. We make sure that they are using this goldmine of real life data.

Q Whilst connectivity is certainly emerging rapidly and very strongly in the drug delivery business (and elsewhere), careful attention needs to be paid to the value proposition. "Connectivity for connectivity's sake" is not enough. What is Biocorp's value proposition to the industry?

A We're working, together with our pharma partners, to develop the best solutions tailored for specific business cases. Improving clinical outcome is the final objective but different ways are open to reach that goal and different steps to climb. First, have the patients equipped with the system, then be sure they will use the device in the long-run by working on the user experience and the benefits the user can gather from using the technology. Then ensure that the pharma company can achieve a return on investment in the technology. This could be from improved clinical outcomes and/or better adherence, better quality of life.

Q Finally, I wondered if you could tell us what lies ahead for Biocorp in the short, medium and longer term? What are the general trends and drivers impacting on the business, any short-term upcoming milestones, and any longer-term business objectives and strategy goals?

A In the short-term we already have exciting ongoing partnerships with pharma companies for our current line of products in various therapeutic areas including diabetes, growth hormones, Parkinson's disease, rare diseases, asthma and COPD, so we would like to keep expanding into the many additional therapeutic areas where our products are applicable, and keep increasing their potential through various partnerships in terms of functionality, desirability, and design etc.

Beyond our current line of products, we want to use our triple expertise – in medical devices, electronics and software – to support our customers in their future projects. Whatever the product, the packaging, or the delivery system, we can design and build a connected solution. We are reviewing the potential of many different types of drug delivery system, beyond inhalation and injection, there are a lot of companies coming to us with projects involving different delivery systems and this is really exciting for us and somewhere we can identify many new opportunities. We already answer specific needs and we have some specific *ad hoc* projects in the pipeline, and we would like to continue doing this.

In the long-term, Biocorp's DNA is obviously innovation so we invest significantly in R&D to anticipate future needs and develop solutions to meet these needs in various therapeutic areas.

In parallel to all of these efforts we're building a network to guarantee sustainable use of the connectivity features we develop. We're continually working on our compatibility and our interoperability with existing and emerging digital platforms to make sure patients using our devices can maximise the connectivity benefits. One of the possibilities is to cross over information, for example. So we ensure that our apps and platforms will not be isolated from the digital healthcare ecosystem but, on the contrary, highly integrated with it, which can guarantee usage and success over time.

I believe we are right at the beginning of the wave of connectivity in this area and maybe, in ten years' time, every type of delivery system will somehow be connected.

"We're continually working on our compatibility and our interoperability with existing and emerging digital platforms to make sure patients using our devices can maximise the connectivity benefits. One of the possibilities is to cross over information, for example. So we ensure that our apps and platforms will not be isolated from the digital healthcare ecosystem but, on the contrary, highly integrated with it, which can guarantee usage and success over time."

ACKNOWLEDGEMENT

Arnaud Guillet would like to acknowledge the invaluable assistance of Eric Dessertenne, Biocorp's Chief Operating Officer, in the preparation for this interview.

ABOUT THE COMPANY

For 20 years, Biocorp has been designing, developing and manufacturing medical devices for the pharmaceutical industry, enhancing drug reconstitution, safety, packaging and delivery. Today, Biocorp continues to innovate in medical plastics, bringing new solutions to the market such as the Newguard™, an integrated passive safety system for PFS compatible with nest, and the Biopass, a reconstitution system with an integrated needle ready to inject.

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

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

BIOCORP

Arnaud Guillet
Business Development Associate
T: +33 6 48 28 51 16
E: aguillet@biocorp.fr

Contact:
Eric Dessertenne
Chief Operating Officer
T: +33 6 08 02 14 51
E: edessertenne@biocorp.fr

Biocorp
Parc Technologique
Lavaur-La-Bèchade
63500 Issoire
France

www.biocorp.fr

HOW CONTEXT & CONNECTIVITY CONTRIBUTE TO A FULL PICTURE OF HEALTH

In this article, Erika Vazquez, Marketing Associate, MC10, shows how recent technological advances make it possible to gather detailed contextual data about patients and gain true insights into whether their treatments are genuinely improving their quality of life, using examples of recent industry collaborations to highlight how pharma companies are already moving rapidly in this direction.

In a study evaluating the effectiveness of a drug designed to control heart rate, monitoring a subject's pulse over a period of time will undoubtedly help answer the primary question: is the drug effective at controlling the patient's heart rate?

While the answer to that primary question may be yes, researchers must consider what else happened while the patient was being treated with the drug. Perhaps the subject's heart rate was well controlled, but the subject became more sedentary and less active. Or perhaps the subject experienced increased restlessness during sleep. The heart rate might be controlled, but that doesn't mean the treatment is successful. Without the surrounding contextual data, comprehension of a subject's response to treatment is incomplete.

As the US healthcare system becomes increasingly outcomes based and accountable, evaluating therapeutic efficacy requires researchers to consider the bigger picture of a subject's health. In the past, the data available to a physician was limited to the information that could be gathered through a patient history, physical exam, and lab tests. An evaluation of health was limited to a snapshot of one tiny moment in time. For example, a cardiogram takes six seconds to acquire, but there are 86,400 seconds in a day.

Today's technology provides the opportunity to examine those other 85,394 seconds to find the problem. With the help of wearables and novel data-capture tools, we can now look at efficacy over time as we observe the patient in their daily life (Figure 1). These healthcare data collection devices provide a much more accurate and complete assessment of compliance and medication efficacy. The modern day ability to look at a patient's data within the context of their own natural habitat, for example their work, school or home settings, provides a level of validity that simply is not attainable in the artificial environment of the doctor's office.

From academia to pharma, wearables are providing robust physiological data to reach study conclusions. As Validic (Durham, NC, US), a provider of digital health data analysis solutions, points out, activity and sleep data collected by wearables[1] can help trial sponsors to "uncover important patterns such as a participant being less active on days that a medication dose is missed or a participant sleeping more after taking the medication, indicating drowsiness as a possible side effect". This contextual data also serves as a "useful indicator of behavioural health, providing researchers with a more objective means to understand how a participant may be feeling while taking a drug".

In Pfizer and IBM's Project Blue Sky Initiative to study Parkinson's disease progression with wearables,[2] multiple metrics matter. "IBM and Pfizer aim to get a more holistic view of the patient by measuring a number of health metrics, including motor function, dyskinesia, cognition, sleep, and various daily activities," MobiHealth News reported.

> "A cardiogram takes six seconds to acquire, but there are 86,400 seconds in a day. Today's technology provides the opportunity to examine those other 85,394 seconds."

Ms Erika Vázquez
Marketing Associate
E: evazquez@mc10inc.com

MC10, Inc
10 Maguire Rd
Building 3, 1st Floor
Lexington
MA 02421
United States

www.mc10inc.com

Figure 1: With the help of wearables and novel data capture tools, we can now look at efficacy over time as we observe the patient in their daily life.

> "Activity and sleep data collected by wearables can help trial sponsors to "uncover important patterns such as a participant being less active on days that a medication dose is missed or a participant sleeping more after taking the medication, indicating drowsiness as a possible side effect."

When mobile apps and wearables are used as complementary tools in research studies, the full potential of connectivity and context becomes attainable. Apps encourage compliance through reminders and can easily collect subjective data from study participants, providing the context to understand fully the targeted and accurate physiological data wearables capture.

Oklahoma State University (Stillwater, OK, US) researchers evaluated the feasibility of a novel methodology for assessing "physiology, behaviour, and psychosocial variables". The study used two objective sensors (a BioHarness (Zephyr, Annapolis, MD, US) and a wActiSleep-BT monitor (ActiGraph, Pensacola, FL, US)) and a mobile app to monitor each subject's daily routine over a 20-day period.[3] The results suggested that wearable sensors combined with ecological momentary assessment technologies (in this case, app questionnaires) are capable data-generating tools for developing "dynamical systems models of high value health behaviours such as sedentary activity, moderate to vigorous physical activity, sleep, and diet". Additionally, results indicated that "a wearable sensor holds promise for linking subjective feeling states with physiological data and has the potential for informing intervention development".

Takeda USA (Deerfield, IL, US) and Cognition Kit (a joint-venture between Cambridge Cognition (Cambridge, UK) and Ctrl Group (London, UK) are "collaborating on a study to assess whether mobile apps and wearables with continuous monitoring capabilities can be used to glean new insights into major depressive disorder[4] that could drive better treatment."

The Cognition Kit app collects physiological data and evaluates cognition. MobiHealth News explained that the study aimed to "use continuous monitoring to catch under-recognised symptoms of major depressive disorder, thereby providing a more holistic view of the user's mental health".

For GlaxoSmithKline's clinical trial leveraging Apple's ResearchKit to study rheumatoid arthritis,[5] the company focused on "asking patients the right questions". GSK Chief Medical Officer Murray Stewart told Clinical Leader, "Carrying that a step further, we also know rheumatoid arthritis patients can be prone to suffer from depression. Designing questions that deal with depression can also be recorded on the app and allow researchers to better understand the patients and data. This will help researchers to get a more holistic view of the health of a patient."

By utilising mobile technology and wearables, researchers gain a comprehensive overview of subjective and objective data that was previously unattainable. Success is no longer measured by assessing if drugs and procedures do what they are supposed to, but by measuring whether or not the patient is better for it. Evaluating contextual data helps to measure therapy success through the lens of quality of life.

This article is based on the author's March 2017 blog item "The Value of Contextual Data in Health Monitoring".

REFERENCES

1. *Plumer J, "Wearables in clinical trials: it's about correlation and context". MobiHealthNews, October 10, 2016.*
2. *Pai A, "Pfizer, IBM partner to create wearable sensors system to study disease progression in people with Parkinson's". MobiHealthNews, April 7, 2016.*
3. *Brannon E et al, "The Promise of Wearable Sensors and Ecological*

Momentary Assessment Measures for Dynamical Systems Modeling in Adolescents: a Feasibility and Acceptability Study". Transl Behav Med, 2016, Vol 6(4), pp 558-565.

4. *Mack H, "Takeda and Cognition Kit partner for Apple Watch-based study on depression". MobiHealthNews, February 27, 2017.*
5. *Miseta E, "GSK Uses Apple ResearchKit in Rheumatoid Study". Clinical Leader, February 21, 2017.*

"Success is no longer measured by assessing if drugs and procedures do what they are supposed to, but by measuring whether or not the patient is better for it. Evaluating contextual data helps to measure therapy success through the lens of quality of life."

ABOUT THE COMPANY

MC10 is a private company, backed by a syndicate of financial and strategic investors, that is improving human health through digital healthcare solutions. The company combines its proprietary ultra-thin, flexible body-worn sensors with advanced analytics to unlock health insights from physiological data.

MC10 has received widespread recognition for its revolutionary technology and was recently named in Fast Company's Most Innovative Companies in 2016 as a leader in healthcare.

ABOUT THE AUTHOR

Erika Vázquez joined the MC10 team after graduating from Tufts University (Medford, MA, US). She shares the company's vision of rethinking the boundaries of technology to help improve human health and our understanding of the body.

ON drugDELIVERY

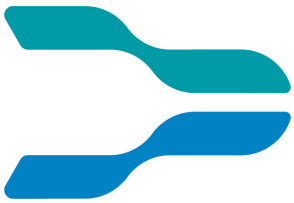
2017/18 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
July 2017	Novel Oral Delivery Systems	DEADLINE PASSED
Sept 2017	Wearable Injectors	July 24th
Oct 2017	Prefilled Syringes	Aug 21st
Nov 2017	Pulmonary & Nasal Drug Delivery	Sept 25th
Jan 2018	Opthalmic Drug Delivery	Nov 20th
Feb 2018	Prefilled Syringes	Dec 22nd
Mar 2018	Skin Drug Delivery: Dermal, Transdermal Microneedles	Jan 20th
Apr 2018	Pulmonery & Nasal Drug Delivery	Feb 19th
May 2018	Injectable Drug Delivery: Devices Focus	Mar 19th
June 2018	Connecting Drug Delivery	April 23rd
July 2018	Novel Oral Delivery Systems	May 21st

SHL GROUP

Innovation Beyond Injection

Solutions for Today on the Path to Tomorrow



SHL GROUP

NOT JUST ANOTHER GADGET: INSIGHTS INTO DEVELOPING DIGITAL SOLUTIONS THAT WORK

Smart connected devices are becoming increasingly widespread in all areas of life but their actual value and usefulness can sometimes get ignored. To avoid this happening in healthcare, SHL Group believes that the answer is to address four key questions which help to ensure that patients' needs are kept at the centre of any innovation and the value of the new technology is clear.

Over the last decade, the Internet of Things has become a day-to-day phenomenon. Smart, connected objects are becoming so widespread in every aspect of life that sometimes the question of their inherent value is left out. Picking up on this trend a website called the Internet of Useless Things[1] has even appeared, listing a number of particularly meaningless hypothetical applications of the new technology. To avoid developing devices that illustrate this tendency, it is important to take a step back and consider how to apply the available technical solutions.

> "The main purpose of any innovation must be centered on the idea of making patients' lives as healthy and comfortable as possible."

In the area of drug delivery, it is important to remember that the ultimate gatekeeper for any innovation will always be the final user – the patient. An important difference from consumer gadgets is that patients do not want a connected device just to stay on top of the latest trend. From a wider perspective, they would prefer to be healthy and not to have to use any device at all. So, the main purpose of any innovation must be centered on the idea of making patients' lives as healthy and comfortable as possible.

At SHL, we take patient-centric design and innovation seriously. To guide our research and development, we ask the following questions:

- Will it be accepted in the real world?
- Where do we start?
- How do we create additional value?
- Who will benefit?

Below we will introduce some insights into how these questions might be answered when starting a project.

WILL IT BE ACCEPTED IN THE REAL WORLD?

In short, the answer is yes. More people around the world are accepting digital tools in healthcare, including electronic health records (EHRs), wearables and mHealth. According to one survey, more than 75% of respondents would like to use digital healthcare services, as long as those services meet their needs and provide the level of quality they expect.[2] Moreover, older patients, often considered reluctant to accept new technology, are almost as likely to turn to digital solutions as younger ones.[2,3] Finally, even doctors, who remain somewhat sceptical about the value of digital health, are actively engaging with it –

SHL Group
#136, Kuo Sheng 2nd Street,
Taoyuan District,
Taoyuan City,
Taiwan

www.shl-group.com

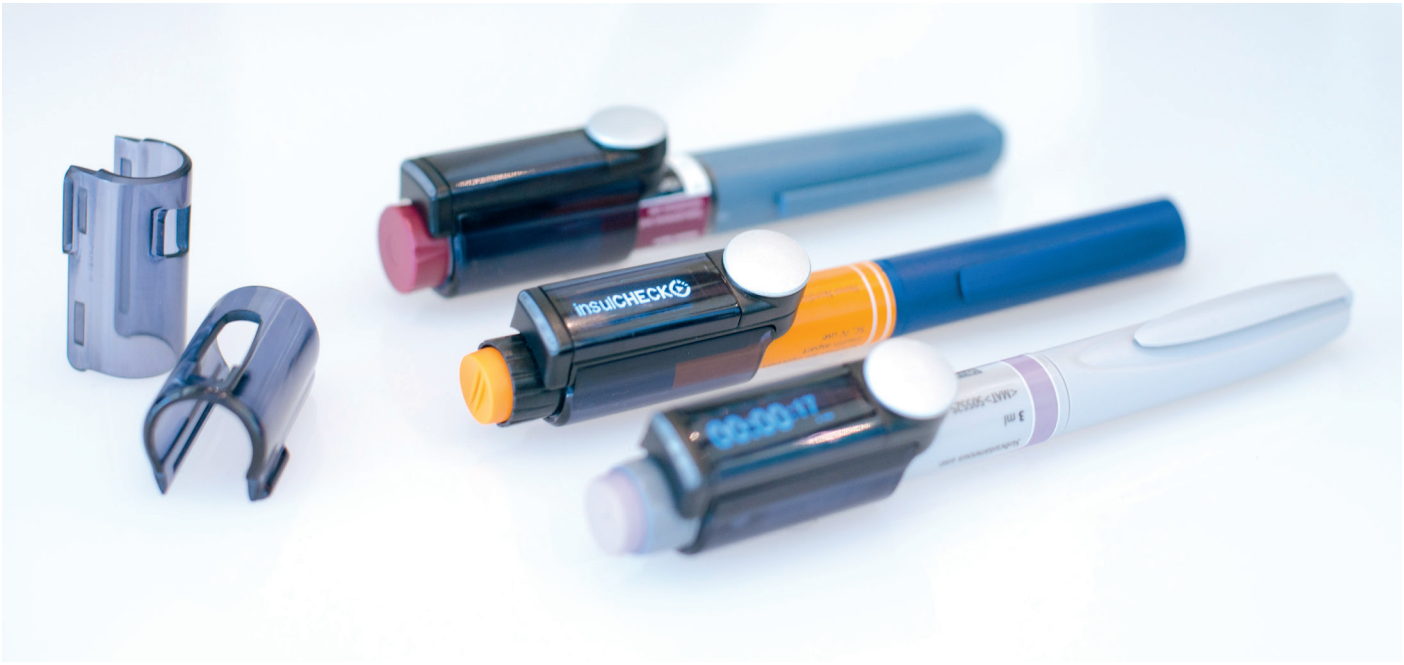


Figure 1: The InsulCheck add-on device for existing insulin pens illustrates a gradual approach to functionality: starting from a simple timer that is already available, InsulCheck is also being developed into a connected device to which further functions such as dose and temperature measurement can be added.

> "It is better to have one good function that works properly than ten functions that are of no use."

recommending apps, asking patients to wear devices for monitoring and, in general, feeling that these innovations are not just momentary trends.[3,4]

WHERE DO WE START?

The patient-driven approach to device development starts with the question: "What are the patient's needs?" At the very basic level, a well-designed device should fulfill the patient's needs while at the same time possess functions that are reliable and of good quality.[2] No innovative feature will be appreciated if the device doesn't work as it is supposed to, or if it is difficult to understand or use.

For the data records collected by a smart device, the same rule would apply to data management and representation. It is important to make it easily understandable and show real insights rather than a vast flow of raw and meaningless data points.

It is better to have one good function that works properly than ten functions that are of no use. Therefore, it might be a good approach to start small and increase functionality incrementally to ensure the usefulness and quality of each new feature (Figure 1).

HOW DO WE CREATE ADDITIONAL VALUE?

Once we have got the basics right, it is time to consider how and by what means we can create additional value with the new features. The availability of sensors and wireless technology means that we can track, guide and record almost every step of a user's interaction with the device. Segmentation and customisation become particularly important at this stage as different patient groups, therapies and use scenarios will require different functionality.

For example, people with multiple conditions using several different medications would clearly benefit from a therapy management system that could automatically incorporate and analyse the data about different medications and their interaction (Figure 2).

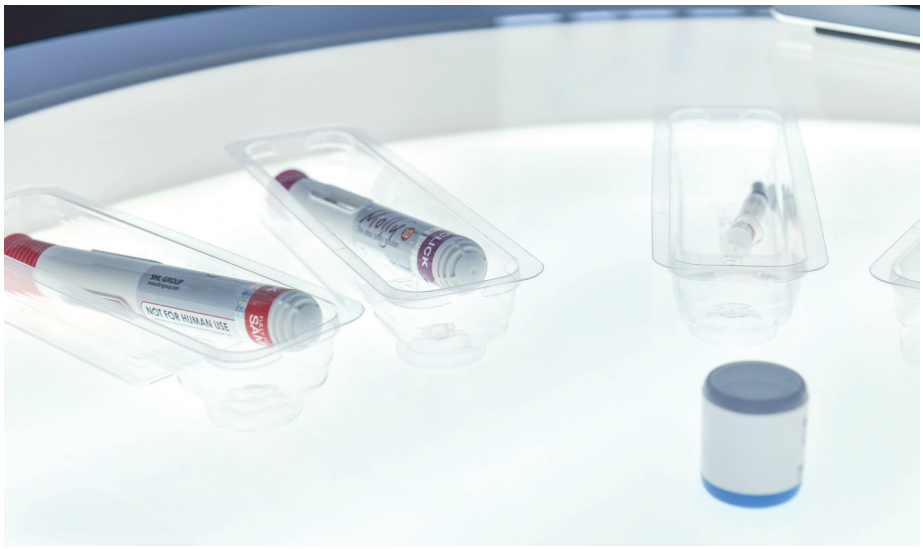


Figure 2: An extension of the Molly C RU (Figure 3) technology, the FlexRec system for multi-medication tracking illustrates how connectivity can work across different drug delivery formats. Paired with a therapy management platform, this concept design can significantly improve and simplify the patient experience.

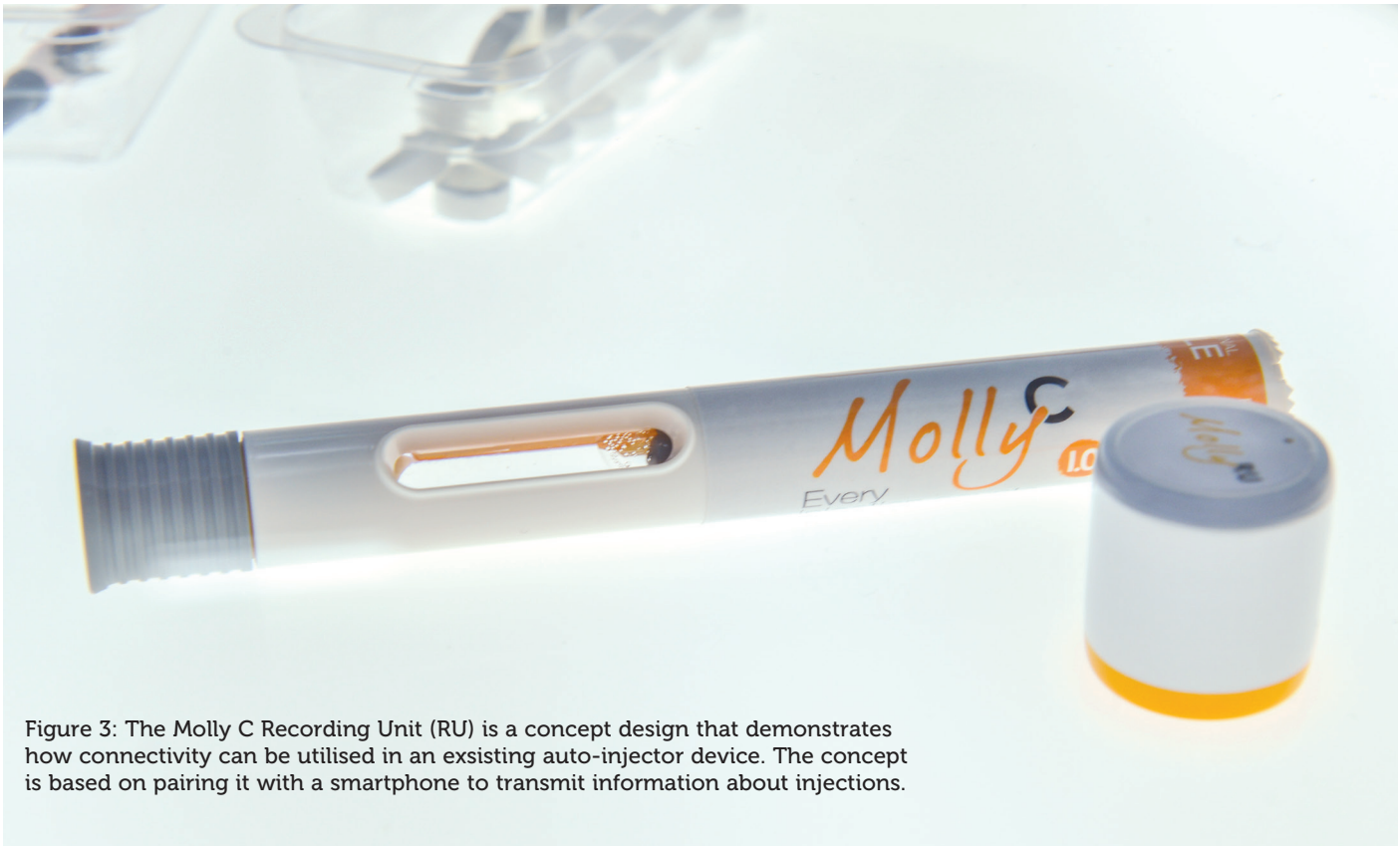


Figure 3: The Molly C Recording Unit (RU) is a concept design that demonstrates how connectivity can be utilised in an exsisting auto-injector device. The concept is based on pairing it with a smartphone to transmit information about injections.

"A connected medical device is not merely another gadget that will entertain the user for a few months and then be forgotten."

In the case of chronic diseases, adherence is one of the most important factors affecting outcomes. Thus, for these therapies it is important to design a drug delivery and therapy management system that will support patients' existing contextual cues (such as particular routines or locations) and will aim to modify long-term behaviour.[5]

Figure 4: A simple add-on device can significantly improve outcomes for diabetics.

In a setting of clinical trials, connected solutions can increase efficiency and patient recruitment by removing the need to input data manually and travel regularly to the study site. Moreover, with continuous monitoring and reliable data records, the results of such studies would be more powerful and might provide novel end points (Figure 3).[6,7]

The important thing to remember is that with the addition of new functionality, user experience must remain accessible and simple. It should also be customised in accordance with user needs, providing relevant information as well as proactive feedback and guidance.

WHO WILL BENEFIT?

Taking into account the needs of all stakeholders is essential in any healthcare project. The patient must be at the centre of our thinking, but other players have to benefit too.

The value of new technology for the patient is clear. First and foremost, improved adherence leads to better health. A study by Minnock[8] shows how a simple add-on device to remind users about the time since last injection can significantly improve health outcomes and reduce hypo- and hyperglycaemic incidents for diabetics (Figure 4).

Patient comfort and freedom is an important benefit of using connected solutions. More independence away from healthcare services, training and advice at patients' fingertips, the opportunity to share information with loved ones – all these features make lives easier and safer.

Doctors already agree that the use of wearables helps patient engagement.[3] Even though they may not see mobile technologies replacing face-to-face visits, the availability of data on, for example, whether the patient administers the medication properly, will help to assess, evaluate and modify the therapy. Together with environmental factors recorded by the app or a wearable device, this will provide a more detailed picture of the condition's management.

Pharmaceutical companies are also interested in increasing adherence to make sure that prescriptions are filled so as to secure optimal treatment outcome. As mentioned above, connected technology creates several benefits and opportunities in clinical trials. Moreover, as the competition in many therapeutic areas is constantly increasing due to the maturity of the market and research in generics and biosimilars, a connected device paired with a therapy management tool will allow market differentiation and product lifecycle management.

Payers will benefit from the reduced costs and evidence of outcomes. According to a US study on an mHealth-based diabetes monitoring device, it creates a potential total saving of US$34 billion (£27 billion) annually in direct medical costs.[9] In addition, the availability of rich, real-world data can ensure that the effectiveness of treatments is evaluated in more informed and personalised ways.

Another valuable effect of the data is that it can provide device manufacturers with an unprecedented amount of real-world feedback on the use of the device. Even though human factors studies are already an essential part of the design process, they are subject to the limitations created by the artificial environment of the study. At the same time, looking at how people use the device in their day-to-day lives, what problems they face and what prevents them from compliance can guide the design process for future models.

NOT JUST ANOTHER GADGET

A connected medical device is not merely another gadget that will entertain the user for a few months and then be forgotten. To provide a truly valuable experience for patients and other stakeholders, it needs to be developed with a thoughtful approach. By answering the four questions described in this article, it is possible to develop a successful product that will provide both short- and long-term benefits. The key lessons to learn are:

- Patients of all ages are open to the digital healthcare experience
- Start small with good quality core functions
- Gradually increase and personalise the new features ensuring at every step that they satisfy unmet needs
- Incorporate the device into a wider architecture by providing a therapy management system or an app and making good use of data.

REFERENCES

1 *http://www.internetofuselessthings.io/*

2 *Biesdorf S, Niedermann F, "Healthcare's Digital Future". McKinsey and Co, July 2014. (http://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/healthcares-digital-future)*

3 *Accenture 2016 Consumer Survey on Patient Engagement, 2016. (https://www.accenture.com/us-en/insight-research-shows-patients-united-states-want-heavy)*

4 *"The Digital Doctor Report". Ipsos Healthcare, 2015. (https://www.ipsos-mori.com/_assets/digitaldoctor)*

5 *Stawarz K, Rodriguez M, Cox A, Blandford A, "Understanding the use of contextual cues: design implications for medication adherence technologies that support remembering". Digital Health, 2016, Vol 2, pp 1-18.*

6 *Celia F, "Sensors, technology open the door to new era for clinical trials". Medical Media & Markets Web Page, March 7th, 2016.*

7 *Myshko D, "Smart Medtech: The Smart Healthcare Environment". PharmaVoice, Nov/Dec 2015.*

8 *Minnock D, O'Donnell S, Doyle G, Canavan R, O'Shea D, "Examining the effects of an insulin pen compliance device on HbA1C and lifestyle on individuals living with Type 1 diabetes mellitus". Diabet Technol & Therapeut, 2017. (Ahead of print)*

9 *Snyder G Bandyopadhyay S, "Next-generation "smart" MedTech devices: preparing for an increasingly intelligent future". Deloitte Center for Health Solutions, 2015. (https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/smart-medtech-increasingly-intelligent-future.html)*

ABOUT THE COMPANY

SHL Group is one of the world's largest solution providers in design, development and manufacturing of advanced drug delivery systems. We work with leading biotechnology and pharmaceutical companies to develop drug delivery devices, including compact disposable auto-injectors, reusable pen injectors and complex inhaler systems.

SHL has been investing significantly into R&D allowing us to enhance our broad pipeline of "next-generation" drug delivery devices. In particular, we initiated several forward-looking initiatives exploring new technologies and future developments, including comprehensive connectivity offers. Developing these projects in-house allows us to customise existing platforms in our pipeline or develop completely new bespoke devices based on the unique requirements of our customers. With locations in Taiwan, Sweden and the US, our experienced engineers and designers develop product enhancements and breakthrough drug delivery solutions for clients globally.

BEYOND CONNECTIVITY: ENABLE & FLEX ANNOUNCE THE ENABLE SMART DEVICE

In this article, Matthew J Huddleston, Vice-President, Research & Development, Enable Injections, and Angela Wright, Vice-President, Strategic Partnerships & Business Development, Digital Health, Flex, talk about their collaboration to integrate Bluetooth connectivity into Enable's latest Smart On-Body Delivery Device. The authors go on to describe how the partnership has also been expanded to encompass Flex's Digital Health Platform, the world's first medical-regulated, HIPAA-compliant, open architecture platform of regulated connected medical devices.

Macro trends are driving fundamental shifts in healthcare: the renewed focus on achieving the Triple Aim[1] through technology; the growth of the aging population versus the clinical infrastructure and supply of available clinicians is shifting the preferred site of care to the home; the proliferation of connected devices that are transmitting a wealth of data are enabling telehealth and remote care; and, in the near future, machine learning and predictive algorithms will be capable of generating real-time, personalised insights from collected data that will ultimately enable automated clinical decision making and drive behaviour adoption.

Today's dynamic healthcare technology landscape and connected devices are driving device OEMs and pharma companies to think about their business models differently, expanding beyond traditional device development and "the pill" to a world where smart medical devices enable real-world insights and the delivery of personalised patient experiences. For medical device technology and pharma companies, the evolution of connected devices and digital health will ultimately unlock opportunities for more direct patient engagement and improved drug adherence, while also providing insights with the potential to reduce both clinical trial costs and time-to-market for new drugs. Smart medical devices encourage transparency and accurate information sharing between patients and their physicians, ultimately driving targeted diagnosis and effective personalised remote monitoring. All these efforts are leading to improving health outcomes and maintaining patient independence effectively, while lowering the overall cost of care.

ENABLE-ING DEVICE CONNECTIVITY

Through the use of the latest sensing and connectivity technologies, traditional mechanical drug delivery devices are being transformed into smart, connected devices.

Enable Injections has developed injection devices that enable patients to self-administer high-volume/ high-viscosity drugs, enabling and promoting patient freedom and mobility (see Boxed Text "The Enable On-Body Delivery Device" on Page 24). "Our commitment is clear – continue to develop products designed to provide the user with a safe, simple, and discreet drug delivery experience," says Mike Hooven, President and Chief Executive of Enable Injections.

Flex is the *Sketch-to-Scale*™ solutions provider that designs and builds *Intelligent Products for a Connected World*™. Three years ago, Enable Injections

Mr Matthew J Huddleston
Vice-President, Research & Development
T: +1 513 326 2820
E: mhuddleston@enableinjections.com

Enable Injections
2863 E Sharon Road
Cincinnati
OH 45241
United States

www.enableinjections.com

Mrs Angela K Wright
Vice-President, Strategic Partnerships & Business Development, Digital Health
T: +1 512 289 4060
E: angela.wright@flex.com

Flex
6201 America Center Drive
San Jose
CA 95002
United States

www.flex.com

"In our commitment to further differentiate ourselves through innovation, we're excited to announce the development of our connected healthcare platform – The Enable Smart Device."

and Flex partnered to develop Enable's customised wearable injection technology. Flex and Enable Injections collaborated to develop scalable, high-volume manufacturing solutions for Enable's core technology and have expanded that partnership to develop Enable's next generation of devices. "In our commitment to further differentiate ourselves through innovation, we're excited to announce the development of our connected healthcare platform – The Enable Smart Device," says Jeannie Joughin, Vice-President of Corporate Development.

Following the strategy of designing simple systems for maximum effectiveness with minimal interaction, Enable Injections developed a smart device system to provide

Figure 1: The Enable Smart Device with the button cover in place (top) and the button cover removed showing the chip (bottom).

three key pieces of information about the operation of the drug delivery system:

1. When the device is powered on
2. When the device has started dose delivery
3. When the delivery has been completed.

"The user interaction is simple. The user opens the Enable app on their phone and the Enable Smart Device will do the rest. There are no additional steps to use the device," Joughin explains. The core features of the Enable Smart Device (see Figure 1) include:

- Small board footprint – the entire electronics package fits inside the existing button and is less than 3/8-inch (9.5 mm) in diameter. This allows for easy removal of the electronics (button) for electronic disposal and recyclability.
- Coin-cell battery – a simple, well knownpower source for a long operating- and shelf-life. The battery is isolated from the electronics via the safety strip until the time of use. Removal of the safety strip by the patient activates the circuit.
- Embedded microprocessor-based system for low energy and small footprint.
- Position sensing system (IR emitter/receiver combination) to detect the location of the button within the Enable Injector to allow for state position.
- Bluetooth low power transmission for low power consumption taking advantage of the prevalence of cell phone proximity to the user.

In 2015, it was estimated that 69% of the population in advanced countries own a smartphone.[2] To leverage this existing platform, Enable Injections felt utilisation of Bluetooth communications was the most efficient and effective means of providing data to the user, and selected Bluetooth Low Energy (BLE) as the optimal system to integrate into this product.

BLE is a newer version of the Bluetooth specification, introduced in Bluetooth v4.0, and has seen wide adoption in applications such as wearable fitness sensors. BLE is designed for low power, low cost applications that require lower data throughput rates than traditional Bluetooth connections such as audio streaming or hands free phone connections. There are two major types of connections defined in the Bluetooth standard: standard (bonded) mode and broadcast (also known as "beacon") mode. In standard or bonded connections, a host (smartphone with installed app) creates a saved connection with a peripheral (e.g. a drug delivery device).

In this scenario, through the pairing process, both the host and the peripheral share data to create a permanent connection that allows sharing between only one host and one peripheral. This method has the advantage of a secure connection allowing the exchange of encrypted information that cannot be decoded without the encryption key. However, a major disadvantage to this method is that the pairing process can be cumbersome, requiring user interaction as well as increased power consumption from the peripheral, as both the receive and transmit radios require power for communication.

In broadcast mode (also called a "beacon"), the peripheral sends out data at regular intervals that can be read by any nearby host. In this scenario, the peripheral only broadcasts data; data is never received. There are several advantages to this mode:

- Only the transmit radio on the peripheral device is powered, minimising power consumption.
- As the device does not need to listen for data from the host device, further power savings are achieved through lower power, sleep mode, waking up only when new data needs to be broadcast.
- Additionally, as the device is a transmit-only mode, the hardware can never be hijacked or loaded with malicious software. This eliminates the risk of unauthorised remote control of the device.
- The software is loaded onto the device in the factory, preventing unauthorised alteration once deployed.

"As the device is a transmit-only mode, the hardware can never be hijacked or loaded with malicious software. This eliminates the risk of unauthorised remote control of the device."

> "To progress along the full healthcare continuum, medical device and pharma companies need capabilities that extend well beyond adding connectivity to a device, requiring a digital health software stack that is "medical grade" to support clinical use cases, diagnosis and treatment, as well as data privacy and security."

While it is possible that other Bluetooth-enabled devices could listen to the broadcast from the Enable Smart Device, without the proper application installed, the data would simply consist of an unusable list of binary numbers, lacking any text or other readable identifiers. Because of this, the lack of an encrypted connection does not expose any sensitive user information. The data will also never contain any identifying patient information – such as names or identification numbers – which could be associated with a specific individual, thus allowing full compliance with the US Health Insurance Portability and Accountability Act (HIPAA).

An important attribute of the connected healthcare implementation within the Enable system is that it doesn't affect the essential performance functions of the drug delivery device. The electronic feature of the device only reports the status of the device and in no way alters the mechanical drug delivery function. Even in the event of a critical failure of the Bluetooth components, such as the battery, the device will complete the delivery of the drug and provide the user with visual feedback as to the device status.

Utilising the BLE broadcast mode and through a tiny electronic chip in the button of the device, Enable Injections can deliver real-time device performance information in a small, low cost, convenient package.

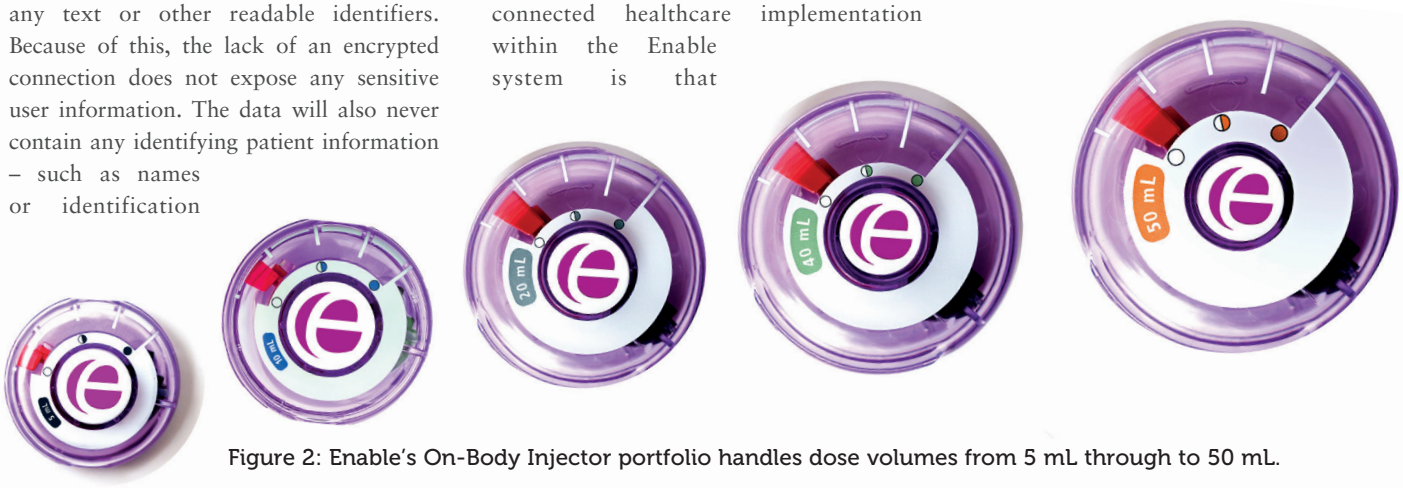


Figure 2: Enable's On-Body Injector portfolio handles dose volumes from 5 mL through to 50 mL.

THE ENABLE ON-BODY DELIVERY DEVICE

The right balance between dose volume, viscosity and in particular delivery duration is becoming increasingly important to pharmaceutical and biotechnology companies for SC injection therapies.

Enable Injections' wearable high volume injectors (see Figure 2) are capable of delivering higher volume – 5 mL, 10 mL, 20 mL, 30 mL, 40 mL, and 50 mL all available – at a desired flow rate over periods suitable for a particular product, minimising pain and delivering product in a predictable manner.

The injector design is based on over 12 years of research in minimising injection pain with numerous human factors studies conducted. The Enable Injector incorporates a unique pause function that allows the user to pause the injection at any time.

The Enable injector and transfer system are customised to the specific product characteristics. By using three different transfer platforms, which utilise established primary containers (syringe and vial), the advantages to the product manufacturer include cost savings and shorter time to market.

Minimising user error is an engineering and design challenge for wearable injector developers. Today's most advanced injector minimises any confusion by requiring only a few simple steps for patients – the "3 P's" of Enable Injections are:

- Place the injector onto the skin
- Pull the safety tab
- Press one button.

Enable Injections provides the smallest profile, wearable device for large volume product delivery, and is ready to partner with the biopharmaceutical industry to enable and empower patients requiring chronic administration of lifesaving or life enhancing therapies.

Updated from the article, "Pharma Company Innovation & Lifecycle Management: Delivery Devices as the New Key to Product Success" by Jeannie Joughin, which appeared in ONdrugDelivery Magazine, Issue 70 (Sep 2016), pp 34-37.

EXPANDED PARTNERSHIP FOR REGULATED DATA PLATFORM

To progress along the full healthcare continuum, medical device and pharma companies need capabilities that extend well beyond adding connectivity to a device, requiring a digital health software stack that is "medical grade" to support clinical use cases, diagnosis and treatment, as well as data privacy and security. Maintaining scalability and flexibility for such a solution requires ongoing monitoring and maintenance, including preventing security threats. The functional components of such a solution would, at minimum, require user management and preference, patient and physician engagement and patient and medication data management. A home-grown, siloed solution like this can be cost-prohibitive to build and maintain, and could take over two years to implement.

Flex has a unique view of the world, being on the leading edge of technology development in virtually every industry, and having evolved from a long tradition of high-tech/electronics hardware design and manufacturing. "Given our engagements on the xmedical device side, we quickly recognised the need for our partners to harness their new data sources and convert these into insights. Our partners leverage these insights not only to drive positive behaviour adoption, but also to fully understand the value of their products," says Kal Patel, Senior Vice-President of Digital Health at Flex.

Flex recently introduced Digital Health solutions to its portfolio of products and services, offering the world's first medical-regulated, HIPAA-compliant, open architecture platform of connected medical devices tied to a complementary, cloud-based software stack for commercialisation and scale (see this issue, Page 60, for more details). The Flex Digital Health Platform as a Service captures medication adherence data and relays bioinformatics data, enabling the conversion of raw data into actionable insights to enable clinical decision making, accelerate patient health engagement, and drive better health outcomes.

Enable Injections and Flex are expanding their collaboration to include the Flex Digital Health platform. Enable's Smart Device will be pre-integrated to connect to the Flex Digital Health ecosystem, offering Enable's pharma partners the ability to integrate with this open platform easily to gain immediate access to patient data across multiple devices, gaining more direct engagement with patients to drive adherence, while avoiding the high upfront development and ongoing maintenance costs.

"Enable Injections is excited to expand our partnership with Flex to leverage this added capability, offering our pharma partners a solution beyond device connectivity, with the ability to plug into this ecosystem," Hooven commented.

CONCLUSION/SUMMARY

Building on their existing three-year collaboration, Enable Injections and Flex are developing The Enable Smart Device, integrating Bluetooth Low Power communication and IR sensing into Enable's On-Body Injector in order to provide three pieces of information about the system: when it's powered on; when it starts delivery; and when it completes delivery.

The integrated electronics are small, fitting inside the button of the device, and low cost; communication is broadcast-only and thus saves power and is wholly secure and HIPAA compliant. User interaction with the smart system is simple and intuitive – the patient simply opens an app on their phone and the device does the rest. The patient just uses the device to deliver their medication exactly as normal.

Building on their existing three-year collaboration, Enable Injections and Flex are developing The Enable Smart Device, integrating Bluetooth Low Power communication and IR sensing into Enable's On-Body Injector in order to provide three key pieces of information: when the device is powered on; when drug delivery begins; and when delivery is complete.

The integrated electronics are small, fitting inside the button of the device. Communication is enabled by low cost broadcast, providing secure, HIPAA-compliant data transmission and minimising device energy usage. User interaction with the smart system is simple and intuitive – the patient simply opens an app on their phone then uses the device to deliver medication as normal. The data transmission is automatic.

Beyond device connectivity, the Enable Smart Device is pre-integrated into Flex's Digital Health Platform, the world's first medical-regulated, HIPAA-compliant, open architecture platform of connected medical devices, giving Enable's pharma partners the ability to integrate with this open platform easily to gain immediate access to patient data across multiple devices, gaining more direct engagement with patients to drive adherence, while avoiding the high upfront development and ongoing maintenance costs.

REFERENCES

1. *"The IHI Triple Aim". US Institute for Healthcare Improvement Web Page, 2017. (http://www.ihi.org/Engage/Initiatives/TripleAim)*
2. *http://www.pewglobal.org/2016/02/22/smartphone-ownership-and-internet-usage-continues-to-climb-in-emerging-economies/technology-report-01-03*

ABOUT THE COMPANIES

Enable Injections is a late stage start-up company that has developed a disposable wearable injector to deliver high-volume, high-viscosity drug biological products (up to 50 mL) to the subcutaneous tissue. The system utilies standard container closures (syringes or vials) and can automatically mix solutions or solubilise lyophilised product. Founded by medical device veterans the company has R&D, operations and manufacturing facilities in Cincinnati, OH, US.

Flex is the *Sketch-to-Scale*™ solutions provider that designs and builds *Intelligent Products for a Connected World*™. With approximately 200,000 professionals across 30 countries, Flex provides innovative design, engineering, manufacturing, real-time supply chain insight and logistics services to companies of all sizes in various industries and end-markets. Flex partners with a broad spectrum of healthcare OEMs to provide complete innovation, design, build, service and data solutions that make its customers more competitive in the areas of medical devices, drug delivery, diagnostics and medical equipment.

ABOUT THE AUTHORS & CONTRIBUTORS

Matthew J Huddleston serves as Vice-President, Research and Development and Feasibility for Enable Injections. He is an experienced medical device professional with over 20 years' experience in start-up environments with emphasis in project management, design, development, manufacturing, regulatory and intellectual property. He has several issued and pending patents in the medical device field including soft tissue and cardiovascular fixation devices and delivery instruments, histologic automated embedding systems, laparoscopic visualisation devices, and automatic injection devices. He is a professional engineer and a licensed patent agent. Mr Huddleston holds a Bachelor of Science in Mechanical Engineering from Purdue University (West Lafayette, IN, US) and a Master of Science in Biomedical Engineering from The Ohio State University (Columbus, OH, US).

Angela Wright, Vice-President of Strategic Partnerships & Business Development for Digital Health at Flex, is responsible for developing strategic partnerships for Digital Health solutions and driving new business growth.

With more than 11 years at Flex, Ms Wright has deep expertise working closely and strategically with a range of customers across every industry including healthcare, enterprise infrastructure and consumer technologies. She has led several strategic initiatives whereby leveraging Flex's range of cross industry capabilities and global solutions delivered Flex customers with creative and innovative solutions to drive competitive value. Upon joining Flex in 2006, Wright was focused on one of Flex's top five largest accounts. She drove collaboration across 30 sites globally, supporting 15 product lines driving US$2 billion in business annually. As Vice-President of Business Development and Innovation for the account, she led innovation and business expansion delivering value aligning with customer growth initiatives. Angela holds a Bachelor of Business Administration in Business Management and a Master of Business Administration degree with a concentration in Entrepreneurship from St Edward's University (Austin, TX, US).

Jeannie Joughin, PhD, Vice-President of Corporate Development at Enable Injections, is responsible for business development, strategic alliances, alliance management, marketing and clinical activities. She previously held various scientific positions including Senior Research Scientist, Post-Doctorate and Senior Post-Doctorate positions in Australia at The Alfred Hospital, The Walter & Eliza Hall Institute, as well as internationally in Austria (University Clinic, Innsbruck) and Switzerland (Ludwig Institute for Cancer Research, Lausanne). Dr Joughin began her career in the pharmaceutical industry in 1992 as a Clinical Research Manager with Bristol-Myers Squibb.

After successfully completing several marketing roles in the National Stroke Foundation, MediMark International and Mayne Pharma, Dr Joughin joined CSL Biotherapies in 2005 as Director, Pharmaceuticals Marketing and In-licensing. She assumed responsibility for a portfolio of pharmaceutical products from several licensing partners in various therapeutic areas. As Vice-President, Business Development at CSL Behring, Joughin was responsible for managing business licensing arrangements and relationships. This involved close liaison with CSL Behring's Commercial Development Team in the US, Germany and Switzerland.

Mike Hooven, President & Chief Executive Officer, Enable Injections, has more than 30 years of experience in the medical device industry in a broad variety of technical and clinical areas. He is the founder of five medical device companies and holds over 100 issued and pending US patents.

Mr Hooven is the founder, and a director of AtriCure, Inc (Nasdaq ATRC), a medical device company that manufactures and sells surgical devices to treat the most serious forms of atrial fibrillation. AtriCure has grown rapidly to become the market leader, with over 200,000 procedures performed. AtriCure completed a successful IPO in 2005. He previously held positions as the Chairman and CEO of AtriCure, and the Founder and Chairman of Enable Medical, a surgical device manufacturer that was acquired by AtriCure in August of 2005. Hooven founded Enable in 1994 and, prior to that, he headed up all internal product development at Ethicon Endo-Surgery from 1988 to 1994. He held engineering positions at Siemens/Pacesetter from 1986 to 1988, and at Cordis Corporation from 1981 to 1986. He earned a BS in Physics and an MSc in Mechanical Engineering from the University of Michigan (Ann Arbor, MI, US).

Dr Kal Patel, Senior Vice-President of Digital Health at Flex, has held a variety of leadership roles across biopharma, healthcare delivery and digital health. Prior to joining Flex, he served as Chief Commercial Officer at Doctor on Demand (San Francisco, CA, US), a leading video telemedicine provider, where he was responsible for all business and commercial functions, including marketing, business development, partnerships, implementations, operations and account management. Prior to Doctor on Demand, Dr Patel founded and led Amgen Digital Health, with responsibility for setting and executing a strategy focused on incubating and commercialising a portfolio of digital health products and programs that supported Amgen's drugs. Previously, he held leadership positions at, Novartis and The Boston Consulting Group. Patel has a Bachelor's degree in Economics from the University of Chicago (Chicago, IL, US), an MBA from its Booth Graduate School of Business, and an MD from its Pritzker School of Medicine.

Deliver more.
Wear less.

5/10mL **20/30mL**

enable injections

Enable your portfolio!

LEARN MORE AT WWW.ENABLEINJECTIONS.COM
FOR INVESTIGATIONAL USE ONLY

CONNECTED COMBINATION PRODUCTS: US ANALYSIS WITH POTENTIAL IMPLICATIONS WORLDWIDE

Here, Napoleon Monroe, Managing Director, New Directions Technology Consulting, from the US perspective and with an emphasis on human factors, automated identity and regulation, provides an overview of the current status of connected combination products, including points from recent conferences focusing on the topics.

Combination products have become a major feature of pharmaceutical treatment as biotech and other specialty pharma make up an ever larger share of healthcare treatments. Specialty products, which now represent a huge portion of the pharma market, require special care by definition.

Securing the benefits of specialty products by ensuring compliance with treatment regimens, and controlling costs, demands the use of combination products by patients and other non-professionals. Yet use of combination products by the laity brings a high degree of complexity to the approval process. The complexities are largely related to human factors.

Combination products connected to smart phone apps are now reaching the market in the US and abroad. Also, clinical trial approval is no longer enough. Stakeholders are demanding real-world evidence. Service is becoming part of the product value offered by biopharma companies, and the potential for connectivity to play a part in this is clear. Gathering evidence and providing service can be difficult but both present opportunities to assist patients and address some difficult regulatory questions.

There have recently been waves of partnering in the area of connecting combination products, including investment in services, devices and intellectual property. Many different designs are being developed, and numerous business models adopted. More venture capitalists are investing in connected adherence devices too. Global population health management as an industry is expected to grow to US$31.6 billion (£24.7 billion) by 2020,[1] and nearly $200 million was invested in related start-ups last year.

We should expect to see many more wearables and "carryables," including injectors, pens, inhalers, pumps and patches being connected to the Internet of Things (Figure 1). Telemanagement can offer numerous advantages including, for instance, guiding the patient through the placement, refill and use of such delivery systems through their smartphone.

However, the real world is a wild, uncontrollable place. Some regulatory questions about the real world are not easily addressed. Human factors questions arise regarding design, labelling, validations, risk assessment, risk management, change management, training, algorithms built into devices, gamification and even disposal.

The Parenteral Drug Association (PDA) and the Automated (product) Identity and Data Capture (AIDC) community regularly convene with the US FDA to help stakeholders work on regulations and standards for healthcare products. The recent PDA Combination Products Interest Group (CPIG) Conference (May 2017, Bethesda, MD, US) featured a session on connected combination products.

While other conferences include discussion of regulations and some include content on the regulation of connected combination products, the CPIG meeting was an entire day of wide-ranging discussions on combination products – including several hours devoted to

> "The recent PDA Combination Products Interest Group (CPIG) Conference featured a session on connected combination products."

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

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

www.mmedhealth.com

connectivity. The event was oversubscribed. Senior FDA staff presented and engaged in a lively Q&A. There are still many open questions, and guidances and standards in the works. Connectivity was characterised several times as being a hot topic within both the agency and the industry.

Additionally, presenters at another event, the FDA Unique Device Identification Conference (June 2017, Baltimore, MD, US) provided fascinating insights on unique device identifiers (UDIs) for devices, and automated identity for drug and combination products. Many FDA automated identity initiatives remain works in progress. The FDA UDI conference this year went beyond compliance to the many potential opportunities and rewards related to gathering real world evidence using AIDC (including UDI) as the language for the "source of truth" in healthcare. While the conference title was "UDI" there was discussion on automated identity for drug products. There were suggestions for broadening the scope of the conference and more co-operation between interested organisations.

This article attempts to share some personal observations and analyses from my perspective as a participant in the conferences. I will briefly highlight some of the complex regulatory requirements for combination products and some implications for stakeholders.

As discussed below, while connectivity adds to regulatory complexity in some senses, connectivity may also be the solution for *eliminating* some of the complexity in the real, wild world. Perhaps connectivity and automated identity will have to suffice until automated intelligence matures to address all the ever-changing, real world combinations and permutations.

REGULATORY FUNDAMENTALS

There are developers who do not believe that apps and products such as connected pill boxes are medical devices. Depending on their claims, labelling, and the market and FDA's interpretations, these developers may be correct. However, great care should still be taken with understanding risks and managing the human factors. This is the case even if the app or dispenser is not a medical device. Even low-risk devices such as pill boxes should be well designed and validated to avoid risks.

Some of the regulations, FDA definitions and existing and forthcoming standards relevant to the regulation of connected combination products, including drug delivery systems, are summarised in the boxed text on Page 30.

"While connectivity adds to regulatory complexity in some senses, connectivity may also be the solution for **eliminating** some of the complexity in the real, wild world."

Figure 1: Many more wearables and "carryables," including injectors, pens, inhalers, pumps and patches will be connected to the Internet of Things.

Dosing Products, Human Factors, Automated Identity & Regulation

Dosing products used by practitioners may be regulated simply as medical devices or container closure systems. Syringes, sold unfilled, for example, are generally (legitimately) used by healthcare practitioners. Practitioners are trained to use syringes correctly, and use them frequently.

Dosing products, sold filled with drug or biologic products, used by patients, non-professional caregivers or practitioners usually will be regulated as combination products. Most pens and auto-injectors

[Continued on Page 31...]

SUMMARY: REGULATIONS, DEFINITIONS & STANDARDS

What is a medical device? The FDA states that a medical device is an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is:

- recognised in the official National Formulary, or the US Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals
- and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolised for the achievement of any of its primary intended purposes.

Note that software can be a medical device.

Now, what is a combination product? FDA defines a combination product as a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under 21 CFR 3.2 (e), a combination product is defined to include:

1. A product comprised of two or more regulated components (i.e. drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labelling of the approved product would need to be changed (e.g. to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

There is no formal FDA definition of a connected combination product.

What is the US Unique Device Identifier Regulation? In September 2013, FDA issued a final rule to establish a system to identify devices through distribution and use. This rule requires the label of medical devices to include a unique device identifier (UDI), except where the rule provides for an exception or alternative placement. The labeller must submit product information concerning devices to FDA's Global Unique Device Identification Database (GUDID). The primary data carrier is a GS-1 2D barcode. Serialisation is an option.

What are the Drug Supply Chain Security Act (DSCSA), and the requirements for Rx product serialisation? The Drug Quality and Security Act (DQSA), was signed into law on November 27, 2013. The DSCSA is Title II of the DQSA, under which, manufacturers must put a unique product identifier on certain prescription drug packages. Specifically, they must serialise products using a data carrier – a 2D bar code by November 2017 unless FDA delays implementation. The rest of the supply chain has more time before they need to use of the serial numbers. The serial number will be used for product returns and suspect product investigations.

Once products are serialised, manufacturers and other stakeholders can more easily know what product is in which patient's hands. Some manufacturers believe that these regulatory requirements for automated identity (serialisation) can enable improved patient support and supply chain programs. With the expense mandatory, they are positioning to use the big data generated.

What is the UPC code? This is the well-known retail barcode. While UDI and DSCSA are used for tracking, they do not contain cost information, UPC codes are used in National Council for Prescription Drug Programs (NCPDP) standards for claims/reimbursement, rebates and e-prescribing. All of these automated identity initiatives are works in progress at FDA and at the payers. The old National Drug Code (NDC) will eventually disappear.

What is coming in the interrelated new Quality Management Standard, ISO 13485:2016 and the new EU medical device regulation (Regulation (EU) 2017/745, April 5, 2017)? In short more alignment of ISO13485 with FDA regulations and requirements for automated identity. Some UK NHS Trusts appear to intend to introduce automated identity well before the EU implementation dates. There are initiatives in other countries as well.

[...Continued from Page 29]
are generally used by patients or relatively untrained individuals acting as caregivers. The lack of training for the laity as distinguished from the professional population leads to greater potential for errors in the use of products. The human factors issues become evident when one considers all the variables in the real, wild world.

Patients and caregivers are trained initially, and supplied with instruction sheets, but use their dosing products less frequently, and may not understand or may forget the instructions. FDA could be somewhat less concerned about human factors with syringes for professional use than they are with human factors related to dosing products patient or caregiver use.

These, plus the key fact that the FDA does not regulate the practice of medicine, are the main factors determining the regulatory schemes into which dosing products will be placed. The specifics of the product, the claims made, labelling, content of the submission and the risks associated with use will also determine how strictly the product is regulated.

If used or refilled by the patient or other non-professionals, syringes, pens, auto-injectors, inhalers, transmucosal nasal administration devices, transdermal patches and pumps (refilled by patients) should be considered initially as combination products. Even droppers and spoons which can impact patient outcomes may be regulated as combination products. Filling the reservoir of a pump can be complex. This is borne out by some pump recalls and reported deaths.

These facts argue for better training, instruction and product support for combination products, and connectivity can provide support to help ensure proper use. As with consumer products, instruction at the time of combination product use can be essential to successful use.

Consumer health aids such as most consumer apps and products which the FDA does not now regulate will not be discussed here, except to say that any product on which FDA has decided to exercise regulatory discretion (not to regulate) will not be regulated, unless and until FDA decides not to exercise regulatory discretion.

Political Change

Before last year's US presidential election, Congress passed the 21st Century Cures Act with bi-partisan support. Some sections of the Act may help simplify approvals. There is also further discussion in the new administration that regulations should be simplified. Whatever is decided about simplification, FDA will still be charged with regulating to ensure safety and efficacy. The mandate that a product be safe and effective before introduction leads to many questions in a regulatory review. Regulating algorithms designed to answer all possible situations in the real world becomes very difficult. Many regulatory interpretations and guidances are likely coming in the future. The timing however is unsure.

ROLE OF CONNECTIVITY POST MARKET

As we are waiting for clarity, the importance of addressing the real, messy post-market world grows, as exemplified in a study published in JAMA earlier this year.[2] It found that among 222 novel therapeutics approved by the FDA from 2001 to 2010, 71 (32.0%) were affected by a post-market safety event. Post-market safety events were more frequent among biologics, therapeutics indicated for the treatment of psychiatric disease, those receiving accelerated approval, and those with near-regulatory deadline approval. That post market safety events are common after FDA approval, highlights the importance of continuous monitoring of the safety of novel therapeutics throughout their lifecycle.

A plethora of factors seem to be converging to support the case for, and highlight the potential benefits of, connectivity post market. These include:

- The rise of the specialty sector
- Issues related to laity injection
- The cost of developing specialty products such as biologics (generally 22 times more than small molecules) and their profitability[3]
- Recent approvals of competitive specialty products (for example the epinephrine pen from Adamis Pharmaceuticals (San Diego, CA, US)
- The emergence of biosimilars.

At the PDA CPIG meeting, a question was raised from the floor about the impact of social media on the post-market regulation of combination products. Patients share information with each other in open forums. FDA may receive information directly from patients and FDA programs previously called Signals, Sentinel; now called NEST (National Evaluation System (for health) Technology) will probably mine data. NEST was also a topic at the FDA UDI Conference.

Besides being a tool for classic FDA pharmacovigilance, the serialisation required of pharma by the US Drug Supply Chain Security Act will be used to record combination product use. This will provide data for adjudging comparative efficacy, which will provide information for analysis upon which to base decisions on reimbursement and value based purchasing decisions. It will not be surprising, therefore, if we find pharma serialisation being used in pharma marketing soon, and in patient social media as well.

At the PDA CPIG conference, a discussion of the levels of support for combination products was received with great interest and triggered some thoughts about why telemedicine and medication telemanagement have failed. The human element in human factors can't be eliminated.

Also reported in JAMA, a randomised clinical trial in 53,480 enrolees of a pharmacy benefit manager (PBM), showed basic reminder technologies such as a pill bottle strip with toggles or digital timer cap, to be ineffective compared with a standard pill box.[4] The investigators asked, to what extent three low-cost reminder devices could improve medication adherence among individuals who are

> "Written diaries are recognised to be inaccurate. They provide little information for support and they are not real-time so any review of a diary is after-the fact. Even automated diaries and smart connected packaging still provide relatively little support. Some may provide a flood of data but little actionable information. These are all low- or medium-support approaches."

"High-support connected options with limited algorithms providing guidance to professionals for their interventions could be the model of the future for high-risk situations. This model allows professional intervention using judgements and other available information on patient situations in real time, as they materialise."

receiving therapy but are poorly adherent, and found no statistically significant difference in adherence between those in the control group and those who received a reminder device.

However, written diaries are recognised to be inaccurate. They provide little information for support and they are not real time so any review of a diary is after the fact. Even automated diaries and smart connected packaging still provide relatively little support. Some may provide a flood of data but little actionable information. These are all low- or medium-support approaches.

Other factors that should be considered are:

- Hot competition for ownership of the patient relationship and the patient's data
- Fear about providing and possible misuse of data
- Many bright shiny healthcare toys are time consuming, not intuitive, and don't provide perceived value or actionable information
- All sensor-based systems can be fooled. Even with direct observation or a chip on a pill a determined patient can probably fool the system.
- Judgements and the many types of information on patients which can be available in a central monitoring facility are hard to integrate into algorithms.

Future research should therefore focus on effective targeting of interventions and strategies that ensure sustained medication use.

High-support connected options with limited algorithms providing guidance to professionals for their interventions could be the model of the future for high-risk situations. This model allows professional intervention using judgements and other available information on patient situations in real time, as they materialise.

Such judgements, made by licensed professionals practicing medicine, are not FDA regulated. This is the equivalent of a "Genius Bar" (one of Apple's many trademarks) for medication adherence. Service may be costly, but less so than working as we do now in the current uncontrolled, wild, messy world. Even if regulated, this type of information system may be classed as a Medical Device Data system (MDDS) which is FDA Class I and FDA 510(k) exempt.[5] Nonetheless, quality System regulations should still be followed to ensure an accurate system

In the long run, a high-support system may be less expensive and more effective. High support s ystems could even be better for engendering loyalty than direct-to-consumer (DTC) advertisements. Indeed a Wharton expert's research report showed pharma's DTC advertisements: work for "initiates," who, however, on average, are less compliant with treatment; and expand utilisation for entire classes of drugs.[6]

But what about the implications in a value-based, real world evidence environment?

WHAT ARE HCPS SAYING ABOUT CONNECTED HEALTH?

Some medical and pharma practitioners remain sceptical, saying things like:

- We don't/can't get paid for this
- My time is limited, better spent diagnosing/marketing
- I'm already overwhelmed and can't deal with innovations
- I can't be pinged whenever a patient/customer fails to act or wants to chat
- It's EMRs/EHRs all over again. The systems aren't built for our workflow
- How does all this fit into HIPPA? What about privacy?
- Hacking is all over the news. This has to be a security threat
- I've seen some of these toys; they are all worthless
- Patients abandon apps because they are a pain
- The Affordable Care Act is being repealed.

However, most of these points are of course in contention.

Others in growing numbers, are saying: "Connected healthcare is an opportunity!" It could be an opportunity in Medicare/Medicaid (CMS), hospitals, PBMs, payers (including third-party admins), plan sponsors, wellness/PERS providers, community health centres, pharma companies, individuals and patient advocacy groups.

Pharmacy chains are numerous, they're local and are in regular contact with patients. Pharmacists can sell devices and service to other stakeholders. All stakeholders, by definition have an interest in – and many can be paid for – medication therapy management.

CONCLUSION

The evidence that poor adherence and compliance with pharmaceutical therapies are problems worth addressing is now abundant. Numerous examples are cited elsewhere in this issue of *ONdrugDelivery Magazine*. To provide two further examples from the many available, firstly, an Express Scripts 2015 Drug Trend Report updates the estimated US cost of medication non-adherence to $337 billion per year, up from the customarily cited $290 billion annual figure.[7] This increased amount still does not capture all societal costs. Secondly, a November 2016 CapGemini / HealthPrize Technologies report raises estimated global pharma revenue losses due to non-adherence to $637 billion, up from $564 billion in 2012.[8]

Connectivity can provide the solutions the healthcare profession needs, for example:

- Improved outcomes through enhanced compliance
- Information to meet requirements for real world evidence (RWE), demonstration of product value
- A "sentinel" to learn direct information from patients to enable improved service, CAPA, clinical trial completion
- Better understanding of human factors
- Product loyalty

- Added value to biopharma products
- Reduced overall costs for many stakeholders.

This article contains opinions, not advice. Your regulatory advisers can provide specific guidance. These observations are not endorsed by PDA, FDA or other entities. PDA would almost surely welcome your participation in future CPIG conferences.

The author and his clients have commercial interests in medication telemanagement: www.freepatentsonline.com/8149111.html.

REFERENCES

1. *"Population Health Management Market By Component (Software, Services), End User (Healthcare Providers, Healthcare Payers, Employer Groups, Government Bodies), Mode of Delivery (Web-based, Cloud-based, On-premise), Region – Global Forecast to 2021". MarketsandMarkets Report, February 2017. (www.marketsandmarkets.com/Market-Reports/population-health-management-market-263411936.html)*
2. *Downing NS, et al, "Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010". JAMA, 2017, Vol 317(18), pp 1854-1863. (http://jamanetwork.com/journals/jama/article-abstract/2625319)*
3. *Walker N, "Nice Insight Overview. Biologics: The Driving Force in Pharma". Pharma's Almanac, Global Pharmaceutical Supply Chain Trends, Q2 2017 Edition, pp 6-9.*
4. *Choudhry N, Krumme AA, Ercole PM, "Effect of Reminder Devices on Medication Adherence The REMIND Randomized Clinical Trial". JAMA Intern Med, 2017, Vol 177(5), pp 624-631. (http://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2605527)*
5. *"MDDS Rule". US FDA Web Page, July 8, 2014. (www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/MedicalDeviceDataSystems/ucm251897.htm)*
6. *Alpert A, "Cause and Effect: Do Prescription Drug Ads Really Work?" Wharton University of Pennsylvania Web Page, January 4, 2017. (http://knowledge.wharton.upenn.edu/article/prescription-drug-ads)*
7. *"2016 Drug Trends Report". Express Scripts. (http://lab.express-scripts.com/lab/drug-trend-report)*
8. *Moore T, Chawla S, Firlik K, "Estimated Annual Pharmaceutical Revenue Loss Due to Medication Non-Adherence". CapGemini/HealthPrize Technologies Report, November 2016. (http://managedhealthcareexecutive.modernmedicine.com/managed-healthcare-executive/news/what-billions-lost-pharma-revenue-means-managed-care)*

THE POTENTIAL OF CONNECTED DEVICES FOR TACKLING ASTHMA

Including results from a clinical trial in asthmatics, comparing outcomes from smart inhaler use with standard inhaler control, Garth Sutherland, MSc, Founder & Executive Director of Adherium, and Jon-Paul Sherlock, PhD, Head of Respiratory Digital Health at AstraZeneca, explain how a strategic partnership between pharmaceutical companies and digital health companies can achieve improved outcomes through joint initiatives.

Asthma is a chronic disease characterised by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. According to the American Academy of Allergy, Asthma and Immunology an estimated 300 million people have been diagnosed and suffer from asthma globally,[1] resulting in an estimated economic burden of more than US$100 billion (£78 billion).[1] While asthma is the most prevalent chronic disease among children, it remains under-diagnosed and under-treated, creating a significant burden on individuals and families. And that burden is predicted to increase, with another 100 million diagnosed patients by 2025.[1]

Symptoms of asthma may occur anywhere between several times a day or week, and for some people become worse during physical activity or at night. Although the fundamental causes of asthma are yet to be completely understood, the strongest risk factors for developing the disease are a combination of genetic predisposition and environmental exposure to inhaled substances and particles that may provoke allergic reactions or irritate the airways. Other triggers can include cold air and physical exercise.

While asthma cannot be cured, the condition can be controlled by appropriate management, enabling patients to enjoy a good quality of life. The current gold standard treatment is a combination of short-term and long-term medications, with short-term medications used to relieve symptoms and long-term medications used to control the underlying inflammation and prevent symptoms and exacerbations.

However, the Global Initiative for Asthma (GINA) 2017 report[2] showed that 70-80% of asthma patients are unable to use their inhaler correctly, meaning that these medications often do not have the intended effect (Figures 1, 2 and 3).

THE RISE OF DIGITAL HEALTH SOLUTIONS

Connected devices are increasingly being adopted by consumers for health and fitness monitoring. The last few years have seen increased adoption of digital health management tools by patients, including wearables and apps, to manage their health and have access to their data. National health services around the world are seeking digital solutions to transform the treatment of chronic diseases to improve patient outcomes and ease the economic burden.

Moreover, pharmaceutical companies are partnering with digital health technology companies to accelerate research and development of devices and platforms to bring these digital tools to patients. Enabling self-monitoring and management of long-term conditions has been identified as a way for healthcare systems to reduce the overall cost of care.

Healthcare providers and pharmaceutical companies are increasingly using technologies to engage patients with chronic conditions in directed self-management of their conditions. Empowering patients to engage with their condition, through supported self-management and personalised approaches, can instil an

> "The need for a course of oral steroids, a marker of severe exacerbations, was 53% more common in children who did not use the smart inhaler compared with those who did."

Jon-Paul Sherlock
Head of Respiratory Digital Health
T: +44 7824 350620
E: jon-paul.sherlock@astrazeneca.com

AstraZeneca
Pharmaceutical Technology & Development, Ground Floor
Derwent, Macclesfield Campus,
Charter Way
Macclesfield
SK10 2NA
United Kingdom

www.astrazeneca.com

Garth Sutherland
Founder & Executive Director
T: +64 9 307 2771
E: info@adherium.com

Adherium Limited
204 Quay Street
Auckland, 1010
New Zealand

www.adherium.com

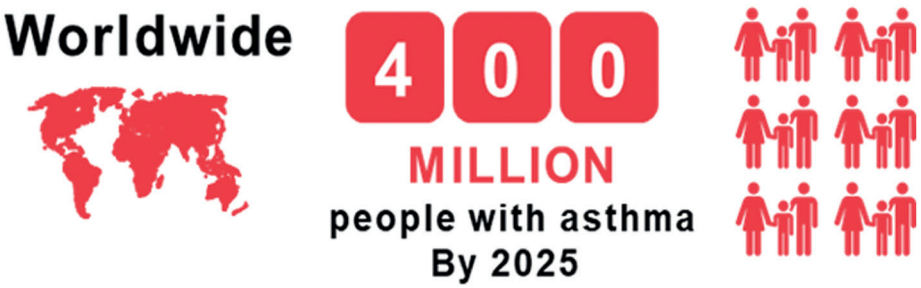


Figure 1: 400 million people are estimated to be diagnosed with asthma by 2025.[3]

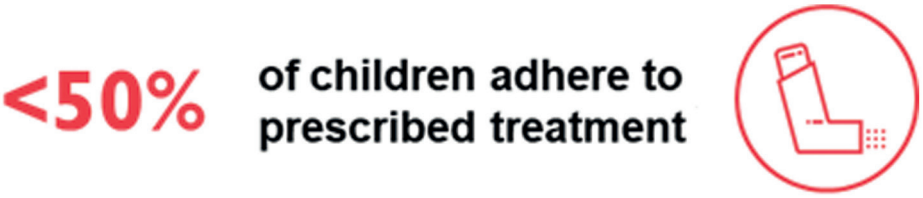


Figure 2: Less than 50% adhere to their prescribed treatment.[4]

Figure 3: Increasing medication adherence could see a 60% reduction in hospitalisation.[5]

> "Smart inhalers can now also monitor the inhalation technique meaning patient education to ensure that the correct inhalation technique is used can be reinforced."

increased sense of responsibility. This, in turn, can result in appointments with clinicians becoming less frequent.

Once deployed, digital platforms that link a monitoring or management device to cloud-based software for storing data, can be accessed by both the patient and the healthcare practitioner. This helps to ensure that exacerbations in a patient's condition can be identified and action can be taken to reduce emergency admissions and, in extreme cases, avoid fatal complications.

INCREASING ADHERENCE WITH SMART INHALERS

One of the greatest barriers to improving the health of asthma patients is drug adherence. Various tactics have been tried to increase adherence, from professional education and advice from clinicians and pharmacists to family support. Unfortunately, all have proved to be complex, time-consuming and costly, with modest results.

Smart inhalers have been recognised as a novel approach to promoting adherence by monitoring medication use for respiratory diseases, including asthma.

Smart inhalers can be used by adults and children, with initial research showing a willingness among the asthma population to carry a connected device. This means there is a significant opportunity for the use of smart inhalers so that people with asthma, healthcare professionals and national health services can use the data to help improve outcomes and reduce costs.

With all digital solutions, some training will be needed to familiarise patients and clinicians with the device and associated software. This may include fitting the device correctly and checking inhaler technique. Patients will also need to be advised of what data are captured and how they are able to view them. Smart inhalers can now also monitor the inhalation technique meaning patient education to ensure that the correct inhalation technique is used can be reinforced.

DIGITAL HEALTH INITIATIVES

An example of the digital health initiatives taking place between pharmaceutical companies and digital health companies is the strategic partnership between Adherium and AstraZeneca. The shared aim is to support respiratory patients through the introduction of new technologies and innovations in digital healthcare.

This digital health initiative is focused on demonstrating that new technologies can be combined with medication to help patients achieve improved outcomes. Because these technologies evolve incrementally in a real-world setting with the experience and input from healthcare professionals and patients, they are not only making great strides towards delivering the future of digital health, but most importantly, adding value to existing treatment options.

Turbu+

Turbu+ is the first programme to come out of this initiative, with the aim of reinforcing the efficacy of AstraZeneca's existing inhalers in real life by establishing the right behaviour early in a new treatment. This will be achieved through provision of reminders and motivational messages to patients by incorporating Adherium's Smartinhaler™ technology, which has been shown to improve adherence when compared with standard care.

The enhanced Smartinhaler™ device sends the captured data via Bluetooth to an app, and the device programme tracks the patient's treatment regimen. As well as supporting patients, the device provides their healthcare professionals with secure and accurate information, which gives them a deeper understanding of how their patients are using their medication in real life. It not only equips them with information on actual medication use to make better treatment decisions and treat the patient efficiently during consultation, but reassures them to what extent their treatment plan is being followed.

GROWING CLINICAL EVIDENCE OF IMPROVED OUTCOMES

Patient adherence to prescribed medications represents a significant issue for chronic disease management. Approximately 50% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time.[6] In the UK a child is admitted to hospital every 20 minutes because of an asthma attack.

Numerous clinical studies and peer-reviewed papers highlight the need for a widespread digital solution, such as smart inhalers, that promotes adherence to medication. Meanwhile, clinical studies have shown that asthma patients are achieving 80% adherence to preventative medication when using a smart inhaler device with a 61% reduction in oral steroid use.

For example, the UK-based year-long STAAR study, carried out at Sheffield Children's Hospital and led by the University of Sheffield's Dr Robert Morton and colleagues, aimed to assess whether introducing digital adherence monitoring into routine practice could improve clinical outcomes in children with poorly-controlled asthma.[7]

In the study 38 children were in the intervention group using adherence monitoring smart inhaler with medication reminders and feedback in the clinic, and 39 children received usual care as part of a control group. Drug use data were collected and children's health outcomes were assessed at each three-month follow-up.

> "The big data that can be gathered from devices and platforms will determine the way in which digital solutions can be improved and, in turn, how care can be improved."

The study found that adherence to prescribed medication averaged 70% in children using a smart inhaler compared to 49% in the control group ($p<0.001$). The study also found that increased medication adherence through use of the smart inhaler device and data platform was maintained over the 12-month period of the study, with nearly half of the children using the smart inhaler maintaining average adherence rates of >80% over the 12 months.

The study also found improvements in outcomes. The adherence improvement among children using the smart inhaler was associated with significant reduction in asthma exacerbations – episodes of progressively worsening shortness of breath, coughing, wheezing and chest tightness – which can be life threatening. The need for a course of oral steroids, a marker of severe exacerbations, was 53% more common in children who did not use the smart inhaler compared to those who did. ($p=0.008$).

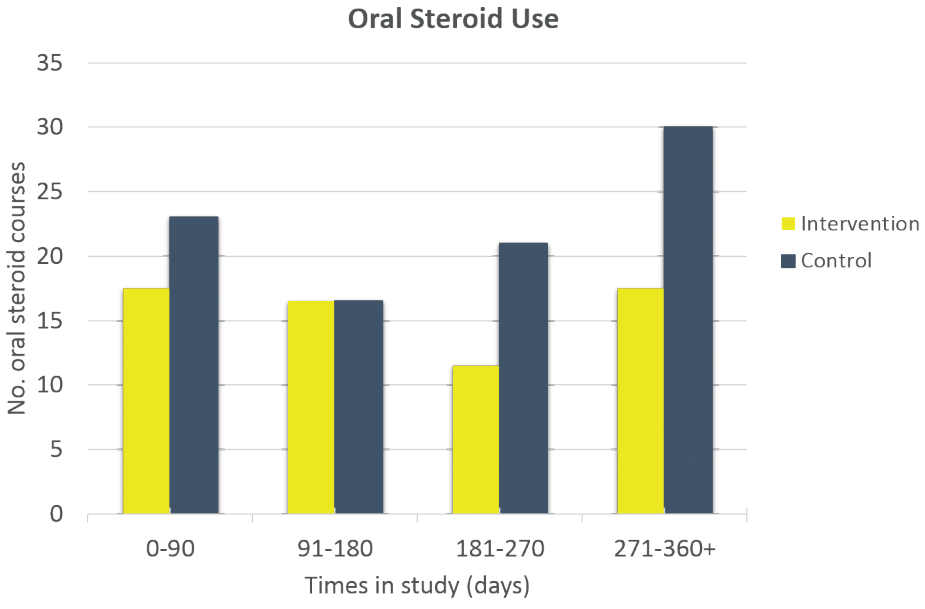


Figure 4: The intervention group saw an increase in adherence to medication and a reduced need for courses of steroid medication.[7]

Furthermore, the hospitalisation rate was five times greater in the control compared with the intervention group ($p<0.001$). This approximates to the prevention of 12 hospitalisations in one year among the children in the intervention group, making a cost-saving argument for introducing smart inhalers into routine practice.

Through the course of the study, the clinical benefits observed within the intervention group increased compared with the usual care group, particularly at nine and 12 months, with the intervention group requiring fewer courses of oral steroids, hospital admissions, days off school and GP/emergency department visits.

The study concluded that existing digital technologies should be introduced to patients to improve asthma care and that more should be done to ensure that people with asthma are able to benefit from a connected way of managing their condition (Figure 4).

CONCLUSION

Multiple clinical studies have already demonstrated that smart inhalers can lead to improved adherence and, even more encouragingly, associated benefits such as reduced hospital admissions. The introduction of smart inhalers therefore has the potential to realise savings for healthcare providers, while also enabling clinicians to gain increased insights into their patients' behaviours and intervene for improved health outcomes.

The big data that can be gathered from devices and platforms will determine the way in which digital solutions can be improved and, in turn, how care can be improved. While efforts to incorporate digital solutions into national health services will take time and upfront costs, the benefits will outweigh the initial integration with improved patient health seeing reduced healthcare costs.

REFERENCES

1 *"Asthma Statistics". AAAAI Web Page, 2017. (http://www.aaaai.org/about-aaaai/newsroom/asthma-statistics)*

2 *Global Initiative for Asthma Web Page, 2017. (www.ginasthma.org)*

3 *Anandan et al, "Is the prevalence of asthma declining? Systematic review of epidemiological studies". Allergy, 2010, Vol 65(2), pp 152-167.*

4 *Horne R, "Compliance, adherence, and concordance: implications for asthma treatment". CHEST, 2006, Vol 130(1_suppl), 65S-72S.*

5 *Williams et al, "Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma". J Allergy Clin Immunol, 2004, Vol 114(6), pp 1288-1293.*

6 *Boulet L-P, Vervloet D, Magar Y, Foster JM, "Adherence: the goal to control asthma". Clin Chest Med, 2012, Vol 33, pp 405-17.*

7 *Morton RW et al, "STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma". Thorax, 2016, Vol 72, pp 347-354.*

ABOUT THE AUTHORS

Jon-Paul Sherlock is a senior leader in pharmaceutical innovation, leading development of new digital health solutions for emerging and established respiratory medicines. He is a chemical engineer and joined AstraZeneca after completing his PhD. He has held a number of technical and project leadership positions and has worked in all areas and clinical phases of Pharmaceutical Development. Dr Sherlock is passionate about innovation, establishing collaborations between industry and academia and working with small companies to commercialise disruptive ideas and technologies. He serves on the UK Engineering and Physical Sciences Research Council's Strategic Advisory Team for Manufacturing the Future and is a Visiting Professor at the University of Manchester, UK.

Garth Sutherland is the Founder & Executive Director of Adherium, a provider of smart inhaler digital health solutions to the respiratory drug delivery sector. Mr Sutherland is an inventor of 13 patent families related to the Smartinhaler™ platform, and a contributor to over 70 registered designs and a number of trademarks registered or used by Adherium. He has been leading Adherium for 17 years, growing the company from concept to its current group of international companies located in Silicon Valley, Europe, Oceania, and Asia. To date, he has raised more than US$38 million for investment in Adherium's Smartinhaler™ platform, and led Adherium's IPO on the Australian Securities Exchange in 2015. Also in 2015, Adherium signed a 10-year commercial agreement with AstraZeneca for the supply and ongoing development of Adherium's Smartinhaler™ technology, which Mr Sutherland led. He has more than 30 years' experience in the high-technology sector and holds a first-class honours MSc in Physics.

Medicom Innovation Partner
a Phillips-Medisize Company

THE PROMISE OF CONNECTED HEALTHCARE (AND WHY IT'S PROVING HARD TO GET THERE)

Although it seems inevitable that drug delivery devices are becoming part of the connected world, it is difficult to see the precise path to this transformation. Here, Kevin Deane, Executive Vice-President, Front-End Innovation, Medicom Innovation Partner, and Bill Welch, Chief Technology Officer, Phillips-Medisize, show that clear trends are emerging, some helping to push connected healthcare forward and some that are slowing down progress, and describe the opportunities and challenges arising.

Connected healthcare has moved from being an exploratory technology to a subject that is regularly discussed at the executive levels of most pharmaceutical companies. This is not surprising. Smart phones have proliferated, offering users instant access to information and the ability to interact in ways barely dreamt of 15 years ago. The number of connected devices has already surpassed the number of people on the planet, and is growing (Figure 1).

At the same time, devices have become central to the delivery of many new drugs. Biologics are the key blockbusters and, with this, injection systems have become the predominant form of drug delivery (Figure 2).

There is little question that connectivity and data analytics technologies could revolutionise healthcare. Companies such as Google and Apple are making significant investments in this space. Arguably, the increase in drug delivery devices provides pharmaceutical companies with a platform on which to build such technology. However, the entire industry remains remarkably resistant to change.

> "App fatigue, password overload, constant upgrades, poor signal strength, complex user interfaces – general irritations for most of us. However, these minor concerns become significant in healthcare applications."

THE OPPORTUNITIES

Patient-centric benefits are the primary source of opportunities for connected healthcare. Improved treatment, better patient education, patient empowerment and social support all help to build a patient-centric approach. Of course, improving adherence is also a key driver.

Other opportunities include new treatments and new business models that connected healthcare systems make possible. Connectivity is an enabler for reducing waste, saving costs, personalising treatments and improving clinical trials.

Mr Kevin Deane
Executive Vice-President,
Front-End Innovation
T: +44 7714 697326
E: kpd@medicomip.com

Mr Bill Welch
Chief Technical Officer
Phillips-Medisize
T: +1 715 386 43203
E: bill.welch@phillipsmedisize.com

Medicom Innovation Partner a/s
(A Phillips-Medisize Company)
Gimsinglundvej 20
DK-7600 Struer
Denmark

www.medicomip.com

Patients First

For several years, the entire healthcare industry has been adopting a patient-centric view; putting the patient at the centre of our systems. The pharmaceutical industry is adopting a similar approach. However, this is easier said than done.

Digitalisation and connectivity will help to realise this vision, pulling together patient-specific monitoring, diagnosis and treatment information. Helping patients monitor and administer their medication will be fundamental to this, and offers a range of benefits.

First, it will help to improve treatment efficiency. User-friendly devices that simplify drug administration allow for medicines to be taken in the home, easing the burden on hospitals and clinics. Connectivity provides continuous monitoring. Healthcare professionals can support patients in the community, providing additional coaching where necessary and spotting issues before these lead to exacerbations and further hospitalisation.

Connectivity empowers patients. It helps patients take greater control of their condition, providing access to information, the ability to communicate with nurses and physicians and the comfort that the data is monitored by healthcare professionals (HCP's). Interactive training and support tools can be built on these platforms, driving the correct use of devices, including expert guidance and online support where needed.

Finally, these systems can join with social media. Forums such as PatientsLikeMe (PatientsLikeMe, Inc, Cambridge, MA, US) provide a way to share experiences and learn from others going through a similar situation. Many patients find this comforting, supportive and even motivational. Moving care into a home environment has many advantages, but patients can become isolated. Social media and forums can fill this gap, linking patients to others with similar experiences.

Improving Adherence

The initial driver for connectivity is often improved adherence. Poor adherence of drug prescriptions is well documented, generally around 50%. This has a significant impact; hospitalisations increase, patient health deteriorates, costs rise and pharmaceutical companies lose revenue due to unfulfilled prescriptions.

Connectivity offers the possibility of monitoring adherence, though this doesn't

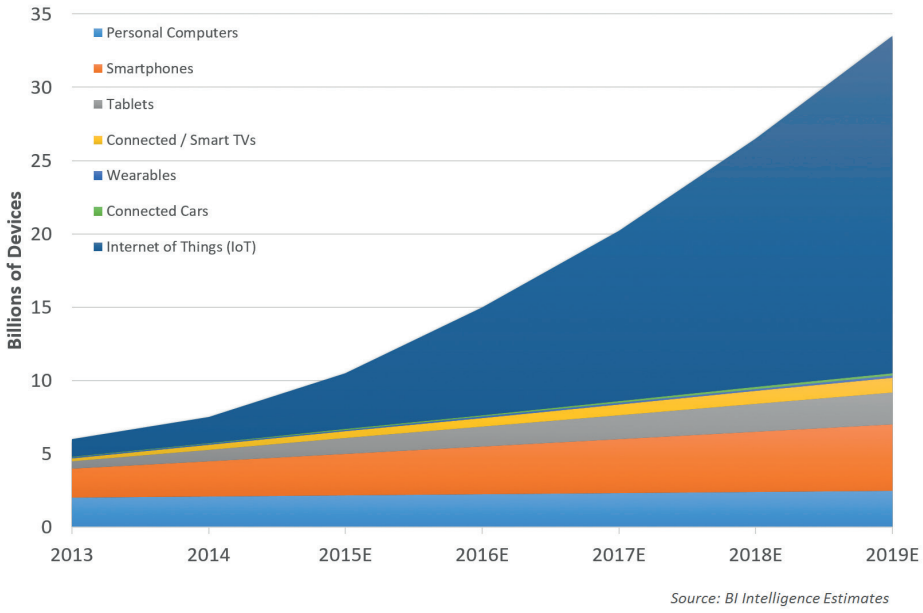


Figure 1: Number of connected devices globally, by year.

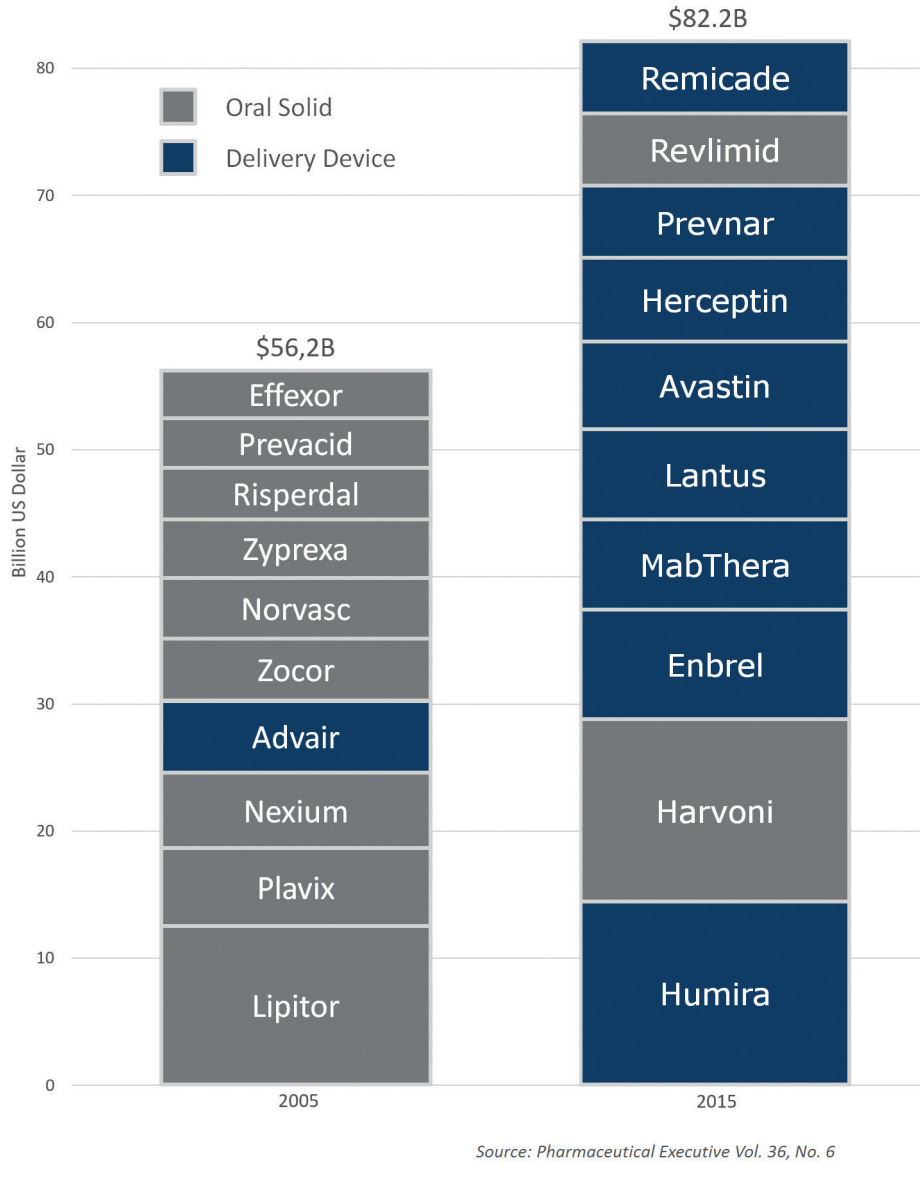


Figure 2: Top 10 drugs in 2005 and 2015.

necessary improve it. We need to understand the root causes of non-compliance to lift adherence rates. Root causes are complex and varied. Simple forgetfulness, feeling better, conflict with lifestyle and image, reinforcing the feeling of illness – all these factor in to the deep-seated psychology of not taking our medications.

So, to improve adherence, connectivity needs both to monitor drug administration and provide motivation and incentives to take medications in a timely and effective manner.

Novel Business Opportunities

Providing a direct line from HCPs to medication use opens up broader monitoring opportunities and new treatment options (Figure 3). Pharmacovigilence could be improved through more accurate knowledge of dose frequency, levels, timing and locations. More accurate data on dosing regimens can help determine if links exist between adverse events and drug intake.

Being able to monitor and control dosing frequency and levels is a key enabler of personalised and stratified medicine. Connectivity to drug delivery devices allows HCPs to individualise dosing regimens and monitor the impact on outcomes. As data sets build through real-world feedback, it will be possible to narrow therapeutic indexes for specific patient groupings, increasing the effectiveness of treatments.

This opens up novel business opportunities for pharmaceutical companies. As healthcare becomes more digital, data on a per-patient basis and across entire disease populations will lead to greater knowledge and improved decision making. This ongoing collection and analysis of data will help refine treatment regimens across patient segments to improve outcomes. In this world, data has value. Ethical concerns exist around monetising the value of this data, but the direct link to patient dosing will be a critical piece of the overall treatment data, and will certainly carry value.

Another area of growing business interest is building service models on top of drug delivery. As outcome-based payment gains traction, pharmaceutical companies are incentivised to ensure patients follow their prescriptions. Companies are establishing a broad range of support services to help patients use their drugs effectively. These services are generally provided free of charge, as pharmaceutical companies look to increase market share or demonstrate effectiveness. Other industries would look to generate revenue from these service models. Such concepts raise legitimate ethical concerns. However, there are a number of specialist service examples, such as dialysis centres, where treatment involves both medication and service delivery to provide improved care.

These models will expand with connectivity, offering improved care models for patients, and potential revenue sources for pharmaceutical companies.

THE CHALLENGES

Although the opportunities are truly transformative, sometimes the industry only sees challenges. These align around technical issues, poor business cases and concerns around data and regulatory risks, as discussed in more detail below.

Is the Technology Ready?

Smartphones have changed our perception of "connectedness". We have instant access to friends, news, music and access to countless other sources of information. This explosion in connectivity has provided significant benefits, but also brings new problems. App fatigue, password overload, constant upgrades, poor signal strength, complex user interfaces – general irritations for most of us. However, these minor concerns become significant in healthcare applications.

> "Companies seem to be focusing on lifecycle extensions of existing products to build pilot systems for connectivity ... Clinical studies are also attracting new connectivity technologies. Larger budgets can support the higher costs during a clinical study, and having real-time reporting of actual dosing can lead to faster, clearer results."

The underlying issue is that the technology on which we want to "piggyback" has been designed for another purpose by another industry; consumer products. The dynamics of this industry directly influence the areas of greatest concern to healthcare developers; stability, usability and cost.

It takes years and significant investment to get drugs to market. Demonstrating safety and efficacy across increasing numbers of disease sufferers is paramount to the ultimate success of a product. Once proven effective, there is reluctance to change. Compare this with the mobile phone business, where even Apple admitted

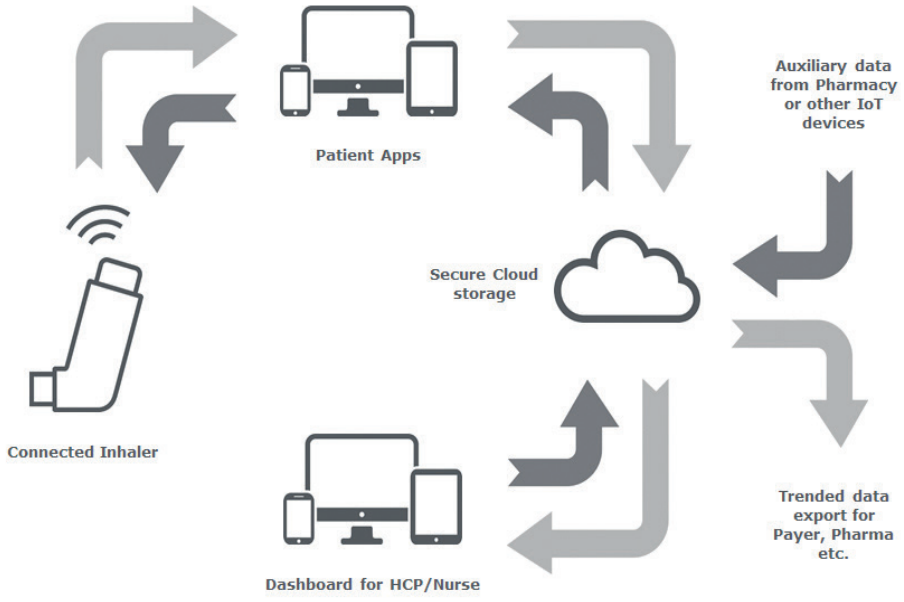


Figure 3: Taxonomy of a connected healthcare system.

last year that it expects customers to change their devices every three years, and target two major operating system (OS) updates over this time frame.

To address this, companies need to define an architecture that segregates the medical elements from the general user elements. Getting this separation right is critical to the viability of a connected healthcare product. Even then, investment is needed to support continual lifecycle management. Maintaining compatibility across multiple platforms is time consuming, but necessary to ensure great patient experiences.

Usability has been a major focus in recent years, driven by a push from the regulators coupled with critical feedback from patients and HCPs. These gains could erode with the advent of connectivity and mobile apps. The majority of connectivity systems are add-ons, requiring additional user steps to fit them onto injectors and inhalers. Without providing clear and immediate benefits, many patients stop using these systems. Connectivity cannot add complexity to taking medication.

Great user interactions will be fundamental to the success of connected products, and will continue to be a requirement of regulatory approval (Figure 4).

Figure 4: Evolving technology supporting healthcare.

Show Me the Money

Many of us can see what the technology can offer, but it is incredibly difficult to build a solid business case around these ideas. Looking at it simplistically, it appears that connectivity adds cost without delivering increased revenue. There are not many CFOs who will fund such programmes for long. Perhaps there are lessons to be learned from new digital technology companies who launch minimal viable products quickly and use these with consumers to find where the greatest benefits are delivered and revenue realised.

It is difficult for pharmaceutical companies to think about minimally viable products. Tight regulation combined with a deep focus on patient safety has driven the industry to relatively long development cycles. With fewer launches, companies squeeze as much as possible into each cycle. However, until the revenue channels are clear, controlling cost is critical. Defining basic feature sets reduces development costs and cost of goods. As it becomes clearer where revenue is generated, further features can be added to grow these revenue channels.

In today's healthcare market, it is very challenging to increase revenue within an existing drug franchise. Drug prices are under significant pressure and the payers won't reimburse for better devices or new service offerings. The best opportunities seem to be around increasing market share (or preventing erosion), demonstrating improved outcomes, increasing drug sales due to improved adherence and offering premium services direct to patients and caregivers at additional cost.

Companies seem to be focusing on lifecycle extensions of existing products to build pilot systems for connectivity. There is perhaps less risk in this approach. Existing data can be used as a baseline when assessing the effectiveness of new technologies. Clinical studies are also attracting new connectivity technologies. Larger budgets can support the higher costs during a clinical study, and having real-time reporting of actual dosing can lead to faster, clearer results.

Data Security & Regulatory Risks

Finally, there are a number of data and regulatory concerns. Healthcare information is very sensitive. Patients and healthcare professionals are rightly worried about medication data being transmitted over commercial technologies. Ultimately, patients will continue to own their own data and will need to opt in to applications that want access or use. However instances have arisen where patient data has been used without consent, leading to a culture of mistrust. Sharing data should lead to improved monitoring and care of individual patients, while at the same time allowing anonymised, disease-specific data sets to be analysed for larger trends. It is possible that such analysis will reveal new insights that will improve treatment.

The proliferation of connectivity and mobile apps has been challenging to regulate as well. The US FDA and the EMEA are clarifying their positions and guidelines in this rapidly evolving space. The number of apps approved by the regulators for medical use has increased significantly in the past two years, driven both by clearer guidance and development companies refining their own internal processes. But this remains a challenging area, as software systems by their very nature span multiple hardware domains. Current practices tend to drive revalidation (at some level) for every new OS release. This can add a significant burden, and cost, to the maintenance of these systems.

SUMMARY

Digital systems and connectivity have the potential to transform healthcare provision. Many different companies will play a role in this. Although these technologies are not their core area, pharmaceutical companies have a leading role to play. Understanding how patients take their medication, and providing support to improve adherence, will be fundamental in this journey. Adding this technology to new and existing drugs will help empower patients to manage their conditions with less hospitalisation, reducing overall healthcare costs and improving treatment effectiveness.

ABOUT THE COMPANY

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

As of May 31, 2016, Medicom became part of Phillips-Medisize Corporation. Phillips-Medisize is a leading global outsource provider of design and manufacturing services to the drug delivery and combination products, consumable diagnostics and medical device, and 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.

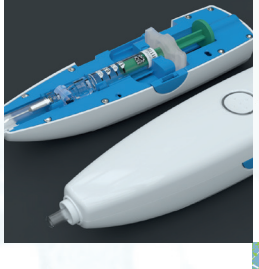
Together Phillips-Medisize and Medicom are becoming one of the leading players within the growing drug delivery device and connected health market.

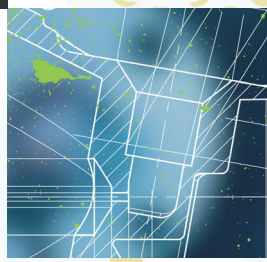
ABOUT THE AUTHORS

Kevin Deane is the Executive Vice-President, Front End Innovation for Medicom Innovation Partner, a Phillips-Medisize company. With over 25 years of experience developing new products, Mr Deane has supported a broad range of drug delivery and medical devices to market, working across the US, Europe and Asia Pacific. He leads Medicom's early-stage development team and coordinates our large-scale developments in Connected Health, from devices to data, pulling together the deep capabilities across Phillips-Medisize, Molex and Medicom. Kevin is based in Medicom's Cambridge, UK office.

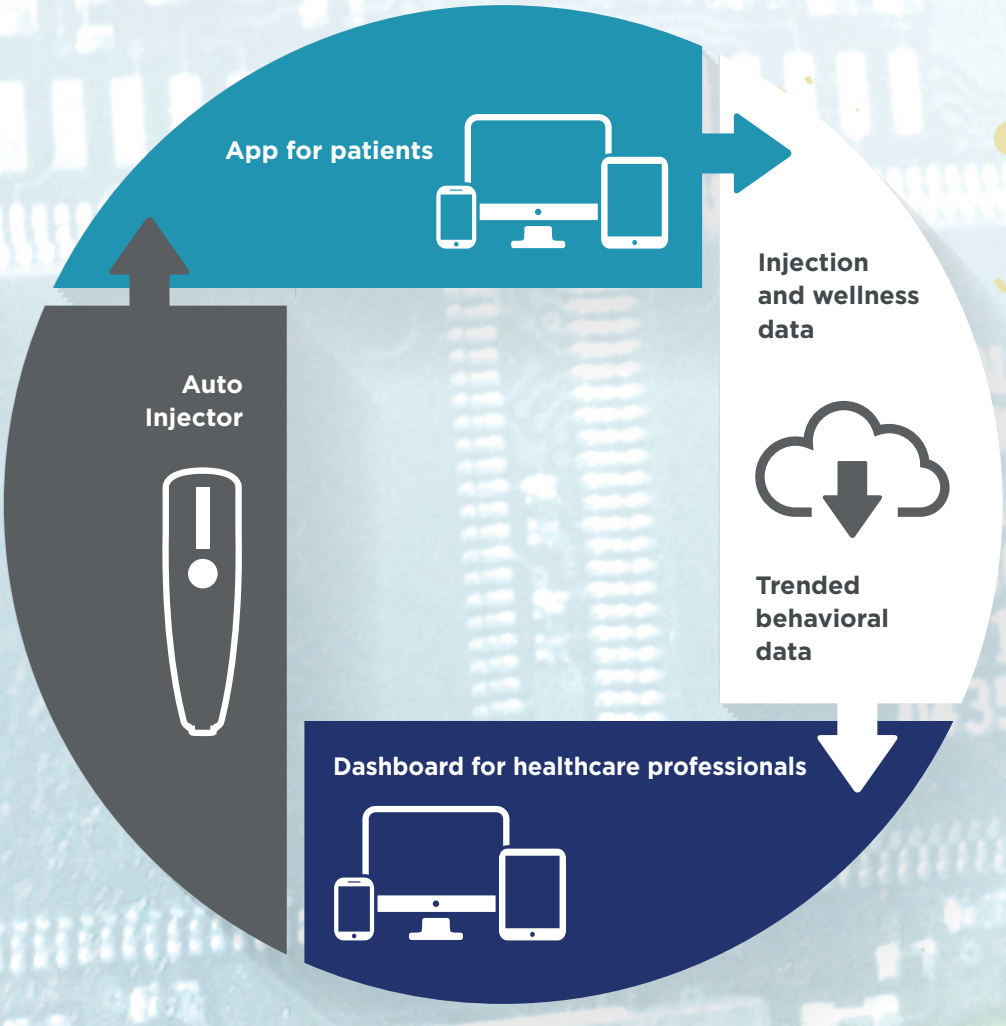
Bill Welch has more than 25 years of contract design, development and manufacturing experience, primarily serving customers in the drug delivery, health technology and diagnostics markets. In his current capacity as Chief Technical Officer at Phillips-Medisize, he leads a global, over-500 person development, engineering, tooling, program management and validation organisation with more than 75 concurrent schemes. He has been with Phillips-Medisize since 2002.

World leaders
in patient centric drug delivery systems





Devices
Connectivity
Connected Health Service Solutions



Medicom
Innovation Partner
a Phillips-Medisize Company

Phillips Medisize
a molex company

H&T PRESSPART

EMBEDDED CONNECTED METERED DOSE INHALERS MEETING REQUIREMENTS FOR MASS ADOPTION

In this article, Benjamin Jung, PhD, Program Manager, eMDI, and Dana Shears, Sales & Business Development Director, the Americas, both of H&T Presspart, describe the role connected devices can play in the treatment of asthma and COPD, discuss the requirements for mass adoption, and introduce their inhaler, the eMDI, which has connectivity fully embedded.

Non-adherence to medication is a critical problem in healthcare, especially in the area of chronic diseases. The resulting economic burden across all diseases is estimated at US$100-300 billion (£77-230 billion)[1] in the US and at €125 billion (£108 billion) in Europe.[2]

Asthma and COPD are considered as major chronic conditions. Today, more than 300 million people have asthma worldwide and this figure is set to rise by another 100 million by 2025.[3] In addition, globally more than 200 million people suffer from COPD[4] and the number of patients will also increase significantly. Uncontrolled symptoms of asthma and COPD affect quality of life, decrease work and school performance and reduce physical activity.[3] Overall asthma is responsible for 250,000 deaths per year[3] and COPD even for more than three million fatalities.[5]

> "In addition to the direct benefits for patients in terms of the clinical outcomes, connected devices for asthma and COPD treatments have potential advantages for a number of other key stakeholders."

The cost burden associated with asthma and COPD is high as well. Healthcare costs, and costs due to lost productivity, have been calculated to be as high as US$92 billion in the US[6,7] and €82 billion in Europe[8] (see Figure 1). Asthma attacks and COPD exacerbations are believed to be the main cost driver. Effective treatment and medications are readily available. In fact, the three main asthma/COPD drugs rank within the top 25 pharmaceutical products by global sales.[9]

Adherence to preventer (controller) medication for asthma and COPD – such as inhaled corticosteroids (ICS) or long-acting beta agonists (LABAs) – is critical to control symptoms.[10] Nevertheless, adherence rates to these medications have been shown to be insufficient and to vary greatly. A meta-study revealed adherence rates of 30-66%, for example, depending on the study population.[11] These rates reflect so-called secondary adherence, which occurs after the first prescription has been filled. Primary adherence, reflecting the share of patients filling the first prescription, is insufficient too.[12] As a result, due to poor adherence, a substantial number of patients do not realise the maximum benefit of their medical

Dr Benjamin Jung
Program Manager, eMDI
T: +44 1254 582 233
E: benjamin.jung@presspart.com

Dana Shears
Sales & Business Development Director, the Americas
T: +44 1254 582 233
E: dana.shears@presspart.com

H&T Presspart
Presspart Manufacturing Ltd
Whitebirk Industrial Estate
Blackburn, Lancashire
BB1 5RF
United Kingdom

www.presspart.com

treatment, often resulting in the overuse of reliever medications, increased exacerbations, frequent hospital admissions, reduced quality of life and even avoidable deaths.[13,14]

CONNECTED DEVICES TO INCREASE ADHERENCE

In general, connected devices are becoming increasingly prevalent in chronic condition management. They track patient adherence, encourage patients to take ownership of their own care, and connect patients better with their providers and other stakeholders in real time. Therefore, they offer a great opportunity to increase adherence and improve the quality of life of patients.

Currently there are a number of approved and marketed connected devices within the healthcare sector. Examples include injector pens, heart rate, blood pressure and blood glucose monitors, and pill packaging and dispensing solutions. In the area of asthma and COPD, connected add-on devices for inhalers (MDIs, DPIs, breath-actuated MDIs and soft-mist inhalers) have been approved by regulatory authorities, are being marketed[15] and used primarily for clinical studies. More recently, embedded device designs have been developed and are being evaluated.

External add-on devices have demonstrated, with proper use, the ability to increase adherence to asthma and COPD medication significantly in clinical studies. The experienced adherence uptake differs to a high degree, as some studies show an improvement above 150% while others show results below 50%. These differences can be attributed to the age and the level of asthma control within the study population and the duration of the study. More importantly, several studies have demonstrated significant improvement in clinical outcomes, including reduced exacerbations, fewer unplanned attendances at the GP or emergency department, decreased hospitalisations and less frequent use of supplemental oral steroids.[16]

In addition to the direct benefits for patients in terms of the clinical outcomes, connected devices for asthma and COPD treatments have potential advantages for a number of other key stakeholders. For physicians, patient monitoring is enhanced, visits can be scheduled more appropriately, patient-physician dialogue is fostered, diagnosis and identification of optimal medication is improved and early warnings due to changing health status can be

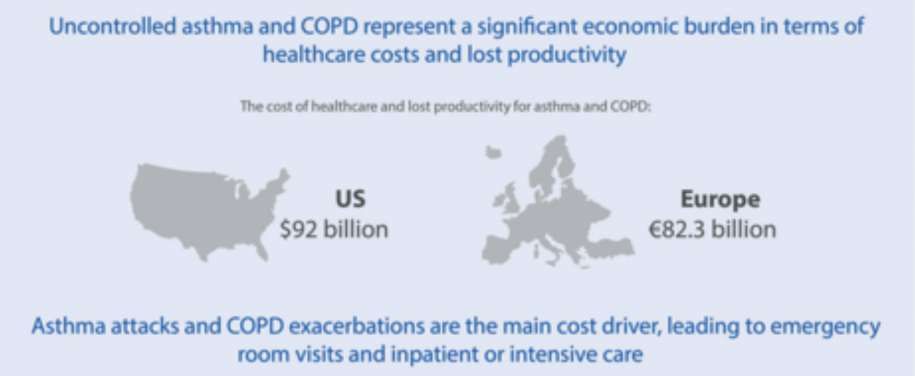


Figure 1: Economic burden of asthma and COPD.

implemented. Payers can potentially realise cost reductions due to improved healthcare utilisation, including fewer hospitalisations. This is especially promising among patients with severe asthma and COPD.[17] Employers may benefit as well, as they will experience fewer missed work days, increased productivity, and potentially a reduction in insurance premiums. Pharmaceutical companies will likely benefit from an increase in refills resulting in greater sales. Additionally, R&D spend could be reduced, as clinical trial outcomes would be more predictable and effective and, post launch, real-life product in-use data can be generated to confirm actual drug therapeutic benefits. Together, adherence and therapeutic benefit demonstrated by real-life data could boost brand image and lead to improved customer loyalty.

REQUIREMENTS FOR MASS ADOPTION

With these potential benefits for various stakeholders possible, why has the adoption of connected devices for asthma and COPD been limited to date? One answer may relate to the fact that, at present, a number of requirements for mass adoption have not been fully satisfied. In an effort to understand why, we have evaluated the situation from four different device-related perspectives: patient, business model, regulatory, and data collection and management.

From a **patient** perspective, broad acceptance is paramount. New devices and products need to be simple and should not present any significant changes to the status quo. The requirement for a patient to add a separate device to their inhaler or perform additional operations, such as recharging or disassembling the device, necessitates the need for further instruction and training. This will lead to a high likelihood of discontinued use. Patient adoption and adherence to the new connected devices for asthma and COPD can be realised through intuitive, discrete and non-reusable designs. These new designs should be based on existing inhaler forms and function similar to conventional "press-and-breathe" MDIs – the most widely used device for administering asthma and COPD medications. Connected devices should also be fully embedded, meaning the electronics are contained totally within the inhaler. This avoids patients receiving an external "add-on" device and an inhaler separately and relying on them to complete the assembly and activation properly.[18]

At the moment, a sound **business model** for connected devices for asthma and COPD is still undefined.

From a pharmaceutical company's perspective, a model based solely on improved sales due to increased adherence is subject to uncertainties, for example regarding the potential increase in primary adherence which is often not covered in studies. The realisation of higher reimbursement by payers is not proven, since validated, accurate data, to-date

> "Data integration between competing systems is critical since there are potentially multiple inhalers, from different pharmaceutical companies used in parallel applying different systems. Therefore, platforms must be designed to permit full data integration between different systems."

is limited and there are some concerns that healthcare cost reduction may not be achieved in all patient subpopulations. As such, cost sharing between payer and patient has yet to be defined and would certainly effect broad market adoption. In light of this, the features and functionality of connected devices and their associated costs should be carefully considered in order to achieve the necessary economic targets and to promote mass adoption. Therefore, the feature set offering the optimum cost/benefit ratio should be realised.[19]

From a **regulatory** perspective, changes or introductions of new technology can be challenging. In the case of existing formulations, any changes related to the drug delivery performance should be avoided. By design, embedded devices should not disrupt the drug delivery pathway or affect product performance in any way. Re-usable, rechargeable or interchangeable device features will present additional challenges and/or limitations to approval and adoption, since patients will need additional training and more extensive instructions to insure correct use of the device and fulfilment of ongoing maintenance requirements.

Conversely, incorporation of previously approved components for critical features, and replication of current device operation and existing form factors will simplify the regulatory pathway resulting in faster speed-to-market and higher gains in market share.

From a **data collection** and **management** perspective, three aspects are key: data quality, data integrity and data integration. Add-on devices can , because of their design, facilitate the generation of less reliable information as compared with fully embedded devices. In some instances, it may be possible for these connectivity devices to be used without dispensing the medication. It is also possible for the patient to use the connectivity device selectively or interchange the device with multiple inhalers.

Real-time, unadulterated data is key to confirming adherence and therapeutic benefit of prescribed medicines. Data integrity should be governed and secured by a system (connected device and platform) designed for zero data loss, proper encryption and the highest levels of security. Furthermore, data integration between competing systems is critical since there are potentially multiple inhalers, from different pharmaceutical companies used in parallel and applying different systems. Therefore, platforms must be designed to permit full data integration between different systems.

Table 1 summarises the requirements towards connected devices for asthma and COPD from different perspectives as discussed here.

Requirement towards connected devices for asthma and COPD	Underlying Perspective(s)
Intuitive, discrete	Patient
Non-reusable, disposable	Patient, regulatory
Minimal changes to the existing products	Patient, regulatory
Fully embedded design	Patient, business model, data
Based on conventional MDI inhaler designs	Patient, regulatory
Feature set with optimum cost/benefit ratio	Business model
Limited disruption to drug delivery pathway	Regulatory
Integration of approved components for critical features	Regulatory
System designed for zero data loss and proper encryption	Data
Enabling data integration	Data

Table 1: Requirements towards connected devices and underlying perspectives.

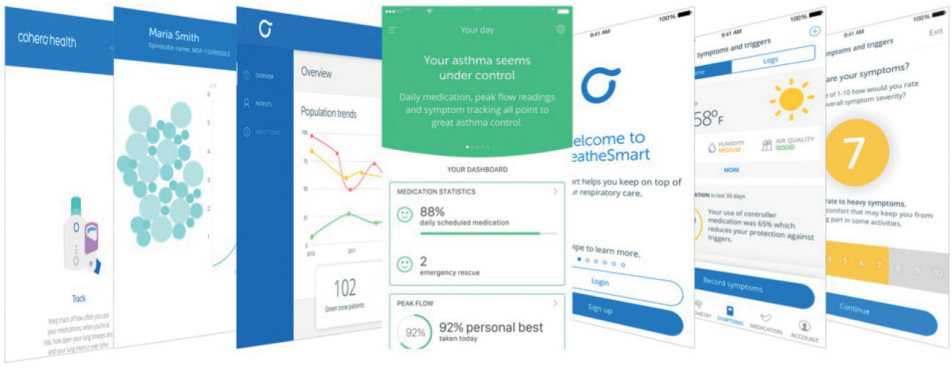


Figure 2: H&T Presspart's eMDI powered by Cohero.

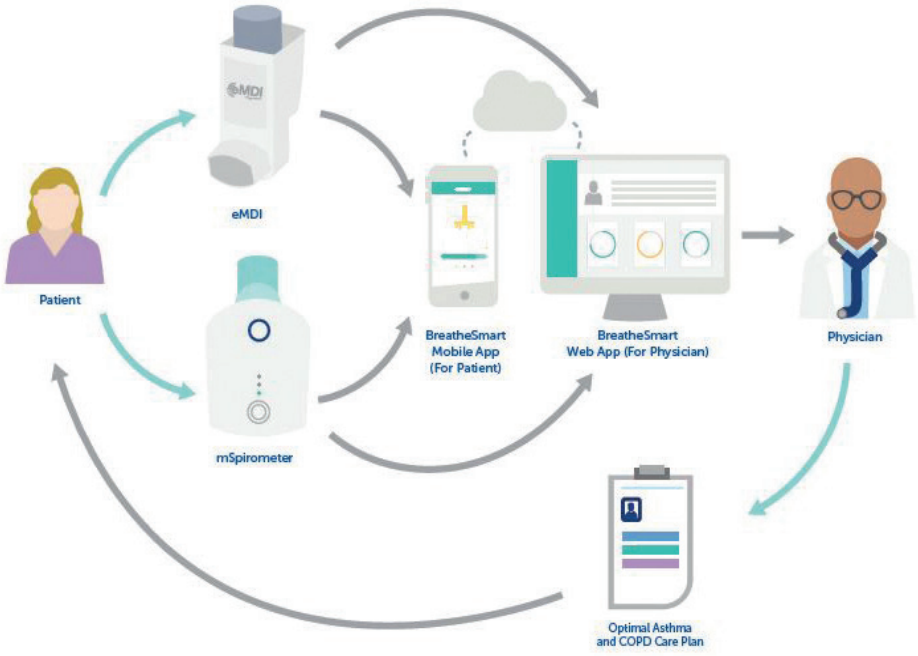


Figure 3: Integration of the eMDI with BreatheSmart from Cohero Health.

> "It is the first fully-embedded, intuitive, connected MDI comprising a feature set with an optimum cost/benefit ratio and allowing fast-track regulatory approval."

H&T PRESSPART'S eMDI POWERED BY COHERO

In an effort to address the ongoing issues of patient adherence in the area of asthma and COPD, H&T Presspart and Cohero Health (New York, NY, US) formed a strategic device development and marketing partnership. The partnership combines H&T Presspart's more than 45-year experience of MDI design and component manufacture with Cohero Health's expertise in digital innovation. As a result of this multi-year collaboration the companies created the first market-ready, fully-embedded, intuitive connected MDI solution: H&T Presspart's eMDI™ powered by Cohero (Figure 2).

H&T Presspart's eMDI powered by Cohero was developed to achieve a broad market adoption by fulfilling the requirements for connected devices – with its pure device design and with its integration with BreatheSmart from Cohero Health.

The eMDI device design represents an evolution of existing inhaler technology. Its connective hardware and software are **fully-embedded** within the actuator design, making it especially **intuitive** for patients to operate, whilst providing increased data quality and greater marketing appeal. The change to existing MDIs' form and function **is limited.** The compact size closely mirrors that of existing MDIs, permitting non-intrusive, **discrete** use by patients.

As a fully **disposable, non-reusable** unit, the eMDI eliminates the need for users to do anything other than press and breathe, as with their **standard MDI**. This eliminates the need for additional training, recharging, assembly or re-assembly. From a risk and reliability perspective, the electronic componentry is **separated from the medication delivery pathway** and the device **incorporates a US FDA-approved mechanical dose counter.**

The eMDI seamlessly integrates with BreatheSmart from Cohero Health (Figure 3), the only comprehensive respiratory disease management platform that enables tracking of both controller and rescue medications, along with clinically accurate lung function measurement via a mobile spirometer. In connection with BreatheSmart, the eMDI enables improved adherence, engagement in self-care and real-time monitoring by caregivers and the healthcare community.

The electronics detect the actuation of the inhaler, adds a date/time stamp, and shares the data wirelessly with a device application, for example on a smart phone, and a cloud. Feedback regarding the patient's actuation technique is also included in the inhaler design. The eMDI powered by Cohero has been designed to capture these key parameters to confirm patient adherence and therapeutic effect without the incorporation of sophisticated, costly sensors and other complicated mechanical parts: Therewith, it offers a **favourable cost/benefit ratio** for global adoption.

From a data perspective, the eMDI in connection with BreatheSmart is **designed for zero data loss, secure encryption** and information storage via a US Health Insurance Portability & Accountability Act (HIPAA)-compliant cloud. The capability for enabling **data integration** with other, even competing systems, has been developed and demonstrated by Cohero Health in a clinical trial in connection with the Koneska Health (New York, NY, US) data platform.[20]

CONCLUSION

With its eMDI powered by Cohero, H&T Presspart has created a versatile product designed to fulfil requirements for mass adoption of connected devices for asthma and COPD. It is the first fully-embedded, intuitive, connected MDI comprising a feature set with an optimum cost/benefit ratio and allowing fast-track regulatory approval. As such, it offers the opportunity to increase adherence and clinical outcomes for patients on a broad scale and to realise the power of real-time, accurate data. In collaboration with pharmaceutical manufacturers, H&T Presspart and Cohero Health are leveraging the potential of the eMDI for asthma and COPD sufferers worldwide. Additionally, they are enabling other stakeholders in overcoming non-device requirements for mass adoption. Together, the burden of insufficient adherence can be eliminated as "drugs don't work in patients who don't take them".[21]

REFERENCES

1 *Benjamin RM, "Medication adherence: Helping patients take their medicines as directed". Public Health Rep, 2012, 127(1), pp 2-3.*

2 *EFPIA, "Patient adherence – 50% of patients don't take their medicine properly".*

3 *Akdis CA et al, "Global Atlas of Asthma", EAACI, 2013. (http://www.eaaci.org/GlobalAtlas/Global_Atlas_of_Asthma.pdf)*

4 *GARD Web Page, "Chronic respiratory diseases". (Accessed May 2017: http://www.who.int/gard/publications/chronic_respiratory_diseases.pdf)*

5 *WHO Web Page, "Burden of COPD". (Accessed May 2017: http://www.who.int/respiratory/copd/burden/en)*

6 *Ford ES et al, "Total and state-specific medical and absenteeism costs of COPD among adults aged ≥18 years in the United States for 2010 and projections through 2020". Chest, 2015, 147(1), pp 31-45.*

7 *CDC Web Page, "Asthma in the US", May 2011. (Accessed May 2017: https://www.cdc.gov/vitalsigns/asthma)*

8. *Gibson GJ et al, "The European Lung White Book: Respiratory Health and Disease in Europe". European Respiratory Society, 2013.*

9. *PMLive Website, "Top 50 pharmaceutical products by global sales". (Accessed May 2017: http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales)*

10. *Stern L et al, "Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data". Ann Allergy Asthma Immunol, 2006, 97(3), pp 402-408.*

11. *NICE, "Smartinhaler for asthma – Medtech innovation briefing", NICE, 2017.*

12. *Fischer et al, "Primary Medication Non-Adherence: Analysis of 195,930 Electronic Prescriptions". J Gen Intern Med, 2010, 25(4), pp 284-290.*

13. *Williams LK et al, "Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma". J Allergy Clin Immunol, 2004, Vol 114(6), pp 1288-1293.*

14. *Levy ML et al, "Why asthma still kills - The National Review of Asthma Deaths (NRAD)", Royal College of Physicians Report, May 2014.*

15. *Monroe N, "Connected Combination Products: Past Present & Future". ONdrugDelivery Magazine, Issue 68 (June 2016), pp 4-10.*

16. *NICE, "Smartinhaler for asthma - Medtech innovation briefing", NICE 2017.*

17. *Mäkelä MJ et al, "Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD". Resp Med, 2013, Vol 107, pp 1481-1490.*

18. *GSK Web Page, "How smart is your inhaler", November 2016. (Accessed May 2017: http://www.gsk.com/en-gb/behind-the-science/innovation/how-smart-is-your-inhaler)*

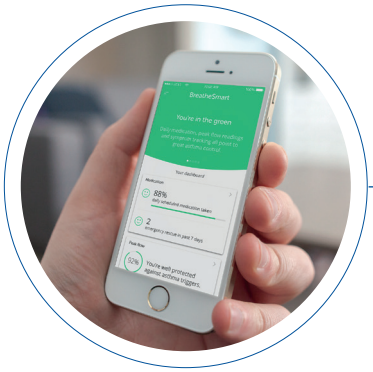
19. *Asthma UK, "Smart asthma: Real-world implementation of connected devices in the UK to reduce asthma attacks". Asthma UK, 2017.*

20. *Cohero Health, "Successful Integration: How CoheroHealth's Mobile Health Technology Powers Clinical Trials", Cohero Health, 2016.*

21. *Dr C. Everett Koop, Former US Surgeon General.*

H&T PRESSPART

eMDI powered by cohero



Smartphone app connectivity to allow real-time tracking and care management

Mechanical Dose Counter

Introducing the next generation MDI

For more information contact H&T Presspart:

www.presspart.com
eMDI@presspart.com

H&T Presspart are pleased to introduce the first market-ready, fully-embedded, intuitive and connected metered dose inhaler (eMDI) established to optimize care of patients ensuring from asthma and COPD.

The eMDI integrates seamlessly with BreatheSmart from Cohero Health, the only respiratory disease management platform that enables tracking of both controller and rescue medications, along with clinically accurate lung function measurement, in real-time.

ADDRESSING EVOLVING HEALTHCARE NEEDS WITH DIGITAL HEALTH: CONNECTING DRUG DELIVERY

Sundeep Kankanala, PhD, MBA, Vice-President, Research & Development at BD Medical - Pharmaceutical Systems, and Chris Franzese, Lead Clinical Analyst at Matchstick, explain how BD is increasingly moving towards providing solutions rather than products, particularly in the field of diabetes. Two frameworks have been created to improve the impact of the connected solutions now available for dealing with chronic disease – "Duality of Smart" and "Collect, Understand, Act".

Over the last several decades, advances in medical science have extended life expectancy substantially. However, the implications of increased longevity in an ageing population have placed chronic diseases among the most common causes of mortality worldwide. According to the Centers for Disease Control and Prevention (CDC), seven of the top 10 leading causes of death in the USA can be attributed to chronic diseases, and about half of all adults have at least one chronic condition.[1]

To accommodate this growing trend, clinical practice and the pharmaceutical industry have shifted their therapeutic focus towards managing persistent disease long-term, significantly extending the duration of care across the healthcare continuum.[2]

Simultaneously, the advent of biologic therapies has revolutionised chronic disease treatment. These novel therapies have not only unlocked the ability to manage intractable diseases, but in many cases, also offer safer alternatives to historically toxic medicines.[3]

As a result, drug development is largely centered around these high-cost, specialty medications. In 2016, eight of the top 10 best-selling drugs were biologics, and similar drugs will comprise up to 30% of the pharmaceutical pipeline by the end of this year.[4,5]

Although the benefits of biologics are profound, they do come at a price. The annual costs per patient for these treatments may range from US$10,000 to more than $150,000.[6]

The costs also extend beyond the financial. Nearly all biologics are far too large, complex and polar to be administered orally.[7] Thus, they must be injected via one of three routes: intravenous (IV), intramuscular (IM) or subcutaneous (SC). Traditionally, trained professionals delivered medicines via these delivery modes in a healthcare setting. Due to significant pressures to reduce the growing costs of healthcare, patient care is increasingly shifting to the home,[8] where patients are being asked to administer these medicines themselves.

> "To date, there are over 50 self-injected medications being used to treat a variety of diseases,[9] and the demand for delivery devices will continue to increase alongside drug development."

Dr Sundeep Kankanala
Vice-President,
Research & Development
BD Medical-Pharmaceutical Systems
T: +33 4 76 68 37 30
E: sundeep.kankanala@bd.com

BD
One Becton Drive
Franklin Lakes
NJ 07417
United States

www.bd.com

Mr Chris Franzese
Lead Clinical Analyst
T: +1 973 753 0383
E: hello@matchstick.com

Matchstick, LLC
712 Main Street
Boonton
NJ 07005
United States

www.matchstickllc.com

"Through their ability to collect a variety of information, smart devices have the potential to impact stakeholders positively across the healthcare continuum."

ENABLING SELF ADMINISTRATION

Innovation in drug delivery devices has empowered patients to self-administer injectable medications safely and cost-effectively in the comfort of their own homes. Devices range from prefilled syringes (PFS), safety syringes and pen injectors, to auto-injectors (AIs) and large-volume wearable injectors (LVIs).

To date, there are over 50 self-injected medications being used to treat a variety of diseases,[9] and the demand for delivery devices will continue to increase alongside drug development. Nonetheless, as therapies continue to evolve, delivery devices must as well.

One strategy is to develop smart devices that support a better patient experience and provide critical information to other stakeholders.

BENEFITS OF SMART DEVICES

Through their ability to collect a variety of information, smart devices have the potential to impact stakeholders positively across the healthcare continuum:

Patients
These devices can increase patients' confidence in managing their disease by:

- Confirming the drug is at room temperature and ready to inject
- Confirming that the injection was correctly performed
- Providing feedback that the injection has initiated, is proceeding, and the dose volume has been delivered
- Utilising a personalised engagement model to encourage adherence and reduce anxiety.

Healthcare Providers
Healthcare providers (HCPs) can make better treatment decisions for their patients because the devices:

- Provide medication adherence data-based analytics to guide therapeutic decisions and assess efficacy of treatment
- Confirm effectiveness in patients' training and injection management.

Payers
Devices can provide population health data to evaluate outcomes and cost-effectiveness of therapies by:

- Providing aggregated adherence data for different therapy regimens.

Pharma
Pharmaceutical companies can know that patients are taking their medications, that their devices are usable, safe and effective, and that they are offering differentiated value in the market because the devices:

- Provide aggregated confirmation of adherence to therapies
- Provide feedback on dose delivery
- "Accelerate clinical trials"
- Create a more inviting user experience, reducing patient anxiety, and driving medication adherence.

CONNECTED SOLUTIONS

As a leader in drug delivery, BD is uniquely positioned to meet the growing need for connected solutions. BD products touch patients billions of times each year, enabling the company to understand the needs of patients and caregivers.

As care delivery transitions from clinic to home, BD is taking our expertise in the acute care environment, and translating that to address the needs of patients and caregivers at home.

BD has been working on digital solutions in various business units across the company. Recognising that truly meeting patient needs requires transitioning from a drug delivery provider to providing interconnected disease management systems, BD has invested in consolidating its digital expertise to develop fully-integrated, drug delivery solutions.

"The creation of BD Digital Health demonstrates leadership recognition that digital health is here to stay, and BD must build a strong capability in this area to provide direction and growth for the future," says Dave Icke, Vice-President and General Manager, BD Digital Health. "The new business unit provides a centre of innovation that expands upon BD's base of software expertise, to create technologies, capabilities and platforms that can help make existing BD technologies smart to increase value to the system and establish new services, capabilities, and solutions that address unmet needs in healthcare."

BD's connected solutions are built on a foundation of expertise in primary containers, clinical injection, and drug delivery. The result is improved overall device performance, ensured drug compatibility, minimised risk of system failures, and enhanced patient experience. To achieve this, BD applies two unique frameworks for their connected systems.

Duality of Smart
BD's "Duality of Smart" approach considers that features need to fit specific market needs – not every patient or situation requires the same degree of connectivity.

BD approaches smart technology on a continuum ranging from "local" to "connected" solutions.

A local smart delivery device provides information only to the patient, based on what the device senses. Because communication occurs directly from device to patient, connectivity to external devices is not needed.

A connected smart device allows data to flow off the device wirelessly (e.g. via Bluetooth or RFID) to a receiving unit, namely a patient's phone or cloud server.

Information sent to a patient's phone may be used solely by that patient, such as contextual instructions for use, which would enable patients to move through the injection steps displayed on the phone's interface as they progress through the injection. Data sent to a cloud server may be used to aggregate information for other stakeholders, such as caregivers, healthcare providers, payers or manufacturers.

The Duality of Smart approach supports scalability of smart solutions, allowing pharmaceutical brands to choose which option to pursue aligned to their unique patient needs.

Collect, Understand, Act
BD's "Collect, Understand, Act" framework ensures that connected solutions provide the greatest benefit to the target patient population. This three-phase approach centres around gathering the right information, translating it into an actionable form and presenting it in ways that engage patients when they need it, wherever they are.

"This modular approach provides pharmaceutical companies with a viable platform technology option, which can offer smart features or not, depending on the needs of different patient populations and therapies."

Figure 1: BD Vystra™ disposable liquid pen (below) with smart pen technology (above).

Collect: The Collect phase focuses on accumulating data, whether actively from the patient or passively from the smart delivery device. Collected data could include drug administration metrics, information logged by patients themselves, and data sent from other connected devices. Regardless of data type, it requires normalisation to be useful.

Understand: In Understand, algorithms and analytics help transform data into useful insights for patients or other stakeholders.

"What we're trying to deliver are actionable, personalised insights, captured through smart devices," says Icke.

Act: The final phase, Act turns insights into solutions, and delivers them to patients in the moment that they need them, wherever they are. This is where creating a positive patient experience and rich data sets, combined with BDs expertise in healthcare, delivers a patient engagement engine that could result in better clinical outcomes.

"Chronic disease patients are rarely afflicted with a single disease. They typically manage a variety of co-morbidities simultaneously. To be successful, solutions must consider the entire patient."

By applying these frameworks, BD is already building patient experiences, capabilities and platforms that have applicability across disease states.

EXAMPLES OF CONNECTED DEVICES

BD is developing solutions that offer ways to manage conditions that fit with patients' lifestyles and needs, starting with smart pen technology and BD's on-body injector.

BD Vystra™ Disposable Pen and Smart Pen Technology

BD's smart pen technology captures irrefutable dose data via a wireless-enabled attachment that allows for communication and integration with other data in a fashion that is compliant with cybersecurity standards.

This innovative attachment converts traditional pen injectors like BD's Vystra pen injector into a smart pen injector. BD Vystra is an intuitive, high-quality and customisable disposable pen injector, which has been validated by rigorous ergonomic and quality assessments to ensure ease of use, comfort, and reliability (Figure 1).

BD's smart pen technology is flexible across other products – it is compatible with all leading diabetes pen injectors in addition to Vystra and offers open application program interface (API) protocols to accommodate multiple data integration approaches. However, BD isn't stopping there to make interconnected diabetes management accessible for all diabetes injectors.

BD On-Body Injector

BD is developing an elegant solution to simplify the lives of patients with an on-body injector designed to deliver time-delayed subcutaneous injections.

The device is comprised of two components: a programmable, body-worn delivery device that can accommodate a total dose of up to 3 mL, in single bolus or multiple doses, and a durable wireless controller that will last for two years (Figure 2).

The design of the device is small and discreet, which affords patient comfort and concealability during wear and injections. In addition, the injector is backed by a new drug administration Current Procedural Terminology (CPT) code to support proper reimbursement.

Unlike BD's Vystra, the on-body injector has inherent smart capabilities, including programmable delayed dosing, (which offers the possibility of fewer doctor visits), secure wireless communication of dosing information, and seamless integration of data with other connected systems.

BD is considering options for applying these technologies beyond diabetes to meet the needs of other patients taking injectable biologics.

Figure 2: BD's programmable on-body injector.

FULLY-INTEGRATED AND PLATFORM SMART TECHNOLOGIES

BD is leveraging the digital capabilities built for diabetes management together with their extensive expertise in providing prefillable primary containers and combination product devices to serve its pharmaceutical customers better.

BD's range of devices can accommodate changing formulation requirements and patient requirements across many disease states, while enhancing the patient experience and delivering information beneficial for a variety of chronic diseases.

BD Libertas™ Wearable Injector

After extensive preclinical and clinical research characterising the injection experience with large-volume SC injections, BD developed the BD Libertas wearable injector to deliver large-volume and/or high-viscosity biologics. BD Libertas, a single-use, disposable, hands-free, prefilled syringe-based delivery system, is flexible and customisable to industry needs, and leverages Neopak™ technology for delivering doses of 2-10 mL (Figure 3).

BD Libertas features a fully-integrated prefilled syringe design that uniquely enables aseptic transfer of drug from the container into the body of the device without user assembly. BD conducted extensive generative research to inform an intuitive, ergonomic design. The injector's two-step "slide-push" button activation is designed to prevent inadvertent activation of drug delivery, enhancing patient experience and preventing high-value drug loss. The device interface features visual, tactile and audible indicators to inform patients about their injection state and provide assurance throughout the injection process, including dose progression and confirmation.

BD Libertas' smart technology utilises a modular approach through a customisable top case that incorporates sensors and electronics. This modular approach provides pharmaceutical companies with a viable platform technology option, which can offer smart features or not, depending on the needs of different patient populations and therapies.

The smart option has the capability to detect data on drug temperature, dose progression, dose confirmation and device errors, provide feedback to patients on these device states and transmit this information via Bluetooth to an app on the patient's smartphone.

Figure 3: BD Intevia™ disposable auto-injector.

Figure 4 : BD Libertas™ wearable injector with Smart option.

Additional developments underway include such a user-friendly app for patient engagement and healthcare provider interaction.

BD Intevia™ Auto-Injector

BD Intevia is an auto-injector platform technology specifically designed for high-viscosity drug delivery. Like BD's other delivery devices, Intevia's development has been rigorously informed by human factors studies, resulting in a slim, intuitive, and ergonomic design with multiple visual and audible indicators to enhance patient experience (Figure 4).

The device also features two-step, push-on-skin activation to avoid accidental or premature injection initiation. Intevia can include a smart option for the auto-injector platform. This will allow for a scaled, cost-effective approach to smart technology, that is flexible to industry needs.

MOVING FROM PRODUCTS TO SOLUTIONS

BD has long been a leader in drug delivery devices. As the market needs evolve, BD is moving from providing products to providing solutions that address the needs of the multiple stakeholders involved in the healthcare ecosystem.

By investing in a digital health business unit that can create platforms to address individual business unit needs, BD is constructing a system that leverages expertise across the company to deliver smart solutions to the market.

BD's ultimate vision for an interconnected disease management system will encompass the entirety of a patient's disease, including all therapies. Chronic disease patients are rarely afflicted with a single disease. They typically manage a variety of co-morbidities simultaneously. To be successful, solutions must consider the entire patient experience.

Collaboration across industry stakeholders provides the path to patient-centered, fully integrated solutions. BD recognises this need and is engaging to build the coalitions required to deliver this vision.

BD Libertas, BD Intevia, BD on-body injector, and BD smart pen technology are products in development; some statements made are subject to a variety of risks and uncertainties.

REFERENCES

1 *"Chronic Disease Overview". National Center for Health Statistics., 2012.*

2 *Royal Philips, "Future Health Index", 2017.*

3 *Bak A, Leung D, Barrett SE, et al, "Physicochemical and Formulation Developability Assessment for Therapeutic Peptide Delivery - A Primer". AAPS J, 2015, Vol 17(1), pp 144-155.*

4 *Philippidis A, "The Top 15 Best-Selling Drugs of 2016". Genet Eng Biotechnol News, March 2017.*

5 *Lyebecker K, "The Biologics Revolution in the Production of Drugs". Fraser Institute, 2016.*

6 *"High-Priced Drugs: Estimates of Annual Per-Patient Expenditures for 150 Specialty Medications". AHIP, 2016.*

7 *Bak A, Leung D, Barrett SE, et al, "Physicochemical and Formulation Developability Assessment for Therapeutic Peptide Delivery - A Primer". AAPS J, 2015, Vol 17(1), pp 144-155.*

8 *R Mathaes et al, "Subcutaneous Injection Volume of Biopharmaceuticals – Pushing the Boundaries." J Pharm Sci. 2016, Vol 105, pp 2255-2259.*

9 *"Self-injectable specialty drugs: 2016 Aetna Specialty CareRxSM Benefits Plan Drug List."Aetna, 2016.*

ABOUT THE COMPANY

BD is a global medical technology company that is advancing the world of health by improving medical discovery, diagnostics and the delivery of care. BD leads in patient and healthcare worker safety and the technologies that enable medical research and clinical laboratories. BD provides innovative solutions that help advance medical research and genomics, enhance the diagnosis of infectious disease and cancer, improve medication management, promote infection prevention, equip surgical and interventional procedures, and support the management of diabetes. The company partners with organisations around the world to address some of the most challenging global health issues. BD has nearly 50,000 associates across 50 countries who work in close collaboration with customers and partners to help enhance outcomes, lower healthcare delivery costs, increase efficiencies, improve healthcare safety and expand access to health.

ABOUT THE AUTHORS & CONTRIBUTORS

Sundeep (Sunny) Kankanala is Vice-President of R&D for the BD Medical – Pharmaceutical Systems (PS) business. His responsibilities include leading product and technology development across the PS project portfolio. Previously as the Director of Smart Device and Data Sciences focus area at BD Technologies, Dr Kankanala lead the development of IT enabled medical device technologies to capture and make meaning – e.g. through patient and clinician decision support – of diagnostic and therapeutic data, to improve outcomes in chronic disease management. He also spent three years in BD's Infusion Therapy business leading the product development of new IV catheters. For his contributions to this program, he was recognised with BD's Wesley J. Howe Award for Technical Innovation in 2016. Prior to joining BD, Dr Kankanala was a Subject Matter Expert in Smart Materials and Advanced Safety Systems at Ford Motor Company (Dearborn, MI, US). His fifteen years at Ford spanned a range of assignments across biomechanics and smart materials to advanced occupant safety systems. He has several peer-reviewed scientific journal papers in smart materials and automotive engineering fields. Dr Kankanala received a PhD in Aerospace Engineering from the University of Michigan (Ann Arbor, MI, US) for his theoretical and experimental work in magnetoelasticity. He also earned an MBA from MIT's Sloan School of Management (Cambridge, MA, US).

Chris Franzese is the Lead Clinical Analyst for Matchstick. In this role, he is responsible for leading a team of clinicians supporting client projects related to combination product and medical device development and usability testing. He also has responsibility for teaching clinical content to the broader Matchstick team and making clinical knowledge relevant to client projects. Mr Franzese is an experienced clinical trial researcher, with 11 peer-reviewed papers on a variety of topics related to usability research for connected medical devices, anticoagulation and clinical laboratory testing. He has a BS in Biology from Loyola University, and is pursuing a concurrent PharmD and MS in Health Informatics from Fairleigh Dickinson University.

Dave Icke joined BD in 2016 to lead the Digital Health Business Unit, supporting the Medical Segment. Prior to BD, he served as a consultant to multiple private and public companies (such as Profusa, Twine Health, Qualcomm and Flextronics) to launch new initiatives in digital health. Until 2014, Icke served as the founding Chief Executive Officer of MC10 – a pioneer in patch-based biometric wearables for digital health, fitness, and medical devices. Earlier in his career he had experience scaling IoT businesses and running P&Ls in semiconductor equipment companies. Icke has a BS in Chemical Engineering from Stanford University, and an MBA from Harvard Business School.

THE DIFFERENCE OF ONE DRUG DELIVERED

FOR BETTER TREATMENT OF CHRONIC DISEASES. Across the healthcare continuum, BD is the industry leader in parenteral delivery devices that help health systems treat chronic diseases. We not only continually advance clinically proven, prefillable drug delivery systems, we do so with a vision to help healthcare providers gain better understanding of how patients self-inject their chronic disease therapies outside the healthcare setting. This is why we partner with leading pharmaceutical and biotech companies worldwide to develop digitally-connected self-injection devices—including wearable injectors and autoinjectors—to capture valuable data that can be shared with caregivers. Discover how BD brings new ideas and solutions to customers, and new ways to help patients be healthy and safe. **Discover the new BD.**

BD Libertas™ wearable injector

BD Libertas™ wearable injector with Smart option

BD Intevia™ autoinjector

Learn more at bd.com/Discover-BD1

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

BD

IMPLANTS CONNECT PATIENTS FOR BETTER, FASTER, MORE PERSONALISED CARE

In this article, Will Rosellini, JD, MBA, Chairman & Chief Executive Officer, Nexeon MedSystems, and Beth Rosellini, DDS, Consultant to Nexeon, describe the rapidly advancing area of local field potential recording of nervous system activity which, via brain-implanted devices, has the ability to record detailed patient data directly and, in conjunction with other devices including drug delivery devices, has the potential to form highly advanced connected and closed-loop systems, taking personalised care and the recording of biometric and other data to a new level of sophistication.

INTRODUCTION

The nervous system functions very much like a sophisticated symphony of interrelated nuances and bold activities, both passive undertones (parasympathetic and sympathetic nervous systems) and more conspicuous expressions (pain and motor nerves). The nervous system communicates via electrical signal to control almost every cell and organ of the body either directly or indirectly. Observation of correlated system stimuli and system reactions provided early intrigue into the power of tapping into or even controlling this communication pathway. Thus, the application of electrical impulses to biological and medical systems has grown in use throughout history to illicit therapeutic responses, and it continues to grow as the science and technology improve around it.

In the past few decades, modern medicine adopted electrical impulse therapy for the treatment of various medical conditions in the form of cardiac pacemakers, deep brain stimulators, among others. Nowadays, most bioelectronics are still limited in use to conditions refractory to traditional pharmacotherapy. But with exponential advancements in hardware, software, machine learning, and leveraging of big data analytics, it is reasonable to hypothesise that the engineering and technology will eventually prove to be more efficacious than prescribed medications and to present with fewer side effects as well.

> "Biometric data and personalised care are being explored and delivered in a way that has never been seen before, which is presenting a whole new frontier in treating disease."

WHERE WE'VE BEEN: DISCOVERING THE WHERE & THE HOW

If you're familiar with the Steve Jobs and Bill Gates race to develop and capture the home computer market in the late 1980s, then you'll quickly be able to get a pulse on the progress that's been made in the field of neurostimulation. The focus over the last 15-20 years has been on development of hardware, and due to the substantial cost, regulatory hurdles, and other barriers to market entry, the majority of this traction has been executed by the largest players in the space: Medtronic (Minneapolis, MN, US), Boston Scientific (Marlborough, MA, US), and St Jude Medical (St Paul, MN, US).

With the capacity and knowledge available, researchers primarily investigated where this neurostimulation therapy could be effective; more specifically, on which nerves and in what parts of the brain to treat chronic neurological diseases such as epilepsy, Parkinson's disease, dystonia, overactive bladder, medication-resistant obsessive compulsive disorder, and others. The field primarily needed to develop and refine the "tools" by which to deliver stimulation inside the body. Secondarily, development of the "map" of the chronically diseased human body needed to be discovered to understand where best to employ these tools.

Mr Will Rosellini
Chairman & Chief Executive Officer
E: wmr@nexeonmed.com

Dr Beth Rosellini
Consultant to Nexeon Medsystems
E: beth@veloverge.com

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

www.nexeonmed.com

Because of this preliminary thrust of research needed, learnings around the mechanisms of action for these neurostimulation pathways have been limited, and the current device-based systems are riddled with issues. Existing devices target large areas of tissue indiscriminately rather than honing in on specific groups of neurons within circuits. Therefore, prescribed dosages of stimulation must balance the benefits of stimulating the desired target tissues and the drawbacks of the side effects associated with stimulating the non-target tissues.

Other issues involve the arduous nature of initial and ongoing device programming as well as the need for follow-up surgeries for battery and device replacement every 3-5 years. Most patients require a bolus of post implantation time spent with their physician to program the device, and there is no accepted best care standard for ongoing monitoring of the therapy. And while patients maintain some degree of pharmacotherapy, the relationship between these intimate systems is vastly under-optimised.

So despite there being great progress in the where and how over the past 20 years in this field, recent scientific advances have made it apparent that there's much to be learned about the why. And the sophistication of the technology is directly proportional to the ability to understand and take action on new learnings.

WHERE WE ARE TODAY: STUDYING AND MASTERING THE WHY

The tremendous implications of this science has caused a proportionate amount of funding to innovate solutions and commercialise products in this space. With the introduction of competition, there have not only been device-centric inventions, but there has also been plenty of clinical application ingenuity as well as system optimisation activity for patients and physicians alike.

Components of the research being explored today in bioelectronics are comparable with learning a new language. Neuro-engineers and their partnering healthcare providers are learning to read and write the electrical signals that travel between the brain and the body's organs and also learning to deliver these messages in a more precise manner. Biometric data and personalised care are being explored and delivered in a way that has never been seen before, which is presenting a whole new frontier in treating disease.

Figure 1: The nervous system communicates via electrical signal to control almost every cell and organ of the body either directly or indirectly.

Known as local field potential recording (LFP recording), certain implantable devices now being rolled out are capable of sensing and interpreting nervous system activity at the site of stimulation. This feedback can be thought of as serving as a "stethoscope to the brain"; so while the brain is being stimulated to illicit a desired therapeutic response, the bidirectional system allows for feedback to be sent and evaluated. While it is relatively commonplace now to stream data from patients, to connect them more frequently and more conveniently to their healthcare providers, that data has been limited to basic biometrics. These newly developed and launched device solutions provide improved alternatives to manual collection of data by a patient either via a digital or manual journal or medical log.

Researchers are learning the language of these neural signals so that we can listen for signals of disease or injury. We are also using bio-electronic medicine technologies to record, stimulate, and block neural signals, which is essentially teaching the body how to heal itself. Real-time streaming of recorded deep brain activity increases the convenience, accuracy, and volume of patient information collected.

Deep brain stimulation therapy has been prescribed worldwide in over 135,000 patients with Parkinson's disease, yet the mechanism of action is not fully understood. The long-term implications of LFP recording include better disease management as well as data-based analysis of a disease and therapy that have been mysterious in many ways for decades. Beyond that, most of these patients do not suffer from only this one morbidity. In fact, many of these patients are burdened with other chronic neurological comorbidities such as depression, dementia, COPD, dysphagia, overactive bladder, to name a few. These comorbidities require a therapeutic pathway as well, but all pharmacotherapy, device-based therapy, and any other solutions, influence efficacy of the others. And whether these patients lack capacity or motivation, their ability to track the nuances of their multi-variable-related status is negligible relative to the passive automation of recording from an implanted device.

Today, we are on the precipice of a technological development and near-term

"The vision for the internet of medical things technology and the interconnectivity of drug delivery includes building and iterating upon all aspects of the current chronic disease therapy delivery model: from the very micro iteration of the type of material used to house the electrode in the deep part of the brain all the way to the macro, population-based trends detectable and actionable as related to disease comorbidity diagnosis and treatment."

Figure 2: Nexeon's Synapse deep brain neurostimulation system includes: leads implanted into the deep part of the brain (front); implantable pulse generator typically implanted in the subclavicular region (left); patient controller (center); external battery recharger (right); and the physician reprogrammer tablet (rear).

deployment that we hypothesise will majorly advance our understanding of complex diseases and how those diseases can best be treated.

The contribution to this current phase of development has been both vast and exciting. Medical device manufacturers such as Medtronic and Nexeon MedSystems are working to make this data stream fast and easy to collect while not compromising the simultaneous delivery of stimulation therapy.

Nexeon is developing its Synapse deep brain neurostimulation system (Figure 2) which includes leads implanted into the deep part of the brain, an implantable pulse generator typically implanted in the subclavicular region, a patient controller, an external battery recharger, and the physician reprogrammer tablet.

As announced in late 2016, GlaxoSmithKline is leveraging devices (already built) to develop unique pathways for drug delivery. Elon Musk, PayPal Co-Founder and, more recently Co-Founder of Neuralink Corporation (San Francisco, CA, US), and Facebook CEO Mark Zuckerberg, have recently announced an investment in the software and big data development associated with the brain-computer interface. All thrusts are of vital importance and appear to be working towards the common vision of improving therapeutic outcomes for patients, easing the pathway in which a physician provides the care, and increasing collective knowledge to make higher quality and more accurate care decisions moving forward.

VISION FOR THE FUTURE: WHERE ARE WE HEADED NEXT?

To say the implications of these technological advancements and increased connectivity will be interesting for healthcare is an understatement. This is a field where the leaders are trained based on the experience of those that came before them as well as the research journals and continuing education courses they have sufficient capacity with which to engage. That capacity is only diminished when considering the government initiatives occuring globally to increase the total number of patients required to be serviced by the healthcare system but without making proportionate increases in the infrastructure that provides that service. Thus, the same number of doctors are seeing more and more patients.

Physicians and neuro-engineers are cautiously optimistic that this never-before collected data will provide the basis for adaptive (deep learning) closed-loop device systems, remote physician management systems with little to no disruption to patient quality-of-life, and individually-optimised therapies with minimised undesired side effects.

Data-driven discovery and decision making provides much of the revolutionary platform upon which this proposed access to care can be delivered. With the progression of the technology, the big data management and outpouring of analytics will facilitate and expedite much of the physicians' process. Additionally it will eliminate the redundant or predictable decisions, such that the physicians' time can be streamlined to focus on what only they can do: diagnose, treatment plan, perform procedures, and care for patients. Additionally, leveraging big data from

"Physicians and neuro-engineers are cautiously optimistic that this never-before collected data will provide the basis for adaptive (deep learning) closed-loop device systems, remote physician management systems with little to no disruption to patient quality-of-life, and individually-optimised therapies with minimised undesired side effects."

implanted patients has been assumed to be a valuable pathway to increasing the quality of care to patients in more rural areas. These smart devices could support physicians who are less experienced or less knowledgeable about a particular therapy by providing therapeutic parameters developed from the data of thousands of other patients managed by leading physicians from anywhere in the world.

The vision for the internet of medical things technology and the interconnectivity of drug delivery includes building and iterating upon all aspects of the current chronic disease therapy delivery model: from the very micro iteration of the type of material used to house the electrode in the deep part of the brain all the way to the macro, population-based trends detectable and actionable as related to disease comorbidity diagnosis and treatment. More specifically, beloware a few of many different ways in which patient therapeutic outcomes will be improved via the interconnectedness of medicine:

- Closed-loop devices. Deep learning and algorithm-based therapy adjustments will eliminate traditional medicine's approach to give "typical" dosage and then guess/check on how to adjust medications or therapy based on patient verbal feedback or physician observation of symptoms. Instead, we will be recording patients' unique responses, as well as many other influential biometrics, to fine tune the perfect drug dosages and/or supporting therapies. This establishes the swiftest pathway to achieving the best therapeutic window with minimal side effects.
- Connectivity of all variables. These devices, charged molecules, sensors, and microchips support an interconnected system in which drugs can be turned on and off, can be driven into specific tissues, and/or can be tracked for patient-specific efficacy in delivery. Data on all of these variables provide enhanced decision making related to ongoing management of the disease.
- Comorbidity management. Monitoring and sensing for closed-loop management of diseases and therapy will open the door to centralising care decisions and management. When a global system allows evaluation of everything from patient compliance to prescribed therapy success and failures, the healthcare provider can advise on best practices for improved outcomes.
- Reasonable hypotheses exist around the impact of big data analysis on multivariable biometrics of biological systems that have never been monitored before. Some in the field speculate that new trends, correlations and patterns will be discovered when connected technology facilitates rapid accumulation and deciphering of patient data points.
- More personalised care delivered via a more accurate process, while providing a platform for patient augmentation. As healthcare providers and patients are relieved of some of the burden of disease and therapy management, it will be interesting to observe how this technology and new capacity are employed beyond taking a patient from sick to healthier or healthy, but instead taking healthy patients to higher levels of performance. It may sound like science fiction, but we're edging closer to a future where precision electronic therapies sit alongside the medicines and vaccines we use today.

ABOUT THE AUTHORS

Will Rosellini, a former minor-league baseball pitcher, holds five masters degrees in addition to a law degree. He is a 15-year veteran of the neurotechnology space and has expertise in accelerating the development of emerging technologies with minimal at-risk capital. From 2005-2012, Rosellini was a founder and served as CEO of Microtransponder, a company developing vagal nerve stimulation for treatment of stroke and tinnitus. He left that position after being treated for and temporarily losing his voice from thyroid cancer. He went on to serve in other Board and C-level positions for various biomedical device companies and research programs, until he came on as Chairman and CEO of Nexeon MedSystems. Rosellini and his team are preparing for an early 2018 German commercial launch of this technology for the treatment of symptoms associated with Parkinson's disease.

Beth Rosellini joined her brother Will over four years ago in his pursuit to resolve much of the unmet needs of patients with chronic neurological disease as well as the healthcare providers who care for them. After studying chemistry and mathematics, Beth went on to get a Doctorate in Dental Surgery, with niche focus on head and neck-related emerging therapy research. In early 2 013, she founded and operated a telemedicine business delivering mobile dental care, clinical engineer service, and telecounselling support in long-term nursing care facilities. She concurrently engaged in various NIH-funded research programs related to neurostimulation in the head and neck as both Industry Expert and Principal Investigator. After exiting her telemedicine business in 2016, Dr Rosellini invested the proceeds into Nexeon and went on to serve in various roles in both clinical and research as well as business development functions. At the end of 2016, she left her position at Nexeon and founded VeloVerge, a medtech- and healthcare-focused business development consulting group that supports emerging therapies from innovative research to impactful commercialised product and ongoing service support. She maintains an ongoing relationship with Nexeon, consulting on various front-end related research and communication endeavours

TECHNOLOGY SHOWCASE: FLEX DIGITAL HEALTH PLATFORM

CONVERTING DATA INTO INSIGHTS

Today's technologies are driving a proliferation of connected smart medical devices that are transmitting a wealth of data. This is driving significant disruption to the delivery of healthcare and introducing the need to harness new data sources, turn data into insights, and use these insights to drive patient, provider and care-giver behaviour change. For pharma, this translates into more direct patient engagement and, therefore, improved drug adherence.

"Generating raw data isn't enough. Pharma and med tech companies must apply the analytics to derive valuable insights from multiple sources of data, applying data science and machine learning to derive more accurate insights, and they must do so at scale."

Over the last few years, leading healthcare companies have been enabling real-time data transfer via smart devices, effectively creating a closed-loop ecosystem that solves the problem of data-gathering in remote settings. However, generating raw data isn't enough. To create value at scale, healthcare companies must leverage analytics in conjunction with these newly created sources of data to identify valuable insights for their patient populations. This evolution requires a differentiated deployment approach in conjunction with integrated digital health solutions.

The speed of development timelines, economics involved and likelihood of success for pharma and med-tech companies are better when leveraging a technology partner that offers a solution that is scaled to support multiple customers, as opposed to a closed system. More importantly, this solution needs to meet and exceed the regulatory, privacy and security requirements that pharma and med tech companies need to adhere to in the US and across the globe.

THE FLEX DIGITAL HEALTH PLATFORM

The *Sketch-to-Scale*™ solutions provider, Flex, leverages investments and its expertise developing connected devices to empower and enable its medical partners in this new connected world. Flex recognises the substantial investment device and pharma companies are being faced with in terms of development and ongoing management costs to support a regulated software-stack, but also an opportunity to harness data from multiple sources to improve patient insight and thereby the patient experience.

"The speed of development timelines, economics involved and likelihood of success for healthcare companies are better when leveraging a technology partner that offers a solution that is scaled to support multiple customers, as opposed to a closed system"

Angela Wright
Vice-President, Strategic Partnerships & Business Development, Digital Health
T: +1 512 289 4060
E: angela.wright@flex.com

Flex
6201 America Center Drive
San Jose
CA 95002
United States

www.flex.com

"The Flex Digital Health group is building the world's first medical regulated, HIPAA-compliant, open architecture platform of connected medical devices, tied to a complementary, cloud-based software stack for commercialisation and scale."

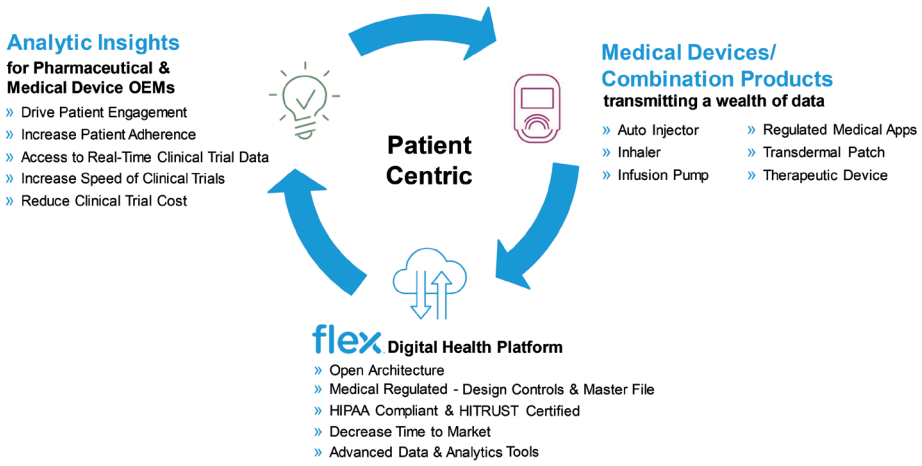


Figure 1: Flex is building a seamless, scalable platform to enable regulated connected medical device adoption.

"Med-tech and pharma companies do not want regulated IT to become a costly barrier to market, nor do they want this type of development and maintenance investment to distract from core innovation and R&D," says Dr Kal Patel, Senior Vice-President of Digital Health at Flex.

Flex estimates the upfront development cost for device manufacturers and pharma companies to implement a connected solution themselves to be in the US$3-$6 million (£2.4-4.7 million) range for a single product. "This cost doesn't even begin to address ongoing maintenance costs, including monitoring, security and updates," says Dr Patel. "Furthermore, how can an individual OEM or pharma company invest enough to ensure their platform is staying at the forefront of privacy, security requirements and product functionality capabilities?"

"The benefits of such a solution are inherent as medications and devices scale to commercialisation, but it also provides the optimal environment for collecting data during clinical trials."

The Flex Digital Health group is building the world's first medical regulated, US Health Insurance Portability and Accountability Act (HIPAA)-compliant, open architecture platform of connected medical devices, tied to a complementary, cloud-based software stack for commercialisation and scale. "We have always remained neutral in the marketplace, partnering with device OEMs and pharma to design and manufacture their products. Through our latest Digital Health solutions, we are complementing our *Sketch-to-Scale*™ capabilities, offering a new engagement model to support device OEMs, pharma, patients, providers and payers," Patel explains.

Flex's Digital Health Platform provides core functionalities required by medical device and pharma companies interested in providing medical regulated software solutions to their end users. The Flex Digital Health Platform delivers an open-standard where multiple partners can introduce devices and apps, while providing the necessary core functionalities developed under the required design controls, such as clear integration points and change control. The Flex offering dramatically reduces the cost and effort for medical device and pharma companies to develop and maintain their own, regulatory-compliant platform. The Flex Digital Health Platform supports clinical use cases (class I, II, III, and combination product) regulated by the US FDA and other global agencies, and manages data privacy compliance requirements for different regions.

As part of the managed platform solution, Flex provides platform monitoring, maintenance, updates, and security threat prevention. The functionalities of the solution include identity management, role management, access control management, user engagement and usability analysis, data ingestion and management, and reporting. As the platform matures, it will be capable of integrating data generated from multiple devices to provide a combined view of the patient for advanced analytics and comprehensive insight generation.

The benefits of such a solution are evident as medications and devices scale to commercialisation, but it also provides the optimal environment for collecting data during clinical trials. "Leveraging a PaaS (Platform-as-a-Service) offers medical device and pharma the opportunity to collect real-time data during clinical trials to determine the right features necessary for commercialisation and scale, without the cost burden," says Patel.

ABOUT THE COMPANY

Flex is the *Sketch-to-Scale*™ solutions provider that designs and builds *Intelligent Products for a Connected World*™. With approximately 200,000 professionals across 30 countries, Flex provides innovative design, engineering, manufacturing, real-time supply chain insight and logistics services to companies of all sizes in various industries and end-markets. Flex partners with a broad spectrum of healthcare OEMs to provide complete innovation, design, build, service and data solutions that make its customers more competitive in the areas of medical devices, drug delivery, diagnostics and medical equipment.

The article, "Beyond Connectivity: Enable & Flex Announce the Enable Smart Device" (see this issue, Page 22), describes Flex's collaboration to integrate Enable Injections' wearable injector with the Flex Digital Health Platform.

NYPRO
A JABIL COMPANY

SMART DRUG DELIVERY: PRAGMATIC APPROACH REDUCES RISK, INCREASES INNOVATION & PATIENT ADHERENCE

Getting patients to adhere to long-term therapy for asthma and chronic obstructive pulmonary disease remains a difficult issue to tackle. Conor Mulcahy, Senior Director, Strategic Projects at Nypro, discusses a smart inhaler which could help solve this problem. A trial device called Ruby was created – fully functional but without any drug – to replicate how a smart inhaler is expected to work and to test how best to produce such a device.

Smart drug delivery systems hold the promise of personalised medicine as they take advantage of the medical "Internet of Things" to drive significant improvements in medication adherence, patient care and, ultimately, health outcomes. When it comes to chronic disease management, connected drug delivery is the key to modifying behaviours and reducing unnecessary healthcare costs.

The emergence of digital healthcare is beginning to change the status quo for device manufacturers seeking a more effective drug delivery method and faster route to company profits amid increasingly tough competition. Makers of inhalers to treat asthma and chronic obstructive pulmonary disease (COPD), in particular, are well positioned to challenge the existing state in long-term therapies by embedding integrated sensors into their devices to take remote patient monitoring to the next level.

According to the Forum of International Respiratory Societies, about 400 million people worldwide suffer from asthma.[1] The WHO estimates that more than 64 million people live with COPD globally.[2] The prevalence of COPD, unfortunately, is on the rise and by 2020, is expected to become the third-leading cause of death worldwide.[3] Therefore, the opportunity to improve adherence to medication is not just aimed at offering symptom relief but at saving lives.

Getting patients to adhere to long-term therapies, however, remains a major impediment to treatment success. The US FDA reports that medication is taken as prescribed only 50% of the time.[4] Connected drug delivery systems that provide actionable patient data (Figure 1) can increase adherence and proper use through personalised reminders and instructions sent to a patient's smartphone. Smart devices that securely and wirelessly transmit usage data are expected to drive major advancements in remote patient monitoring, which could save up to US$36 billion (£28 billion) globally by next year.[5]

> "Connected drug delivery systems that provide actionable patient data can increase adherence and proper use through personalised reminders and instructions sent to a patient's smartphone."

Mr Conor Mulcahy
Senior Director, Strategic Projects,
Pharmaceutical Delivery Systems
E: conor.mulcahy@nypro.com

Nypro, a Jabil company
Corke Abbey
Bray
Co Dublin
Ireland

www.jabil.com/nypro

Figure 1: Connected Eco system.

THE RACE FOR SMART INHALER MARKET ENTRY

The smart inhaler market will reach $191 million worldwide by 2022, according to Allied Market Research.[6] This represents an annual growth rate of more than 60%. Leading the charge are GSK, AstraZeneca and Novartis, as they are making notable progress through collaborations with device firms and technology companies to spur development of next-gen connected drug delivery systems.

GSK, the respiratory market world leader, is entering clinical trials to test a clip-on sensor developed through collaboration with Propeller Health (Madison, WI, US), provider of an FDA-cleared digital health solution for improving outcomes in asthma and COPD. The sensor automatically collects and records data on the inhaler's usage. This information is then wirelessly transmitted to a central data repository for analysis by GSK's clinical researchers. Their goal is to determine how remote monitoring improves patient adherence by empowering them and their physicians to better understand the impact and management of the disease in daily life.

AstraZeneca has begun a clinical trial in collaboration with Quintiles (Durham, NC, US), looking at the impact of mobile medication reminders for COPD sufferers. The programme will use a smart device, mobile app and cloud platform developed by Adherium (see this issue, p 34), a digital health technology leader, to demonstrate how these devices improve medication adherence in patients with asthma and COPD. Meanwhile, Novartis has struck a technology partnership with Qualcomm to develop the first smart inhaler with integrated sensors. Novartis plans to launch its next-generation connect Breezhaler™ by 2019.

The emerging ecosystem for connected drug delivery systems spans a growing list of stakeholders, including original equipment device manufacturers (OEM), drug developers, human factors experts, mobile app developers, cloud platform providers, regulators, healthcare providers and – last, but certainly not least – patients. Clearing innumerable barriers to market entry requires a methodical, pragmatic product development approach, starting with the initial discovery phase where product requirements are conceptualised, vetted and refined in a culminating product requirements document (PRD) that forms the framework for design and development teams.

Fastidious attention to detail is also required during subsequent phases to ensure a smart device reaches the delivery stage at the lowest cost and risk. To illustrate further the potential opportunities and pitfalls of building a smart drug delivery system, Nypro (part of a Jabil company), commenced an internal project, called Ruby, which followed a pragmatic, best-practices approach from conception to proof-of-concept.

Ruby's goal was to create a fully functional device without the actual drug, one that is capable of replicating how a smart inhaler is expected to work. The device would track patient usage and then transmit data from the user's smartphone to a physician for further review and to promote adherence and improved inhalation function performance over time.

INTRODUCING RUBY: REAL-WORLD PROOF-OF-CONCEPT

Even medical device companies with decades of experience in mechanically-driven products can face major obstacles when making the move to a smart device. This is because the process introduces an entirely new set of product considerations, including:

- Sensor integration
- Connectivity
- Mobile technology
- Cloud technology.

The move to smart devices also requires a new way of thinking and modified approach to product planning. Embedding electronics presents a wealth of possibilities and serious considerations that affect lots of variables, not the least of which are privacy, risk management and budget. In addition, there's a high probability of "scope creep" as it can be difficult to gauge what is required to add seemingly simple functionality to a device if the company has little to any expertise or background in electronics.

To simplify and demystify the process of building a smart inhaler, the Ruby project took a widely used inhaler typically used for asthma or COPD and devised an integrated sensor solution for guiding patients through the delivery of a proper drug dose. With the medical mantra "do no harm" as a guiding force, a team of specialists set out to define product requirements using a comprehensive discovery process.

While the discovery phase is typical in any medical device development project, the process becomes more complicated when addressing a connected drug delivery device. The amount of information that can be gathered is massive, which necessitates a rigorous review of each data point to identify which details are shared with the patient, physician, healthcare provider, regulator and other vital stakeholders. A thorough discovery process not only pinpoints the most valuable data points, it identifies the smart functionality that will deliver the most product value in the long run.

Phase I: Define Product Success

The initial discovery phase of any product development project is crucial as it enables the stakeholders to collaborate on defining what success should look like at the end of the project. Sounds simple, but this is often the most arduous and complicated part of the project. Not only is it imperative to scope out product requirements accurately, it's critical to define intended business goals. There's lots of input that needs to be collected, culled and analysed during this phase as multiple systems comprise any connected device.

During Ruby's discovery phase, each constituent was polled to gain insight into potential technology solutions without losing sight of how that proposed capability would impact the business side. Following an exhaustive, iterative review process, a list of product requirements was developed and analysed, starting with seven primary capabilities, which quickly ballooned to encompass 20 types of functionality.

Arguably the hardest and longest phase of the four-step product development process, discovery generates a seemingly endless litany of questions, starting with:

- What do you want the device to do and why?
- What patient problems are you trying to solve with this connected device?
- What are the device's most important attributes?
- What is most important to explain to patients?
- How does the device communicate with the patient, physician, primary care provider and pharma company?
- Are you communicating verbally or with read-outs?
- What does the device need to connect to?

Each set of answers produces an entirely new set of questions that need to be addressed to create a comprehensive PRD. Every PRD follows a logical method of inquiry to identify priorities and eliminate ideas that don't pass the "value" litmus test. If a capability doesn't deliver value to the patient, or offer value to the business, it shouldn't make it into the PRD. Removing it further into the process adds inordinate time, cost and risk.

For Ruby, the iterative process and continual analytical reviews helped set the stage for product design by enabling the team to reduce the initial list of 20 capabilities to six core solution areas, comprising:

- **Communication:** Bluetooth low energy
- **Power Management:** Device on/off
- **User Interaction:** Capacitance touch
- **Device State:** Lever with hall sensor
- **Inhalation Performance:** During drug delivery
- **Software:** Data movement and security

Phase II: Design for Manufacturing Success

An overarching design focus was determining which features might expedite or hinder mass production by applying a series of design for manufacturing and design for assembly principles. A cross-functional team of engineers, human factors specialists and software developers brainstormed hundreds of design concepts and applied different criteria to identify 10 or so options with the lowest cost and least risk. Equally important was understanding if any function could potentially interfere or impact another.

Decisions for some solution areas came faster and easier than others. For example, the team made the decision to use Bluetooth Low Energy for smart phone connectivity because it consumed the least power. The much tougher challenge, however, was determining how to address inhalation performance. After vetting a host of options for checking if the drug had been inhaled correctly, the team settled on the use of a pressure sensor, again because it carried the lowest risk.

In determining how the device would communicate with a smartphone, the team had to assess whether the device would be verbally smart or just connected. As all device makers have finite budgets for power management, the team spent a lot of time determining how best to maximise battery life. User interaction was given substantial consideration because the device had to be simple, easy to use and intuitive to improve and sustain patient adherence.

During the design phase, inhalation performance surfaced as the biggest challenge. Software development, another crucial area, involved a completely different set of requirements to address issues surrounding data privacy and patient confidentiality properly.

Phase III: Test, Optimise, Test

During development, rapid iteration and continuous testing ensured that each function performed as expected. The ideal solution for each function doesn't always make it into the final, developed product as the ultimate choices are ones that present the least risk and enable the product to be developed at the lowest landed cost.

For Ruby, a team of expert system architects addressed competing elements in the top 10 designs to isolate the three options with the greatest potential and least risk. The team performed a series of hazard analyses, working through failure modes for each option. As indicated previously, dealing with inhalation performance was problematic because its addition became a power and space issue.

Another concern was actual placement on the printed circuit board as it was important to locate the sensor as close to the air channel as possible. This meant putting it on the underside of the board, which went against typical, top-down PCB assembly rules.

As Figure 2 illustrates, the pressure sensor was integrated into the bottom of the PCB, and the top surface of the sensor co-incided with the current airflow boundary so it wouldn't impact airflow. Additionally, the top cover of the device was thickened to 0.85 mm to mount the PCBA and not disrupt the existing airflow channels.

A related challenge that surfaced was the need to convert pressure sensor output numbers, which are relayed in milliamps to litre-per-minute as these are units physicians typically deal with.

> "For device makers seeking entry into the smart inhaler market, this case should offer useful insight into what is necessary to get to market quicker as going through FDA regulatory processes can take several years."

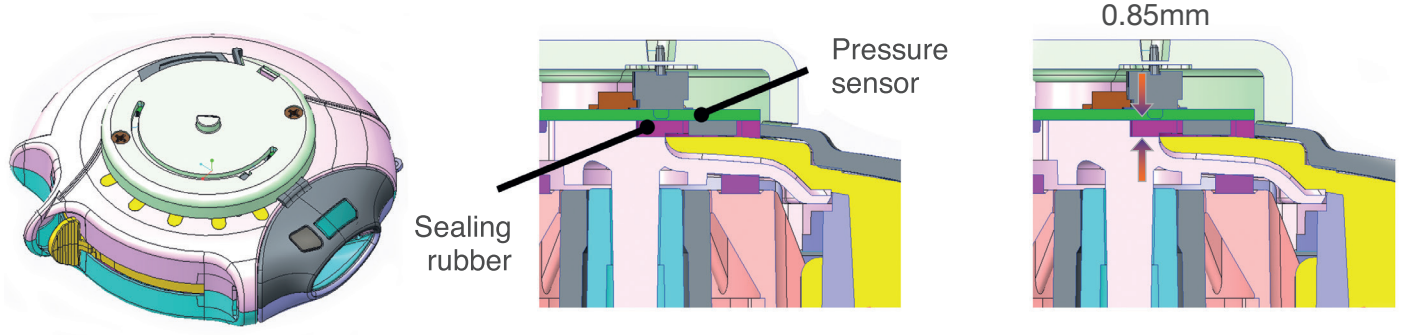


Figure 2: Pressure sensor location.

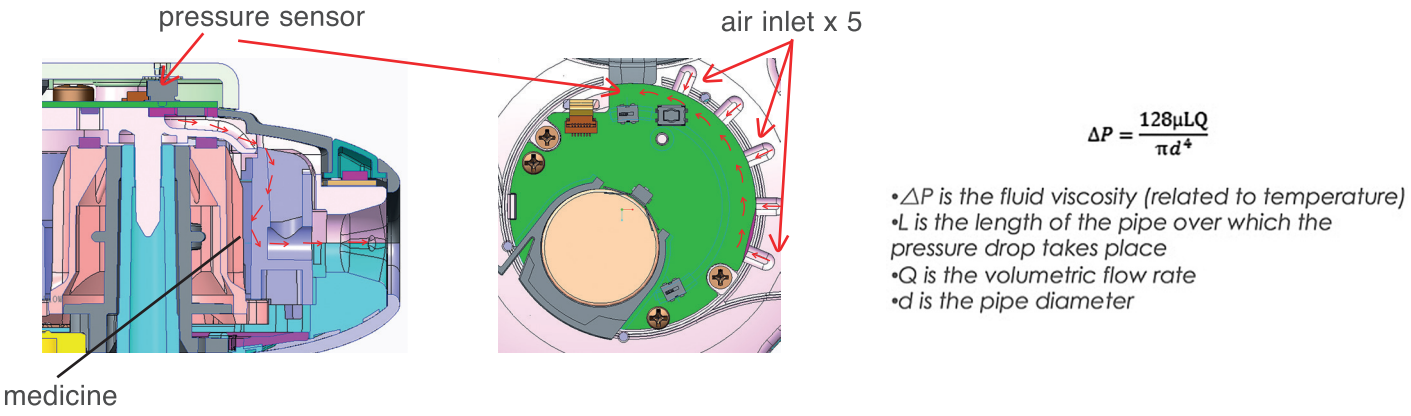


Figure 3: Sensor to Airflow algorithm.

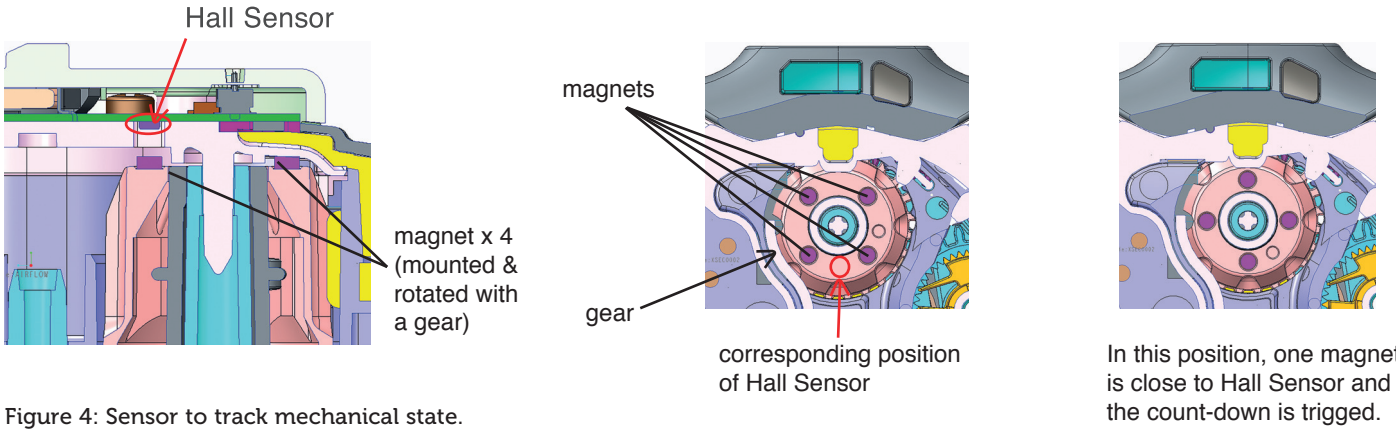


Figure 4: Sensor to track mechanical state.

As Figure 3 shows, the team applied numerous formulae and algorithms to calculate air moving down the channel at different speeds and temperatures. Then those findings were translated into a format that would be meaningful and actionable for physicians.

Another priority was how to determine the optimal way to count each drug dose, which also had to sync with the device's mechanical counter; the mechanical state of each operational step also needed to be tracked. For the proof-of-concept, the team wanted to count each dosing behaviour as well as trigger an alert when the stored dosage went below a certain threshold.

The development team considered multiple options before choosing a hall sensor as the index sensor to track the drug count. They also realised this approach would provide input to device orientation sensor, so data from the hall sensor could be linked seamlessly with other sensors and software logic to provide real-time device status updates.

Additionally, system architects added a six-axis sensor with an accelerometer and gyroscope to detect device motion as the inhaler must be held horizontally to dispense a good drug dose. Not only would this sensor support the requirement to improve proper dose delivery, it could prove helpful from a logistics standpoint as data would reveal if a device had been forcefully shaken, dropped or damaged prior to a patient receiving the device (Figure 4).

Aside from the assorted elements architected for the device, Ruby system architects navigated how each embedded sensor would communicate with the mobile application and how that app would synchronise with a cloud-based platform. To accomplish this, the team focused on the following core software solution areas:

- Cloud server – patient dashboard
- Mobile application – architecture, over-the-air upgrade capability and drug lot use check
- Device firmware – shock/shake and device orientation, patient contact logic, inhalation/exhalation confirmation and environmental sensing.

It's critical to look at the solution holistically as omitting a key piece of either the hardware or software at this stage would add inordinate time and expense once the product is manufactured. For instance, a last-minute decision to add digital certificates during the final development stage can derail the project altogether if the initial chipset for the product lacked the correct library support.

To avoid these kinds of disruptions, the Ruby team went through the detailed PRD and performed a line-by-line comparison to ensure functionality was aligned with expectations for the final proof-of-concept.

Phase IV: Accelerate Time to Market

Thanks to the close collaboration of a cross-functional team that spanned product discovery, design and development disciplines, Ruby's proof-of-concept was produced in about four months. The reference design illustrates technical innovation in design, development and next-generation disruptive advances.

For device makers seeking entry into the smart inhaler market, this case should offer useful insight into what is necessary to get to market quicker as going through FDA regulatory processes can take several years – smart inhalers will be subjected to extremely thorough and lengthy regulatory review.

It is therefore imperative that companies avoid sole-source suppliers and electronics components nearing end of life or not compliant with requirements such as Restriction of the Use of Certain Hazardous

Substances (RoHS) or Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

ABOUT THE AUTHOR

Conor Mulcahy is Senior Director, Strategic Projects, Pharmaceutical Delivery Systems, at Nypro, a Jabil company. In that role, Mr. Mulcahy established a medical device development capability to guide customers through a highly optimised end-to-end product discovery, design, development and delivery process to speed innovation and time to market while lowering cost and risk. A 26-year veteran of product development and new product introductions, Conor brings deep expertise and broad experience to Nypro from a successful tenure in the medical, consumer electronics and military industries.

Having real-time access to digital supply chain data is also important. There's an enormous wealth of information that can be collected, culled and analysed to inform engineering, sourcing and procurement in terms of sensor suppliers, product lifecycles, inventory levels, compliance and more.

CONCLUSION

In bringing smart inhalers to market, device makers need to reduce risk with each step by starting with the end goal in sight. The success of the Ruby proof-of-concept demonstrates that a pragmatic, multi-phase approach is the key to accelerating time to market, reducing risk and achieving the lowest landed cost.

REFERENCES

1 *"Forum of International Respiratory Societies (FIRS) Calls for Better Access to Care and Medicines for Asthma". FIRS Press Release, May 2, 2017.*
2 *World Health Organization (WHO), COPD Fact Sheet, No.315, February 2011.*
3 *Fitzgerald K, "COPD Projected to be Third-Leading Cause of Death by 2020". Managed Healthcare Connect, Vol 11(11), November 14, 2014.*
4 *"Why You Need to Take Your Medications as Prescribed or Instructed", US FDA Special Feature, February 2016.*
5 *Slabodkin G, "Remote patient monitoring to save $36B globally by 2018". FierceHealthcare, July 17, 2013.*
6 *"Smart Inhalers Market". Allied Market Research, November 2016.*

ABOUT THE COMPANY

Nypro Healthcare provides design, manufacturing and supply chain solutions to many of the most well-known brands of medical devices, diagnostics and pharmaceutical delivery systems. Acquired by Jabil in 2013, Nypro helps customers effectively address the rapidly changing needs of payers and providers to cost-effectively sustain and improve lives worldwide cost-effectively.

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2017 PDA Europe Conference, Exhibition

The Universe of Pre-filled Syringes & Injection Devices

The Must-Attend Event for the Pharmaceutical and Biopharmaceutical Industry

Register by 7 Oct 2017 and SAVE!

7-8 November 2017

Austria Center
Vienna | Austria

pda.org/EU-UPS2017

SPECIALTY PHARMA: HOW PRESCRIBING TECHNOLOGY AFFECTS TREATMENT OUTCOMES

The specialty and highly managed drug sector is particularly susceptible to the problems of non-adherence. This is partly due to the complexity of the medication involved and also because Electronic Health Record workflows aren't designed for specialty pharmaceuticals. New solutions are now available though which streamline the whole process and automate difficult areas. Amy Seung, PharmD, BCOP, Senior Director of Clinical Development at AssistRx, explains how they can work.

It is estimated that the pharmaceutical industry loses US$637 billion (£496 billion) globally in revenue annually due to non-adherence to medications for the treatment of chronic conditions – a figure that has risen from US$564 billion in 2012.[1] Although revenue losses are rising, the healthcare industry is rapidly changing and embracing new technology capable of lowering costs, reducing waste in the system and facilitating better patient care.

However, there is one increasingly popular area of pharma that is falling behind the rest of the industry – the specialty and highly managed drug sector. There are currently only a handful of solutions available to help facilitate a prescription management workflow process that enhances the patient experience and reduces non-adherence, a factor – commonly referred to as abandonment – that adversely affects treatment outcomes (Figure 1).

Specialty medications address unmet medical needs in complex, often rare diseases and under-served patient populations. Due to the complex process required to prescribe specialty medicine, time-to-therapy, an element closely related to non-adherence, typically extends beyond traditional prescription drug delivery timeframes.

As the amount of time from initial diagnosis to drug delivery lengthens, there is a strong possibility that the patient's memory recall diminishes, anxiety rises and the condition worsens.[2] These compounding factors further drive non-adherence and a poor patient experience.

> "The complexity of prescribing specialty medication begins with communication and technology gaps among the many groups involved, including physicians, manufacturers, insurers, specialty pharmacies and reimbursement providers."

THE CAUSES

The complexity of prescribing specialty medication begins with communication and technology gaps among the many groups involved, including physicians, manufacturers, insurers, specialty pharmacies and reimbursement providers. Although Electronic Health Record (EHR) workflows streamline and simplify the end-drug delivery process for traditional medication, the process isn't that simple for specialty pharma.

EHRs weren't developed with patients who require highly managed drugs in mind, but rather to simplify the process for those who need traditional medication and are able to pick up their prescription at a local retail pharmacy in just hours. Most often, specialty medications require a more complicated patient introductory process that includes training, clinical follow-up, and other patient services that are only available through a specialty distribution channel.

Dr Amy Seung
Senior Director of
Clinical Development
T: +1 855 421 4607
E: amy.seung@assistrx.com

AssistRx
4700 Millenia Blvd,
Suite 500
Orlando
FL 32839
United States

www.assistrx.com

Figure 1: Adherence: The link between treatment and outcomes.

"One way brands can help their drugs stand out among the crowd is to leverage differentiated positioning."

Figure 2: Improving adherence starts at the point-of-care.

Figure 3: Digital workflows can help accelerate time-to-therapy by 45%.

As a result, providers must go outside of the EHR, using pen, paper and fax-based processes throughout the prescription and delivery process. Resorting to these alternatives not only extends time-to-therapy, but also creates risk of communication gaps and misunderstandings. As a result, the patient experience begins with a faulted prescribing process that may prolong or even hinder final delivery of the medication (Figure 2).

THE OPTIONS

Fortunately, new solutions facilitate workflows that seamlessly onboard providers and patients through the start of therapy all the way through delivery. Solutions, like AssistRx's iAssist, streamline the entire prescribing process and automate pain points, such as completing Patient Enrollment Forms (PEFs), while connecting all parties to one central location of patient information and status.[1]

Assist and other digital workflows accelerate time-to-therapy by reducing the time it takes for patients to get their medications by 45% (Figure 3). Leveraging these integrated technologies can reduce the median number of days from prescription to therapy initiation from 22 days for fax-based processes to just 10 days.[2] Each party involved in the prescription process benefits in some manner from these integrated solutions.

Manufacturers

As more and more drug products hit the market, brands are launching their medicines in a competitive environment – even in specialty pharma, one of the fastest-growing sectors of the healthcare industry. One way brands can help their drugs stand out among the crowd is to leverage differentiated positioning. Software solutions like iAssist enable manufacturers to generate real-world evidence (RWE) by tracking the patient journey from prescription to delivery and all the way through treatment. This data could be used to not only support product pricing, but also to improve patient compliance, adherence and treatment outcomes.

Physicians

Many physicians spend upwards of $100,000 in administration expenses in order to prescribe specialty mediations, paying staff members to input manually various prescription forms, file paperwork and complete multiple enrollment forms.

This manual process is a costly expenditure for physicians from a labour and resource perspective, and a hindrance on treatment outcomes, as it delays speed-to-therapy. Healthcare technology apps streamline processes and facilitate integration among the EHR and third-party networks. Through these technologies, physicians can onboard patients onto a specialty drug therapy through a workflow of configured acceleration services, including ePA, patient eConsent, electronic verification of patient benefits and connection to additional patient services. This type of workflow can reduce costs, close communication gaps and alleviate the administrative burden involved in onboarding.

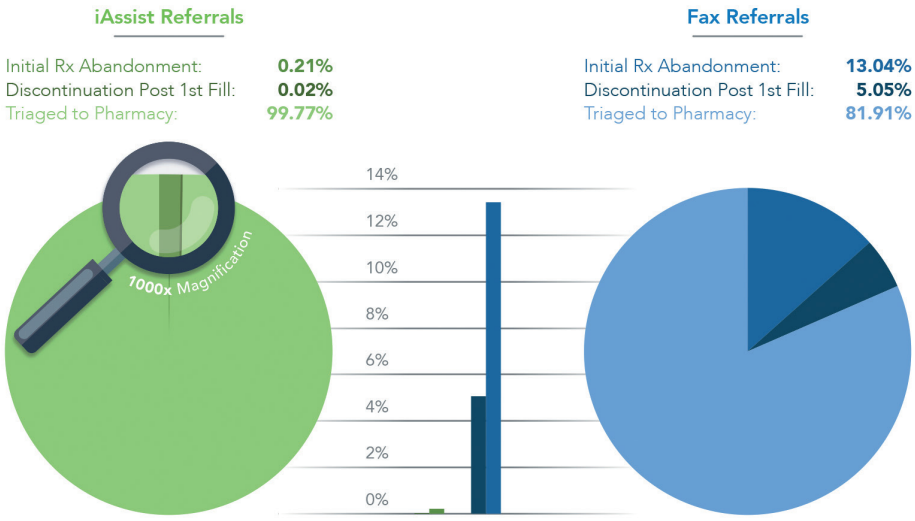


Figure 4: Abandonment rates reported in the Women's Health Drug Case Study.

> "Digital workflow technologies that integrate with EHRs may be the specialty and highly managed drug sector's greatest hope to reduce non-adherence, improve treatment outcomes, and lower revenue losses within the healthcare industry."

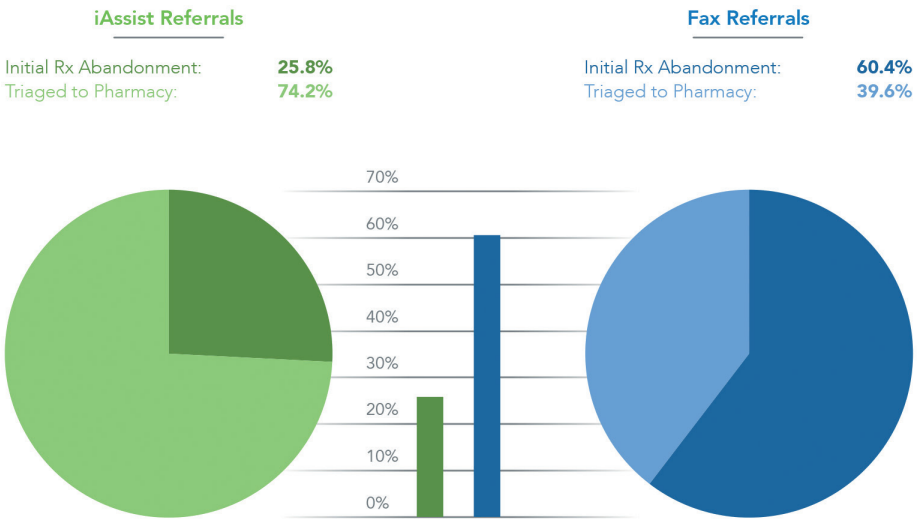


Figure 5: Abandonment rates reported in the Dermatology Case Study.

Insurance Companies

After a physician signs off on a specialty prescription, insurance companies must review the drug and validate the prescription before agreeing to cover the cost. A manual sign-off required for specialty drug prescriptions not only lengthens this process, but also creates headaches for insurance companies when claims need to be investigated. This cost is exacerbated by the fact that insurers spend an incredible amount of money on drugs that may or may not execute as expected or have weakened effectiveness if not taken as intended.

Insurance companies are incentivised to cover drugs that effectively perform the work in which they are marketed. Some manufacturers offer fee-per-value contracts to ensure a quality product, rather than fee-per-service contracts, wherein the medication is the same price regardless of effectiveness. The fee-per-value service assures insurance companies that the drug is sold at the correct price-point even if the cost is high.

However, in order to reach a fee-per-value market, insurance companies need the RWE provided by manufacturers. Thus, leveraging technology solutions capable of capturing such information benefits not only manufacturers, but also insurance companies and policy holders.

SUPPORTING CASE STUDIES

Several recent case studies demonstrate the impact EHR-integrated workflows have on speed-to-therapy and corresponding patient adherence. Since speed-to-therapy is closely related to adherence, this significant margin could have real impacts on patient treatment outcomes.

Women's Health Drug Case Study

The first case study, which leveraged digital workflows to prescribe a women's health product for a highly-motivated audience, found that patients were almost 80 times less likely to abandon their therapy at the initial fill or after their first month of medical treatment. On the other hand, patients generated an abandonment rate of more than 18% when fax-based processes were used to prescribe the health product (Figure 4).

Dermatology Case Study

These same digital workflows were used in the second case study, which measured a dermatology prescribed product for less-motivated patients. Statistics showed that patients whose prescription was written via a fax-based process had abandoned their medication 60% of the time. Through a digital workflow, patients had only abandoned their prescription 25% of the time (Figure 5).[2]

LOOKING FORWARD

According to the WHO, increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments. Digital workflow technologies that integrate with EHRs may be the specialty and highly managed drug sector's greatest hope to reduce non-adherence, improve treatment outcomes, and lower revenue losses within the healthcare industry. Investing in these solutions also aids manufacturers, physicians and insurance companies in providing patients with a collaborative, seamless experience that sets the tone for future patient care.

Should manufactures pursue RWE data for their various products, they will not only drive brand differentiation, but also fair pricing in the market. The fee-per-value method ensures that the level of coverage matches the drug's actual value to the patient, saving costs for both the insurer and the policy holder.

When it comes to aggregating patient information through the EHR and capitalising on that data to make informed decisions, the industry has only touched the surface. As technology within the healthcare industry continues to evolve, providers must ensure that the growing specialty drug sector is not left behind and that integrated workflow solutions are leveraged to meet the needs of this under-served patient population.

ABOUT THE AUTHOR

Amy Hatfield Seung, is the Senior Director of Clinical Development at AssistRx, where she leads clinical strategy for the Caret™ platform. Previously, she was the Oncology Clinical Decision Support and Hematologic Malignancies Pharmacy Clinical Specialist at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital (Baltimore, MD, US), where she also served as Director of the PGY2 Oncology Pharmacy Residency Program. Dr Seung received her Doctor of Pharmacy degree from the University of North Carolina at Chapel Hill, and completed her Pharmacy Practice and Oncology Specialty Residencies at the University of Washington Medical Center and Seattle Cancer Care Alliance (Seattle, WA, US).

Dr Seung serves as a lead consultant in the development of the National Comprehensive Cancer Network (NCCN) Standard Chemotherapy Templates and worked on the NCCN Task Force on Specialty Pharmacy. She is active within the Hematology Oncology Pharmacy Association (HOPA), serves as HOPA's representative to the ASCO CancerLinQ Oncology Leadership Council, and is Past Chair of the BCOP Recertification Committee and BCOP Field Testing Workgroup.

REFERENCES

1. *"Pharmaceutical Companies Lose $637 Billion in Revenue Annually Due to Medication Nonadherence". Press Release, HealthPrize Technologies, November 16, 2016. (Retrieved from: https://healthprize.com/about-us/press-releases/pharmaceutical-companies-lose-637-billion-revenue-annually-due-medication-nonadherence)*
2. *Seung AH, "Leverage Healthcare Technology Applications to Improve Primary Nonadherence". AssistRx White Paper, March 2017. (https://www.assistrx.com/wp-content/uploads/2017/05/ARx-Adherence-March-2017.pdf)*

YPSOMED
SELFCARE SOLUTIONS

SMARTPILOT FOR YPSOMATE: TRANSFORMING A PROVEN AUTOINJECTOR INTO A FULLY CONNECTED DEVICE

In this article, Orfeo Niedermann, Business Development Director, Ypsomed Delivery Systems, provides insights into how connectivity enhances existing autoinjectors and adds value for users, physicians, pharma companies and insurers. Specifically, he sheds light on how SmartPilot, a re-usable add-on with built-in wireless communication and advanced sensors, transforms the standard YpsoMate 2-step autoinjector into a fully connected self-injection system. The article then illustrates how smart devices offer new possibilities to monitor adherence patterns during clinical testing and improve therapy outcomes with real-time, in-use patient guidance and tracking of injection history and success.

With the large number of new biologics the demand for devices for the subcutaneous (SC) self-injection of biopharmaceuticals continues to grow and develop. The need for simpler self-injection procedures and improved patient adherence for autoinjectors, pens and large-volume patch injectors is increasing. Smart technologies offer new possibilities to improve patient adherence and therapy outcome. There are a number of drivers stimulating the development and use of smart and connected devices.

"For connected devices the necessary sensor, transmission and power sources are not yet affordable to be fully integrated into disposable pens and autoinjectors. This is why Ypsomed is developing solutions to combine the strengths of a ready-to-use disposable device with the technical possibilities of reusable devices."

LESS FREQUENT INJECTIONS

With improved formulations and larger injection volumes, new biologics typically require weekly, biweekly or even monthly SC injections. On the one hand, less frequent injections reduce patient exposure to the moments of injection discomfort and the hassle of storing and preparing the drug product. The lack of injection routine, on the other hand, calls for even simpler use of the device and need for more guidance and feedback before, during and after injection.

CHANGES IN DRUG REIMBURSEMENT MODELS

With healthcare costs soaring for newer biologic therapies health insurers are looking to move away from unit priced payment towards outcome-based compensation models for therapies aligned with superior clinical results. This also drives the need for technical solutions that automatically record whether, and how successfully, the patient follows therapy guidelines.

Orfeo Niedermann
Business Development Director
Ypsomed Delivery Systems
E: orfeo.niedermann@ypsomed.com

Ypsomed AG
Brunnmattstrasse 6
CH-3401 Burgdorf
Switzerland

www.ypsomed.com

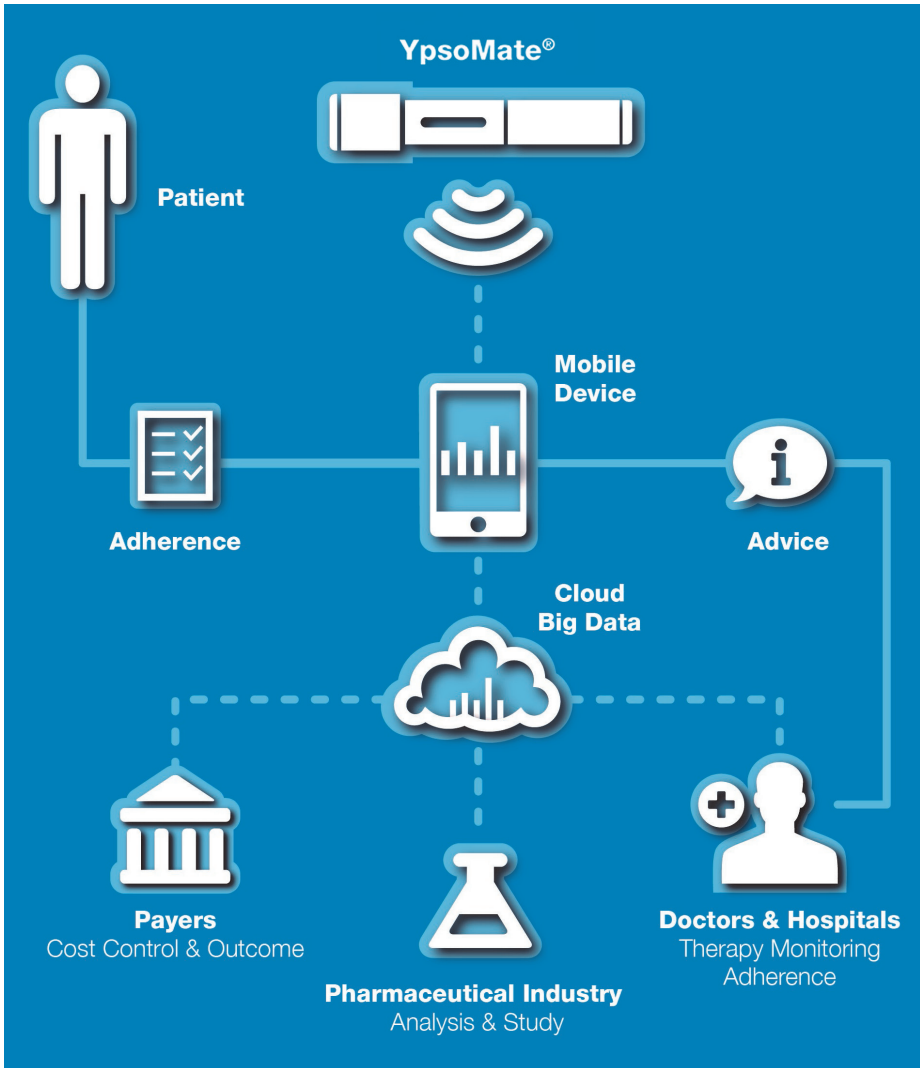


Figure 1: Environment and network interacting with the patient.

ANALYSIS OF REAL-WORLD DATA

Pharma companies are accumulating vast amounts of data about therapies and disease states during clinical trials and post-market surveillance. However, one important factor in the equation is whether patients in self-care environments have correctly administered their medicine. This also calls for a simple and automatic log book for all patient administered doses.

PATIENT & HEALTHCARE INVOLVEMENT

As the internet, mobile devices, social networks and patient forums gather information, patient awareness for their therapy status and effectiveness increases significantly. The acceptance and demand for electronic, connected devices and software is growing quickly and further supporting the need for smart self-injection devices (Figure 1).

SMART ADD-ON TRANSFORMS AUTOINJECTOR INTO A FULLY CONNECTED DEVICE

The world of self-injection pens and autoinjectors has seen a clear trend to prefilled disposable devices. Key drivers are simplicity of use in combination with pharma company needs to improve efficiency of the supply chain and simplify device replacement.

For connected devices the necessary sensors, transmission and power sources are not yet affordable to be fully integrated into disposable pens and autoinjectors. This is why Ypsomed is developing solutions to combine the strengths of a ready-to-use disposable device with the technical possibilities of reusable add-ons.

SmartPilot (see Figure 3) is a reusable add-on for the standard YpsoMate autoinjector that not only tracks and wirelessly transmits the success of injection events but also

> "The device detects and communicates different use states and allows the smartphone to provide real-time step by step instructions in written, animated and audible formats."

Figure 3: Illustration of a patient loading a standard YpsoMate 2-step autoinjector into the fully connected SmartPilot add-on.

pilots the patient in real-time throughout the injection process. This is achieved with advanced visual and audible feedback from the add-on, display of complementary information on a related mobile app, and individualised ergonomics. SmartPilot flexibly transforms a standard YpsoMate autoinjector into a fully connected device.

As SmartPilot is compatible with YpsoMate autoinjectors without further modification, it offers an ideal solution for existing and future YpsoMate customers who want to equip their device with connectivity flexibly as part of product lifecycle activities. SmartPilot may also be used as a means for monitoring and analysing progress of and patients' adherence patterns during clinical trials. In addition, the complementary mobile app may be enriched with questionnaires for patients to self-report their wellbeing and other disease-relevant parameters.

IN-USE GUIDANCE INCLUDING HOLDING TIME INFORMATION

In conjunction with the use of a smartphone and the related mobile app, SmartPilot can provide patients with video-enhanced instructions on how to use the autoinjector. The device detects and communicates different use states and allows the smartphone to provide real-time step by step instructions in written, animated and audible formats. This includes the option of providing precise advice on recommended holding time to reach complete delivery of the drug.

SmartPilot identifies handling errors and instructs patients on corrective actions with the help of the mobile app. As such, the technology complements conventional training methods and trainer devices. Data exchange between SmartPilot for YpsoMate and a patient smartphone is established via Bluetooth Low Energy (BTLE), an emerging standard compatible with all available smartphones and standard operating systems.

ADVANCED TECHNICAL SOLUTION

A key challenge when developing SmartPilot was to identify relevant device status information without physically modifying the existing YpsoMate autoinjector platform.

Ypsomed has developed a concept based on a contactless sensor solution that detects and differentiates between:

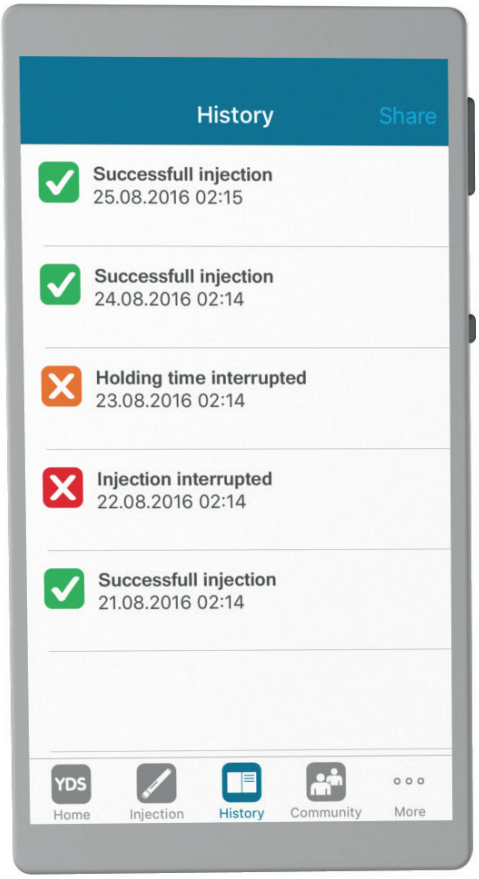


Figure 4: Illustration of information displayed on SmartPilot mobile app: the injection history provides an overview of injection events and indicates handling errors.

- Pushing the device on skin
- Completion of needle insertion and start of injection
- End of injection
- Removal of device from skin
- Locking of needle shield.

SmartPilot can therefore distinguish and recognise errors such as removing YpsoMate from the skin during injection or interruption of the holding time. Such information is recorded, transferred to the smartphone and processed for subsequent analysis (see Figure 4). Availability of such data not only instructs patients on how to use YpsoMate correctly but assists healthcare professionals, caregivers, and pharmaceutical companies. For instance, it may be used specifically to further improve patient training materials, to explain previous unexplained variations in clinical studies, or to support outcome-based payment scenarios.

USE WITH OR WITHOUT SMARTPHONE

SmartPilot also directly provides visual and audible feedback to patients on injection success or errors, without needing to have a smartphone connected during the injection process. SmartPilot provides integrated visual and audible feedback

Figure 5: SmartPilot for YpsoMate, ready for injection.

that guides the patient through the injection process and indicates use errors. It even advices the user on the recommended holding time by means of a flashing LED light and audible feedback (Figure 5).

In addition, SmartPilot has built-in memory to record and store

information covering multiple injection events. It saves use data including date, time and potential use errors on the device itself. Such information then can be read out either by patients and caregivers at a later point in time or by HCPs during a periodic check-up.

LEVERAGING SMART TECHNOLOGIES & INTERNET

The possibilities to enlarge the benefits of the associated smartphone app and internet connectivity are countless and will certainly evolve. The patient can easily be reminded when to perform the next injection. If an injection was not performed as scheduled, the patient will receive a reminder or a friendly personal call to motivate adherence for the next injection.

SmartPilot-related software may also track other health-relevant information around the patient or log patient self-reported health status or wellbeing. For more frequent or larger injections it may be helpful to track and recommend the subsequent injection site (see Figure 6). The patient may also have access to virtual patient forums and online communities to share experiences or injection-relevant information.

CONCLUSION

The YpsoMate family of 1 mL and 2.25 mL devices is enjoying significant success for both originator and biosimilar biologics due to their ease of use based on 2-step, button-less, push-on-skin technology. This is reinforced by Ypsomed's focus on well thought out, flexibly customisable designs manufactured on fully automated manufacturing infrastructure.

The development of SmartPilot for YpsoMate provides pharma companies with the ideal clinical and marketing tool to pioneer the next phase of self-administration device development in a connected world.

SmartPilot allows YpsoMate to be flexibly upgraded into a fully connected device and also provides advanced real-time user feedback. The related mobile app further enables display and analysis of complementary information, such as instructing patients on how to avoid use errors or advising on where to inject next. SmartPilot is suitable to monitor patient behaviours and adherence patterns during clinical trials. However, it also reflects a tool to transform the proven 2-step autoinjector into an internet-of-things enabled device to accelerate further the transition towards outcome-based payment models.

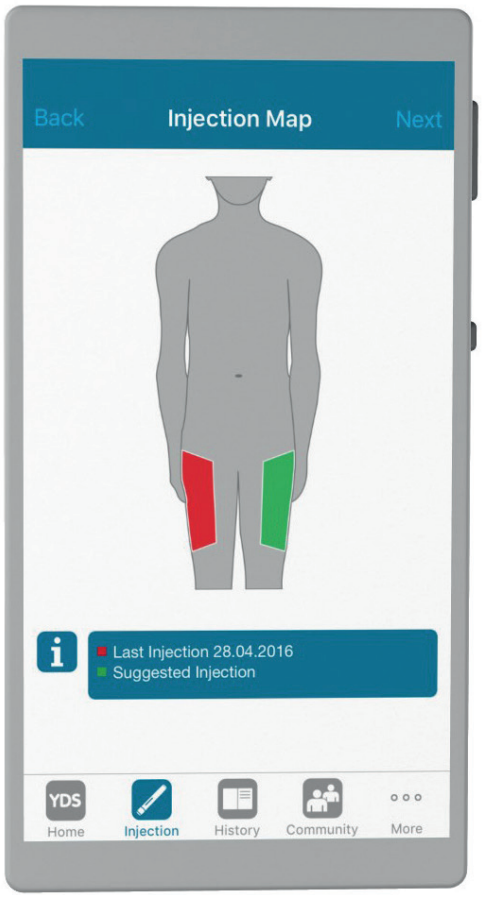


Figure 6: Injection map advising the patient where to inject next.

"The development of SmartPilot for YpsoMate provides pharma companies with the ideal clinical and marketing tool to pioneer the next phase of self-administration device development in a connected world. SmartPilot allows YpsoMate to be flexibly upgraded into a fully connected device and also provides advanced real-time user feedback."

"SmartPilot-related software may also track other health-relevant information around the patient or log patient self-reported health status or well-being. For more frequent or larger injections it may be helpful to track and recommend the subsequent injection site."

ABOUT YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed is the leading independent developer and manufacturer of innovative autoinjector and pen injector systems for self-administration of injectable drugs. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, reusable pens that include automated injection mechanisms and easy-to-use injection devices for drugs in dual-chamber cartridges such as lyophilised drugs. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio. Ypsomed provides its partners excellent technological expertise and full regulatory support for the device relevant aspects of the registration process.

Ypsomed injection systems are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO13485 certified and all processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by both pharma companies and regulatory agencies and supply devices for global markets including US, Europe, Japan, China and India. Ypsomed has more than 30 years of experience and well-established working relationships with numerous leading pharma and biotech companies.

YDS YpsoMate®

Go for simplicity.

swissmade

10041599-MSTR-en/V03

The complete range of 2-step autoinjectors

- Suitable for standard 1 ml long and 2.25 ml pre-filled syringes
- Push-on-skin release for most simple and ergonomic handling
- Clear confirmation “clicks” and large viewing window for optimum patient control
- Easy to customise and flexible platform product assures short timeline and low project risks
- YpsoMate® 2.25 Pro with constant force drive is suitable for a large range of viscosities

For more information visit www.ypsomed.com/yds

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

YPSOMED
SELFCARE SOLUTIONS