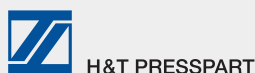


# CONNECTING DRUG DELIVERY



ONdrugDelivery Issue N° 87, June 11<sup>th</sup>, 2018

## CONNECTING DRUG DELIVERY

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

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# CONNECTED DRUG DELIVERY SECTOR OVERVIEW

Here, Tom Oakley, Director of Drug Delivery Device Development, Springboard, gives an overview of the state of connected devices in the drug delivery world, touching on various approaches, benefits and challenges in the sector today.

## THE NEED FOR CONNECTED DRUG DELIVERY DEVICES

Most people would agree that drug delivery devices have improved in recent years, particularly with the increased focus on usability (or human factors). However, adherence remains a challenge and payers are looking for ways to increase the cost-effectiveness of healthcare. One strategy for managing both issues is connecting drug delivery devices to the internet.

The potential benefits of connected drug delivery devices have been much discussed and can be summarised for stakeholders as follows:

- **Patient**
  - Reminders
  - Training
  - Evidence for incentives
  - Hawthorne effect
  - Peer support.
- **Carer**
  - Reminders
  - Training.
- **Payer**
  - (Non)adherence data
  - Reduced costs (50% of patients suffering chronic illness do not take their medication as prescribed, costing US\$100 billion (£75 billion) to \$300 billion annually in avoidable direct healthcare costs in the US alone<sup>1</sup>).
- **Healthcare professional**
  - (Non)adherence data
  - Additional support for least adherent
  - Adverse events.

- **Healthcare provider, or regulatory authority**
  - (Non)adherence data
  - Adverse events
  - Clinical trial data (pre and post market)
  - Population trends.
- **Pharma**
  - (Non)adherence data
  - Adverse events
  - Clinical trial data (pre and post market)
  - Reimbursement evidence
  - Market understanding
  - Product and training improvements
  - Increased sales by increased adherence. (non-adherence causes \$637 billion lost pharma revenue annually<sup>2</sup>).

The disadvantages of connecting drug delivery devices to the internet are:

- Increased cost of devices and infrastructure
- Potential increase in usability risks
- Reliability risks due to technical complexity
- Concerns over data privacy and robustness against hacking and malware
- Unclear regulatory landscape due to the unfamiliarity of the technologies in the regulatory context
- Environmental concerns for disposal of electronic waste.

Nevertheless, for some drugs and indications the advantages are compelling, so we should look at how connectivity could be implemented in a drug delivery device.

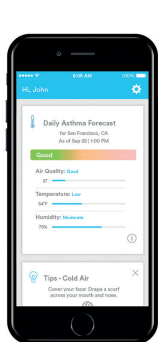
“Devices which have connectivity built into them from the beginning can make significant changes in user interaction. The design being built-in also allows for more substantial changes to the device, such as advanced features and sensing options.”



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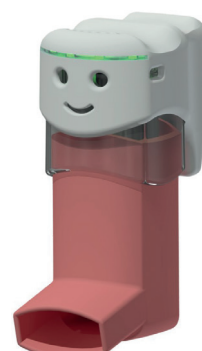
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Propeller Health



Gecko (now Teva)



CapMedic



Biocorp Inspair

## DEVICE STRATEGIES

There are three main strategies for implementing connectivity in a drug delivery device:

1. An add-on, typically to an existing design.
2. An upgrade, which is integrated but does not change the core functionality or use case.
3. Built-in, which can change the core functionality and use case.

Many pharmaceutical companies and drug delivery device manufacturers already have connected devices either on the market or in late stage development. An industry survey of inhalers, for example, shows various companies using one or more of the three strategies.

### Add-Ons

Add-ons (Figure 1) have the advantages that:

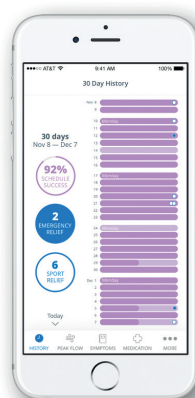
- They can be added to existing devices, in most cases without interfering with the existing device function
- They could be reusable even if the existing device is disposable
- Patients could pay for the add-on themselves, whereas the existing drug delivery device might be paid for by an insurer or national health service
- There is less development risk due to limited revalidation of the existing device.

Of the examples shown in Figure 1, Propeller Health (Madison WI, US) and Adherium (San Mateo, CA, US) are notable because they support a wide range of existing inhalers.

Cohero Health (New York, NY, US) provides a spirometer so patients can measure their lung function. This combination of drug delivery device and diagnostic device is powerful because it can provide direct disease management results to help patients and clinicians assess progress



Adherium Hailie Sensors



Cohero Health's BreatheSmart™ app, HeroTracker™ sensors, and spirometer.  
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Figure 1: Examples of add-ons designed to provide inhalers with connectivity.

and can enable a payment-by-results model rather than the usual pay-per-dose model. Linking delivery devices with diagnostics was pioneered in insulin pens (and to a greater degree, insulin pumps) and blood glucose meters used for diabetes.

The obvious benefit is that the drug delivery device can respond to changes in the biomarker in real-time. In addition, it gives a much better insight than measuring only the quantity and time of dose taken because the patient and healthcare professional can see how the body responds to the drug. The diagnostics could perhaps also be used to identify more subtle problems. For example, if outcomes were poor in a certain area, an investigation might reveal poor training by the local healthcare facility.

Biocorp's (Paris, France) Inspair® measures inspiratory flowrate so can determine both if the patient's breathing profile is correct

and if they actuated the inhaler at the right point in their inspiration. Devices which provide feedback like this can be used for "continuous improvement" training, which is more interactive and personalised than a static training video or patient instruction leaflet. It helps with the "learn-ability" of the device, which was identified as a major challenge in recent industry-wide research performed by Springboard.

However, it is important to consider that add-ons have the obvious disadvantage that the existing geometry is not modified so:

- Add-ons cannot be integrated into the existing device, and thus add bulk to the device, and there are additional use steps to attach them.
- Technical possibilities are limited. For example, it is more difficult to sample the air flow.





Novartis cloudhaler



Presspart eMDI

Figure 2: Examples of existing inhalers upgraded to include connectivity.

### Upgrades

A strategy to overcome the limitations of add-ons is to upgrade an existing design (Figure 2). Novartis is supporting the Propeller add-on,<sup>3</sup> but is also upgrading the Breezhaler to the cloudhaler and adding built-in connectivity by working with Qualcomm Life (San Diego, CA, US).<sup>4,5</sup>

H&T Presspart (Blackburn, UK) is working with Cohero to upgrade standard metered dose inhaler actuators with connectivity.<sup>6</sup> A notable feature of the Presspart strategy is that the connected functionality is optional. That is, the drug delivery and dose counter functions are still entirely mechanical, so the patient can, in principle, use the device safely and effectively even if the electronic functions fail.

An alert reader will notice that the upgraded devices do not change the use steps or core functionality of the devices. If the desire is to use electronics and connectivity to fundamentally change the way that patients (and carers, trainers etc)

interact with their device, it is necessary to build the electronics and connectivity into the device from the ground up.

### Built-In Connectivity

Devices which have connectivity built into them from the beginning can make significant changes in user interaction (Figure 3). The design being built-in also allows for more substantial changes to the device, such as advanced features and sensing options. For example, the 3M Intelligent Control Inhaler actively adapts the flowrate to suit the patient and delivers the dose automatically at the right point in the inspiration. A similar example is Opko's (Miami, FL, US) Insiromatic active dry powder inhaler, and Aptar Pharma (Louviciennes, France) is partnering with Propeller to develop a new connected metered dose inhaler.<sup>7</sup>

The disadvantages of built-in connectivity substantially mirror the advantages of add-ons. For example, a device with built-

in connectivity could be more difficult to make reusable, which adds built-in cost and environmental impact.

### UPTAKE AND RETENTION OF CONNECTED DEVICES

Public interest in connected drug delivery devices has not been measured on a wide scale as of yet, but we can draw inferences from health-related smartphone apps. More than 50% of US smartphone users downloaded a health-related app in 2015. Individuals more likely to use health-related apps tended to:

- Be younger
- Have higher incomes
- Be more educated
- Be Latino/Hispanic
- Have a body mass index (BMI) in the obese range (all  $P < 0.05$ ).<sup>8</sup>

However, weekly retention of apps is poor, even for apps which tend to be associated with hardware such as Fitbit, Garmin and Nike+ (Figure 4). The reasons for people stopping using health apps were primarily:

- |                          |     |
|--------------------------|-----|
| • High data entry burden | 45% |
| • Loss of interest       | 41% |
| • Hidden costs           | 36% |

Out of 1604 people, 662 (41%) said they would not pay anything for a health app.<sup>8</sup>

In November 2017, an analyst from Ernst & Young (London, UK) identified the following hurdles to the widespread adoption of connectivity in drug delivery devices:<sup>9</sup>

- Devices and services
- Evidence
- Data infrastructure
- Business model.

Let us assess the progress and challenges in each area in turn.

### Devices and Services

Merck Group (Serono, prior to its acquisition) launched easypod for human growth hormone in 2006, which gained connectivity in 2012,<sup>10</sup> and RebiSmart for multiple sclerosis, which was launched in 2007 and gained connectivity in 2011. They use the easypod Connect<sup>11</sup> and MSdialog<sup>12</sup> web platforms, respectively, for uploading patient data from the device and adding supporting information manually.



3M Intelligent Control Inhaler



Opko Insiromatic

Figure 3: Examples of inhalers with built-in connectivity.

One of the challenges is gaining regulatory approval of medical devices that connect to smartphones, but AliveCor (Mountain View, CA, US) has pioneered the way here by being the first to gain FDA approval for smartphone-based medical device software with its atrial fibrillation diagnostic app.

In diabetes, Roche has bought the mySugr web platform, whose Bolus Calculator has Class IIb approval in the EU, and the logbook has Class I approval in both the EU and US.

So, we can see that connected drug delivery devices are breaking through onto the market, and the regulatory approval and services around them are entirely feasible.

### Evidence

Payers and regulators (not to mention patients and healthcare professionals) will want to see clinical evidence for the efficacy of connectivity. Fortunately, the evidence is mounting. Data from Propeller Health, for example, shows reduced short-acting beta agonist use<sup>13</sup> and reduced hospitalisations and emergency room visits.<sup>14</sup> Adherium claims similar clinical evidence.<sup>15</sup>

If efficacy is proven for certain indications, we would still need evidence for preference and adherence. Fortunately, several studies have been done in these areas too. For example:

- An observational study on the RebiSmart device found that 91% liked using the device, and 96% found it “easy or very easy to use”.<sup>16</sup>

- An autoinjector patient preference survey found that 82% of BetaConnect patients were “highly satisfied” compared to 67% of RebiSmart and 60% of ExtaviPro patients.<sup>17</sup> The first two devices have connectivity, but the latter does not.
- A retrospective adherence study on patients with multiple sclerosis using RebiSmart found “greater than 95% adherence” over a 140-week duration (N = 110).<sup>18</sup>

It remains to be seen if evidence of negative outcomes, such as data breaches or malware, will start to appear.

### Data Infrastructure

It is logical for companies to roll out their connectivity infrastructure using the following building blocks:

1. Adding connectivity to the drug delivery device.
2. Optionally connecting the drug delivery device to a “mobile medical app”. This can be an app running on a smartphone (such as AliveCor’s KardiaMobile app), or on a dedicated device (such as Abbot’s FreeStyle Libre device).
3. Cloud storage and web apps that can be accessed through a web browser.
4. Electronic health records (EHR)

The main cloud computing providers (Amazon Web Services, Google Cloud Platform and Microsoft Azure) have various offerings that are HIPAA compliant, so can be used for some medical data in the US, but HIPAA compliance is not regarded as

strong enough protection for the data of EU citizens. The recent General Data Protection Regulation (GDPR), which has been in force since May 25, 2018, places further requirements on the controllers and processors of personal data.

Several companies and collaborations are creating cloud technologies to handle data from connected medical devices. For example, Salesforce.com (in the form of its force.com platform), Qualcomm Life and Philips HealthSuite are working on patient data platforms. Roche bought Flatiron (New York, NY, US), which developed the OncologyCloud, claimed by them to be the “industry-leading electronic medical record for oncology, advanced analytics, patient portal and integrated billing management”<sup>19</sup>, Medcom Innovation Partner (Struer, Denmark) is handling the data services for Bayer’s BetaConnect device and Redox (Madison, WI, US) is developing a way to share healthcare data between heterogeneous technologies. In effect, Redox can take data from any input, perform transformations and analytics on it, and then convert it into a given EHR format.

### Business Models

Payers are trying to reduce costs, so simply adding connectivity and expecting to be able to charge more is not a convincing strategy. However, a holistic view of the health economics of a given indication can reveal compelling business models in some cases.

Example business models already in use include:

- A collaboration between Amgen (Thousand Oaks, CA, US) and Humana (Louisville, KY, US) whereby Amgen analyses real-world evidence from Humana’s members with data from wearable devices, apps and smart drug delivery devices.<sup>9</sup>
- A collaboration between Amgen and Harvard Pilgrim Health Care (Wellesley, MA, US) whereby Amgen will fully refund the cost of Repatha if the patient is hospitalised by a stroke or myocardial infarction. Naturally, Harvard Pilgrim will need to show that the patient had adhered to the Repatha regimen and connectivity is a convincing way to do this.
- Abbot did not get reimbursement initially when it developed the FreeStyle Libre flash glucose sensor, so sold it direct to patients. It has since been approved for purchasing by the UK NHS.<sup>20</sup>

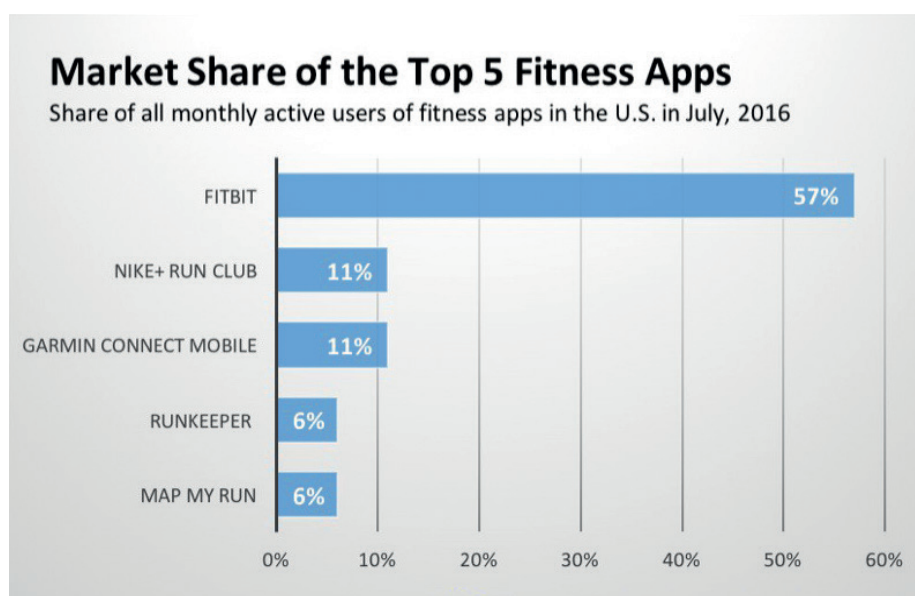


Figure 4: Week-to-week user retention for health-related apps. (SurveyMonkey)

## SUMMARY AND FINAL THOUGHTS

From what Springboard sees in its day-to-day work, every company involved in drug delivery devices either has a connected technology or is developing one. Clinical evidence for improved adherence exists, and evidence for other clinical benefits is mounting. The data infrastructure exists, although systems are not familiar to patients or healthcare professionals yet and there are legal hurdles to overcome when transferring patient data between legal jurisdictions. Traditional business models have struggled, but innovative business models are progressing.

Connected drug delivery devices are already with us, and more are coming to market. The idea that connectivity itself will solve the adherence problem is unrealistic. However, for the first time, healthcare professionals will be able to identify who is adherent and who is not, which will allow them to refocus efforts on those who have the most difficulty adhering.

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Tom Oakley is Co-Founder & Director of Drug Delivery Device Development at Springboard, a leading medical device development company. His first degree was a Master of Engineering from Cambridge University, and he was later appointed the Choate Fellow in human physiology and pathology at the Harvard School of Public Health.

Since 2001, he has focused on creating safety-critical designs for mass production and is named inventor on numerous medical device patents. Since 2005, Mr Oakley led scientific and engineering teams developing new technology in the areas of injection devices, infusion pumps, inhalers, cryogenic surgery, regenerative medicine and electronic blood lancing.

Mr Oakley has delivered lectures and workshops on innovation at the Cambridge University Engineering Department, mentored MBA research projects at the Judge Business School, and been a speaker at various international conferences on innovation and medical device development such as Management Forum, SMi, Pure Insight Masterclasses, MEDTEC and EphMRA.



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## CONNECTED MEDICINE: INSIGHTS FROM PAYERS & OTHER STAKEHOLDERS

Sai Shankar, Director, Business Development – Connected Devices, Aptar Pharma, and Chris Hogg, Chief Operating Officer, Propeller Health, draw upon recent research and their experiences in digital health, including interviews with payers, to explore the current state of connected medicines. They believe there are four key themes which need to be addressed to ensure the promise of connected devices is successfully met.

In the drug delivery sector, there is now widespread belief that connected medicines hold great promise for improving medication adherence, reducing healthcare costs and, ultimately, improving patient outcomes. But what are the executives from the various stakeholders in the healthcare ecosystem thinking?

Aptar Pharma recently recruited a panel of industry executives representing health plans, pharmacy benefit managers (PBMs), integrated delivery networks (IDNs) and life sciences manufacturers to study how these stakeholders perceive connected devices. The research revealed four keys to realising the promise of connected medicines:

- Connectivity and patient engagement
- Adherence
- Coverage
- Cost and adoption challenges.

In this article, we explore those themes and provide a glimpse into the current state of

connected medicines, sharing insights from the study and from Propeller Health's real-world experience in deploying connected medicines.

### CONNECTIVITY & PATIENT ENGAGEMENT

Increasingly, payers, provider organisations, life science companies and PBMs are coming together to better understand and define how connected medicine programmes will work. They are eager to generate data and learnings, and develop appropriate payment models, including how to structure risk-based and outcomes-based contracts.

Like any significant change in healthcare, more work is necessary to make connected medicines truly ubiquitous. Those first steps towards widespread adoption are currently underway, with health plans and PBMs becoming increasingly willing to partner with life sciences manufacturers and digital solutions providers.

Within the EU in particular, there is of course a legislative development, the General Data Protection Regulation (GDPR (EU) 2016/679), which may impact on how the plans for adoption, data generation and interpretation are managed. Recent events also suggest that the US is becoming increasingly cognisant of the reality of personal data breaches and it is therefore almost inevitable that some guidance will be introduced in the US sometime soon.



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"The main lesson learned is that while connectivity is the foundation, a focus on the entire patient journey is critical to delivering positive results."

The study showed that healthcare leaders see the promise of connected devices and improved outcomes for patients, but want strategic partners who can help structure programmes, generate real-world data and showcase results. One panelist, whose company has partnered with a life sciences manufacturer, responded that they had experienced positive results from a connected device adherence programme: “Texting initiatives led to better case management and communication with patients.”

More than 60 connected medicine programmes have been conducted by Propeller, which have highlighted the technical challenges that come with managing tens of thousands of connected devices around the globe, but have also shown significant value from passively capturing medication use data. For example, due to the connected inhaler programme in the city of Louisville, Kentucky, US, rescue inhaler use for people with asthma was reduced by 78% and symptom-free days was increased by 48% (Figure 1).<sup>1</sup>

The main lesson learned is that while connectivity is the foundation, a focus on the entire patient journey is critical to delivering positive results. This requires answering key questions, such as:

- How do patients learn about the connected medicine?
- How do they enroll and onboard?
- What value do they derive personally from the service to make them want to continue using it?
- How do you get this information back to other stakeholders, such as physicians, care teams and payers?
- What are the new care protocols concerning digital, connected medicines?

When connectivity becomes standard in all medication delivery forms, diseases and therapeutic classes, it will be the analytics, user experiences and services built on top of these data streams that will really differentiate solutions. We have seen very different results in engagement, retention and clinical outcomes across different groups, for example:

- **Patient types** – “sicker” patients enroll more often
- **Patient age** – older patients are more engaged
- **Payer type** – Medicaid programmes are more challenging, but possible
- **Clinical involvement** – strong care teams see superior results across most metrics.

## ADHERENCE

For many health plans and PBM advisors, increased adherence is a key goal for connected devices. Additionally, health plans and life science manufacturers want data from devices as proof that a patient is taking their medications, and want hard data on outcomes, such as the effect on the number of emergency room visits by patients and the subsequent impact on cost.

Two PBM and health plan panelists, however, focused more on using technology to improve the information flow between patient and provider, and to increase engagement from the patient through the use of contextual reminders and personalised educational content. Technology used this way, suggested one PBM panelist, allows providers to “have more of a direct patient interaction”.

Despite variances on how connected

health technology can be used, the ultimate goal remains the same: keeping patients healthy and out of hospital.

The results from the commercial programmes conducted by Propeller Health validate this finding. For example, connected device users demonstrated more than double the average adherence when compared with a large national sample (calculated from four large studies of more than 84,000 patients).<sup>2-5</sup> In a controlled study, Propeller was associated with a 58% improvement in adherence in the intervention group after six months when compared with the control group.<sup>6</sup>

There was also increased interest in using connected medicines as a new signal for physicians to determine the appropriate level of therapy for each patient, including to justify a “step-up” treatment – such as a biologic for severe asthma – to improve patient health and reduce hospital visits.

## COVERAGE

Coverage of connected devices is complicated. The consensus among the interviewees was that if the sensor is integrated within the medication delivery device, it will be covered under the pharmacy benefit, and if the device is an add-on or otherwise separable, it will be covered as durable medical equipment (DME). The software or service component of the solution may also be embedded in the drug benefit but will more likely be covered by health plans. This service reimbursement will cover both the service provider and physicians for their time interpreting data. In the US, physical therapy (PT) codes for interpretation of remote monitoring data are coming into use, with the unbundling of CPT code 99091 in January 2018 and a new RPM code expected in January 2019.

Some panelists from the health plans agreed that they will wait for PBM or Medicare guidance before deciding how to handle these decisions in their own plans. They also wanted to see real-world evidence that the device is going to be worth the investment: providing improved outcomes, significant medical value or cost offset, and helping with quality measures and hospitalisations. Only then would they decide how to cover the device and who will pay for it.

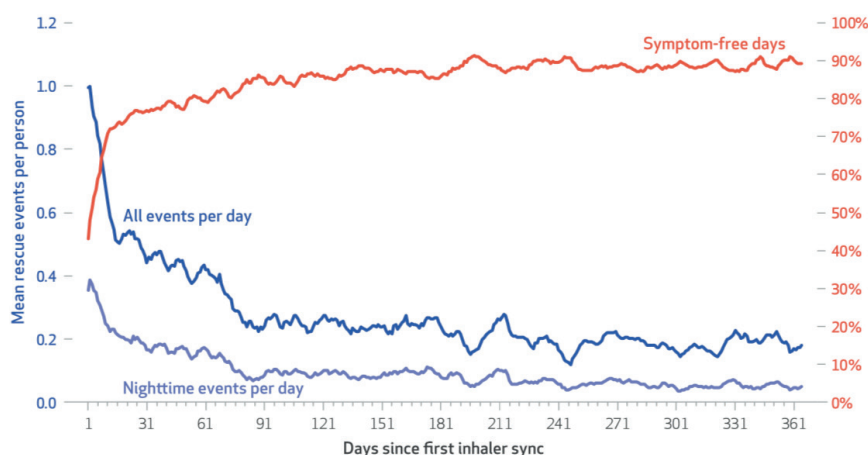


Figure 1: Clinical outcomes of participants with asthma over the 12-month intervention. Chart courtesy of Health Affairs.



## COST & ADOPTION CHALLENGES

Cost was consistently ranked as one of the top concerns for plans looking at implementing connected medications. However, life science companies see this technology as a mechanism to usher in an era of value-based contracting, either with PBMs or directly with health plans, possibly upending the current rebate model, thereby gaining a competitive advantage.

The advisors stated that they expected connected devices will cost more, a factor that must be considered when deciding whether to cover. For many, this added cost is the most important factor, meaning they must be completely convinced that the connected device will improve outcomes. Propeller has demonstrated an ability to achieve this, as well as significant reductions in healthcare utilisation, such as emergency room visits and hospitalisations.<sup>7</sup>

Most health plan advisors said they would engage in financial and risk value analyses to understand both the offset and determine if significant value could be obtained. It would be trickier for PBMs; both PBMs interviewed gave an unequivocal “no” when asked if the rebate could be mitigated. A health plan, however, has a net cost, so they would be willing to sacrifice the rebate with evidence of cost savings in other areas. One study panelist said, “We just want people to take their medications. It’s not over complicated.” In other words, if the providers can use connected medicines to correct compliance, then the device is worth the extra cost.

At Aptar Pharma, we believe that it is important to note that, as connected devices get widely adopted, at scale, the costs will reduce significantly and become less of an issue as the focus shifts to the value connected devices deliver for patients and health plans.

## CONCLUSION

This study and our shared experiences reveal a market that is maturing quickly. Health plans, PBMs, IDNs and life sciences manufacturers are gaining confidence in expanding their connected device programmes – particularly when paired with the right strategic partners, helping them to consider connectivity and patient engagement, adherence, coverage, and cost and adoption challenges.

As this market continues to evolve in the years ahead, we believe it will be a significant driver in reducing healthcare costs and improving patient outcomes.

*BREAKING NEWS: At the time of going to press, Aptar Pharma and Propeller Health announced a major expansion of their 2016 agreement. The companies are to collaborate on the launch of a comprehensive platform to develop digital medicines for multiple therapeutic areas, spanning inhaled, injectable, nasal and dermal medicine delivery forms. The two companies will co-market the platform. In addition, Aptar Pharma has made a strategic equity investment of US\$10 million in Propeller Health.*

## ABOUT THE COMPANIES

Aptar Pharma provides innovative drug delivery systems, components and services to pharmaceutical, consumer healthcare and biotech customers worldwide, spanning a wide range of routes of administration, including nasal, pulmonary, ophthalmic, dermal and injectable. Aptar Pharma’s mission is to provide complete solution services built around its drug delivery systems and to create stage-specific development packages designed to address regulatory needs proactively and accelerate

approval. Overall, six billion components and systems are produced annually across 12 manufacturing sites and are accessed by 1.6 billion patients, and over US\$50 billion worth of pharmaceutical products depend on Aptar Pharma’s systems. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

Propeller Health is a leading digital therapeutics company dedicated to the development and commercialisation of measurably better medicines. Propeller creates products to treat disease more effectively and improve clinical outcomes for patients across a range of therapeutic areas through connectivity, analytics and companion digital experiences. The Propeller platform is used by patients, physicians and healthcare organisations in the US, Europe and Asia.

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**Chris Hogg** is Chief Commercial Officer at Propeller Health, where he leads the company’s San Francisco office with an emphasis on commercial strategy and partnerships with life science companies, payers, provider organisations and PBMs. Prior to joining Propeller Health, he co-founded 100Plus, a mobile health company using personalised analytics to promote healthy behaviours, which was acquired by Practice Fusion in 2013.



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# THE SMART APPROACH TO HARNESSING DATA

We live in the age of big data. Devices and services are now a fully integrated part of everyday life in many countries and the influence of this technology is spreading ever further. As the drug delivery world moves to embrace it, it is important to remember that unseen risks await the unwary. Tom Lawrie-Fussey, Healthcare Digital Strategist, Cambridge Design Partnership, explains further.

“Connectivity” and “smart” have become familiar terms when discussing modern products, stemming from the underlying technology. However, the key unit of merit is not the technology itself but rather what it enables – specifically data, and thus information, about all aspects of the environment and our interactions within it. Where once products were purely transactional, they can now be seen as facilitators of data, enabled by smart or connected technology, with the real business value now residing in the information gleaned from the data the device collects, rather than simply the sale of the devices themselves.

But where to start? The first step is to consider what users are likely to need and want to engage with, letting that drive how you create a product or service that is seen as smart by those who interact with it. You also need a clear idea of how your business can derive value from what you produce. All of which must be underpinned with a keen understanding of what technology can achieve, wrapped up in a model of how it can be deployed and operated.

Context is king – and there are many ways of obtaining a better understanding of it. Bolting on technology is, of course, one option, but there are many others, often involving less development, deployment and analysis costs. Some of the best smart packaging solutions contain no technology – instead, they use an understanding of the on-the-ground problem, and they solve it using innovative thinking, not innovative technology.

An interesting example of smart packaging is the VanMoof bicycle box. This company had significant shipping damage costs; more than 25% of its mail-order bikes were arriving damaged. The company considered adding complex electronic impact-logging equipment to better understand where the shipments were

“Context is also key when it comes to creating patient-friendly drug delivery devices. It would be a mistake to assume, for example, that patients want to have an interaction with your organisation each time they self-administer.”

being damaged. But even these kits require the end user to upload the data – not an easy ask for its customers. So, instead, VanMoof thought more laterally. It realised that logistics companies simply didn’t take sufficient care of its boxes, which were clearly labelled as containing bicycles. It needed a solution that would go further than embedding technology and cost into packaging – the company had to find a way to change human behaviour.

The smart packaging solution? VanMoof made its boxes look like TV boxes. Overnight, product damage dropped by more than 80%. The perception of fragility meant boxes were handled with far more care, with logistics providers knowing all too well the implications of delivering damaged electronic goods. Thus the problem was solved by knowing the local context, instead of adding technology to provide a proxy to context.

Context is also key when it comes to creating patient-friendly drug delivery devices. It would be a mistake to assume, for example, that patients want to have an interaction with your organisation each time they self-administer. Consider instead the idea that, contrary to such an assumption, it’s common for patients to desire less interaction and engagement, preferring to get on with their lives. Instead, you should be measuring “smart” from the patient’s perspective, not yours. Can your new connected offering provide a subtle, legitimate, compassionate



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interface, where the patient feels empowered to contribute and interact, rather than them perceiving the service as being a little invasive and akin to some all-seeing “Big Brother” snooping? When the technology gets out of the way and the only perceived interactions are ones where the patient receives “surprise and delight”, then you have the start of a recipe for success.

Once a suitable method has been deployed that can capture context, and can translate these observations into insights and value, the data collected is the next big challenge for companies to overcome. There’s a tendency to collect as much data as possible. This hunger for data stems from a perception that there may be ways to use it to create new revenue streams in ways not yet understood. Many industries have adopted this future vision where, by crunching sufficient numbers for long enough, with ever-more-powerful data analysis methods, they hope (or in many cases expect) to be able to uncover future value. This is one of the values on offer from “big data” and it seems to be a good bet. However, there remain many challenges that must be better understood to make future digital and data decisions wisely, from a well-informed perspective.

## MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE

Machine learning and artificial intelligence (AI) have quickly become the buzzwords of data analysis. Whilst hugely powerful as an approach, they need to be understood clearly so that the right approach can be selected and deployed for each application, according to the desired outcome.

The machine learning approach only works with the data you give it and, without care, it will likely tell you more about your measurement approach than the thing you are trying to measure. It’s more helpful to think of such tools not as the standalone

answer, but rather as one tool within a large toolbox devoted to extracting value from data, with the key focus being data science. Other tools in the box include classical signal processing and analysis methods, with selection of the most appropriate tool for the job being as important as the ability to wield it. The automated deep dive and pattern matching of machine learning is best deployed when expert know-how has already pieced together part of the puzzle (i.e. worked out roughly where to look), and where scale is a suitable approach to find the solution.

Even then, such output predictions need to be validated by data scientists before any actions are taken. Fully automating this process without expert intervention – and allowing algorithms to link (and potentially confuse) correlation with causation – can deliver unexpected and misleading outcomes that are potentially crippling for an unsuspecting organisation.

## BIG DATA

To achieve success in AI and the various automated analytics techniques now becoming widespread, vast amounts of data are needed. However, there is also a risk here as, once collected and understood, data can’t easily be forgotten. If data collection is largely uncontrolled and widespread, there is a very real chance that what is uncovered forces a company into an awkward strategic situation.

For example, what if such usage data uncovers genuine misuse or a fundamental issue with a top-selling drug delivery device? It may be that this data is only relevant for one demographic, and one use case, but the simple fact of knowing about the existence of an issue creates a hugely complex commercial and legal situation. Such data is almost always automatically backed up and stored. It cannot be undone. The insights, however unpalatable, cannot be unlearned.

In any business there are aspects of day-to-day reality that are known to carry some risks but, with no detailed evidence to the contrary, continue to be implemented and embraced. Such companies, along with their competitors, continue to operate without confronting these issues – often with a sector-wide “blinkered” view of the status quo. Whilst big data could lead to the discovery of new opportunities to innovate, there is a very real chance of it also uncovering some unwanted truths. Collecting and storing big data isn’t cheap

“Whilst big data could lead to the discovery of new opportunities to innovate, there is a very real chance of it also uncovering some unwanted truths.”

and when that data uncovers usage issues, the commercial impact is doubly painful. Companies are then impacted on both sides of the balance sheet. Not only has the substantial investment caused potentially much larger ones, the competition (perhaps those that adopt a fast-follower approach) can continue to sell their own solutions without suffering the same fate (whilst they lack the evidence to suggest they have the same issues). Proof, when it works against the very organisations investing heavily to uncover it, can be hugely costly.

We have seen exactly this behaviour in the logistics market, with a device we helped to develop that could monitor all aspects of a parcel’s condition – such as whether it was dropped during transit or the temperature it was stored at. Such were the capabilities of the device, it could not only tell what method of transport was being used (e.g. car, van, flight) but it could also infer some insights into the speed of those vehicles.

What started as a legitimate desire to better understand the parcel delivery process (and openly share this with the end-consumer) quickly became a new headache, since it could have potentially proven where vehicles were being forced to speed to meet delivery schedules. Whilst the logistics company possessed no direct evidence of such speeding being required to meet its schedules, some of the management team suspected that it may indeed be the case that the industry as a whole was pushing the absolute limits of final-mile logistics to remain competitive.

Such a sensing device, if enabled to collect and process speed information, could have created a potentially huge new problem for the client – a problem that would have only been evident for its own parcels, on its own vehicles. If allowed to proceed to launch in its fully tech-enabled configuration, it could have potentially affected the entire company – whilst its competitors carried on business as usual, watching in amazement, amusement and relief.

“...machine learning is best deployed when expert know-how has already pieced together part of the puzzle, and where scale is a suitable approach to find the solution.”

“Data protection and security regulations, especially for medical data, have very specific requirements – and teeth to ensure compliance.”

Being first to market with new and powerful big data collection technologies brings with it new risks – particularly for those who don’t fully understand the implications of what they think they want to capture. It’s important to have a good understanding of the desired outcomes (and the potentially undesired outcomes) so any new technology can be mindfully developed and deployed. We typically propose data collection nodes that capture the absolute minimum (for now). Whilst this inherently limits the big data analysis opportunities, consider it simply “big data 1.0”, which we believe better represents the risk-reward balance – enabling an organisation to learn

the benefits at each step, before switching on further capabilities and therefore the risk and benefits of further analysis.

Another aspect to consider is customer data. In the experience of Cambridge Design Partnership, we typically find it best to steer clear of patient-specific data. By partitioning the rich contextual information we can extract, and storing this separately from the customer data, many security risks can be avoided. Data protection and security regulations, especially for medical data, have very specific requirements – and teeth to ensure compliance. Rarely do companies actually need much of this data and the risk of data security is significant, with data breaches regularly reported that cause significant damage to consumer/patient confidence. The key (beyond taking sufficient data-security precautions) is to be considered and careful in the data collection strategy. We are able to uncover huge amounts of user insights without ever meeting the patient or knowing their age, background, address, etc. In most cases, we don’t want to know – we’d rather the data highlights if they have a usage issue, and

that such observations weren’t inadvertently skewed by some erroneous causation assumption. We find that the data itself is able to highlight particular behaviours and our own analytics experts and algorithms can quickly identify data patterns, which allows us to draw a remarkably accurate picture of in-home usage, without needing to know the “traditional” user information.

This approach can help to uncover unexpected insights – as people rarely say what they do or do what they say – but also maintains the anonymity of data, reducing unnecessary information management burden. It provides a steer towards innovation opportunities, without committing an organisation to a path it never actually wanted to be on in the first place.

AI, machine learning and big data are here to stay, offering huge potential when harnessed and deployed correctly. It’s important that the risks are balanced against the opportunities before diving in. Large investments are at stake, with the potential for uncomfortable findings which cannot be unlearned.



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# H&T PRESSPART

## THE FUTURE OF CONNECTED ASTHMA AND COPD CARE: A STEPWISE DEVELOPMENT

In a continuation from his previous article in *ONdrugDelivery Magazine*, Benjamin Jung, PhD, Program Manager, eMDI, H&T Presspart, outlines possible scenarios for the likely steps in the development and adoption of connected devices in the field of asthma and COPD care, revisiting H&T Presspart's eMDI and Quantum dose indicator.

### INTRODUCTION

Picking up from our June 2017 *ONdrugDelivery* article "Embedded Connected Metered Dose Inhalers Meeting Requirements for Mass Adoption",<sup>1</sup> steps taken to counter non-adherence to asthma and COPD medication remain insufficient,<sup>2</sup> which has led to a substantial number of patients still not realising the maximum benefit of their treatment, frequent hospital admissions and even avoidable deaths.<sup>3,4</sup> In addition, there continues to exist a significant associated economic burden.<sup>5-7</sup> Previously, we described the role connected devices could play in improving asthma and COPD care, including the requirements for mass adoption, and introduced our inhaler with fully embedded connectivity, the eMDI™, which is designed to address the needs of multiple stakeholders.

In our estimation, the coming years will see a broad introduction of connected

"In our estimation, the coming years will see a broad introduction of connected devices into asthma and COPD care, following a stepwise approach to meet the requirements for mass adoption."

devices into asthma and COPD care, following a stepwise approach to meet the requirements for mass adoption. As an example, new devices should, in general, not present any significant changes to the status quo and, in the specific case of connected inhalers for asthma and COPD, new designs should be based on existing forms and function similar to conventional "press-and-breathe" metered dose inhalers (MDIs).<sup>1</sup>

Nevertheless, the mid- and long-term future of connected asthma and COPD care remains shrouded by a high degree of uncertainty, as key technology and market

"Short-term, it is predicted that devices will be focused merely on tracking patient usage with rather simple sensor technology, for example electrical switches. This offers cost advantages on the one hand and limited changes to the status quo on the other, prompting broad patient adoption."



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developments continue to evolve. One particular challenge is intersection of the rapid pace of technological advancement and change within the electronics sector and the very conservative and change-sceptical pharma industry. This article employs a simplified scenario analysis to provide insights into the future of connected asthma and COPD care in the US and Europe<sup>8</sup> and will, on that basis, also provide a perspective on potential developments of connected care in emerging markets like India, China and South America.

### KEY ELEMENTS CONSTITUTING CONNECTED ASTHMA & COPD CARE

A scenario analysis is generally based on three key steps:

- Key elements describing the field of interest are defined.
- Potential future developments are evaluated.
- The various developments of different elements are combined to define consistent scenarios.<sup>9</sup>

When it comes to connected asthma and COPD care the key elements to consider are:

- Developments in device technology
- Developments in the technology of the platform solution, which encompasses a mobile front-end, cloud-enabled services and a database.
- That the patient point of contact, taken in terms of decision power over drug and regime, might change as smart technology begins to prevail.
- That a sound business model for connected asthma and COPD care is not yet fully defined.<sup>1</sup>

This article will focus on these four key elements. However, other considerations could also have been classified as key. Examples include the supply chain to the patient, which might be shaken up due to the introduction of smart technology, and medications being part of connected care platforms, as embedded devices will probably be introduced to controller medication first and rolled out to rescue medication later.

### LIKELY DEVELOPMENT OF DEVICE TECHNOLOGY

The electronics becoming more intrinsically

embedded has proven to be a key short-term development since this design approach facilitates devices that are intuitive for patients to operate, whilst offering increased data quality and greater marketing appeal compared with add-on devices.<sup>1,10</sup> Short-term, it is predicted that devices will be focused merely on tracking patient usage with rather simple sensor technology, for example electrical switches. This offers cost advantages on the one hand and limited changes to the status quo on the other, prompting broad patient adoption. Additional reimbursement on a wide scale is seen unlikely in that time scale.

Based on the experience of market players within the connected health device space, adding advanced sensors to track technique, such as inhalation flow, next to usage patterns is the next logical step. Examples of advanced sensor technology could include absolute and differential pressure sensors or accelerometers.

Long-term (i.e. more than ten years hence), three additional developments will likely shape the design of connected inhalers:

- On the electronic side, more electronic components, such as capacitors, will be directly printed onto flexible substrates, substituting conventional printed circuit boards (PCBs) with surface-mounted components.<sup>11</sup> Examples for components already being produced in a comparable fashion are high frequency (HF) and ultra-high frequency (UHF) radio-frequency identification (RFID) tags.<sup>11</sup>
- On the connectivity side, we expect new technologies offering direct device-to-cloud connectivity to substitute Bluetooth low energy (BLE) technology, as by then they should offer an improved patient onboarding experience and lower dependencies on third party devices, such as smartphones. Out of the competing technologies, e.g. Sigfox, Zigbee and NB-IoT, from today's perspective NB-IoT seems the most likely "winner", especially due to its roll-out being achievable in a rather lean fashion.
- On the overall device architecture side, the most significant change can be assumed. Comparable with electric cars, where so-called purpose-designed cars offer advantages over conversion-designed cars, connected devices will likely be designed around their electronic and connectivity features, for example offering active mechanisms to regulate the flow-rate in a dynamic fashion.

### LIKELY DEVELOPMENT OF PLATFORM SOLUTION

In terms of the platform solution, it is anticipated that further optimisation of the user interface (UI), in terms of usability, will occur as the key-short term development. This is in line with larger scale studies being conducted by leading platform solution players utilising patient feedback for product refinement.

Mid-term, three likely developments can be expected:

- Platform solutions will be increasingly used to predict certain patient conditions, for example asthma attacks. Rescue inhaler usage could for example be used as a predictor of future severe exacerbations.<sup>12</sup>
- Applications will be more customised to specific patient needs. Taking, for example, the dose-reminder logic, rather than using a single approach across an entire patient population, we could see the use of different algorithms for different patient populations or an algorithm that can utilise harvested behavioural information to tailor itself to the needs of each individual patient.<sup>13</sup> This should lead to an increase in the average efficacy of connected care.
- Furthermore, there will be increased data integration between competing and adjacent systems. This will be required to cope with circumstances such as a patient who uses multiple inhalers from different pharmaceutical companies, each having its own separate software component, in parallel.<sup>14</sup> Additionally this will allow for connected monitoring systems, such as a spirometer, being added to connected care platforms.

Looking beyond that, platform solutions will likely control potentially existing active device functions and will offer dynamic dosage regimes as well as drug choice support to patients.

### LIKELY DEVELOPMENT OF THE PATIENT POINT OF CONTACT

Physicians, partly in combination with other healthcare providers (HCPs), will continue to be the main point of contact for the patient, and make the decisions regarding drug and treatment regime, in the short-term. Access to data from connected care platforms can support both

“Long-term, connected care platforms could become the main point of contact and could make decisions on the regime and partly on the drug to be used by a specific patient.”

HCPs and patients with making informed decisions. Mid-term, we expect at least the perception of the benefits by the patient to change in line with the increased application and platform solution functionality. Long-term, the platform solutions could become the main point of contact and could make decisions on the regime and partly on the drug to be used by a specific patient. In that state, the physician would rather be in a monitoring and gatekeeper role – at least after the initial onboarding. Other players, such as telehealth centres, could foster that development, as they can combine distant patient monitoring and the option for human, non-technology driven intervention.

## LIKELY DEVELOPMENT OF UNDERLYING BUSINESS MODEL

Short-term, the business model for connected asthma and COPD care will probably be driven by improved sales seen by the pharma companies introducing these systems, due to increased patient adherence, even taking into account that this model is subject to some uncertainties.<sup>1</sup> In exceptional cases, we expect to see the costs being directly funded by increased reimbursement. The UK NHS has already started the reimbursement of selected applications via its “Innovation and Technology Tariff”<sup>15</sup> and in Germany individual, tech-orientated insurance companies might fund specific connected care systems via specific selective contracts, called *Selektivverträgen*.

Mid-term, at least a medium probability exists that the majority of payers will move to outcome-based reimbursement, therefore demanding sufficient patient compliance, which in turn can be boosted by connected care. A potential for pharma companies to capture increased reimbursement on a broad basis prevails long-term, as connected care systems by then should offer significant additional value, even taking over some of the tasks traditionally performed by physicians.

## RESULTING FUTURE SCENARIOS OF ASTHMA AND COPD CARE IN THE EU AND US

The discussed developments can be combined to potential short-, mid- and long-term scenarios of connected asthma and COPD care in the US and EU. Table 1 summarises these scenarios along the defined key elements and compares them to the status quo. To summarise further:

- Short-term: rather simple embedded devices will likely replace add-on devices. This will be funded by rising sales due to increased adherence and will lead to classical patient point-of-contact models prevailing.
- Mid-term: technique monitoring and patient-state prediction functions will likely be added to the platforms, partly to cope with increased pressure from the payers via outcome-based reimbursement models.
- Long-term: purpose designed devices driven by advanced platform technology offer the potential for pharmaceutical companies to shape the supply chain and the patient point of contact, capturing increased reimbursement in the process.

Key Element	Status Quo	Short-Term Scenario	Mid-Term Scenario	Long-Term Scenario
Device Technology	Passive add-on devices tracking usage using simple sensors, standard electronics and BLE	Passive embedded devices tracking usage using simple sensors, standard electronics and BLE	Passive embedded devices tracking usage and technique using advanced sensors, standard electronics and BLE	Purpose-designed, active devices tracking usage and technique using advanced sensors, printed electronics and post-BLE technology
Platform Technology	Non-patient customised, simple platform solution encompassing reminders and data display with limited integration capability with competing and adjacent systems	Non-patient customised, usability optimised platform solution encompassing reminders and data display with limited integration capability with competing and adjacent systems	Patient customised, usability optimised platform solution encompassing prediction, technique, reminders and data display with increased integration capability with competing and adjacent systems	Patient customised, usability optimised platform solution encompassing control of active device functions, dynamic dosage regimes, drug choice support, prediction, technique, reminders and data display with full integration capability with competing and adjacent systems
Patient Point of Contact	Physician is main point of contact and decision maker on drug and regime, app perceived as support tool	Physician is main point of contact and decision maker on drug and regime (supported by data), app perceived as support tool, other players evolving	Physician is main point of contact and decision maker on drug and regime (supported by data), app perceived as equally important as physician, other players established	Platform solution (partly in connection with other players) is main point of contact, decision maker on regime and proposes drug, physician in monitoring/gate keeper role
Business Model	Diverse	Increased revenue due to increased adherence, partly increased reimbursement	Increased revenue due to increased adherence, reimbursement depending on level of compliance	Greater revenue due to better adherence, reimbursement depending on level of compliance but increased due to additional value created

Table 1: Future scenarios of asthma and COPD care in the EU and US.

## POTENTIAL DEVELOPMENT OF ASTHMA AND COPD CARE IN EMERGING MARKETS

Whilst emerging markets are no less willing to adopt connectivity and tech-based solutions than the established US and EU markets, most will have issues when it comes to the cost of adopting such solutions. As such, it can be expected that uptake will be significantly slower in these markets, with the possible exception of small, specific pockets or demographics that are less sensitive to cost. When considering these markets, it is worth investigating the possibility of low-cost variations or applications of the technology in order to lay the groundwork for a future scale-up to the fully featured versions when the resources exist to support it.

### H&T PRESSPART'S EMDI POWERED BY COHERO™

To address the ongoing issues of patient adherence in the area of asthma and COPD and to offer the “next step” device and platform technology, H&T Presspart and Cohero Health (New York, NY, US) formed a strategic device development and marketing partnership. As a result of this multi-year collaboration, the companies have created the first market-ready, fully embedded, intuitive connected MDI solution: H&T Presspart's eMDI™ powered by Cohero™ (Figure 1).<sup>1</sup>

H&T Presspart's eMDI powered by Cohero™ comprises the device and platform technology, which will likely be applied in the EU and the US short-term and captures early mid-term functionality.

The eMDI device's connective hardware and software are fully-embedded within the actuator design. The electronics detect the actuation of the inhaler and the patient's actuation technique with the aid of switches, adds a date/time stamp and shares the data wirelessly via BLE with a mobile phone application – the BreatheSmart® application from Cohero Health.

The application, and the respective back-end in turn, form a comprehensive respiratory disease management platform, which reminds patients to take their doses and displays the usage data to them, with the potential to share it with other stakeholders. The usability of the patient interface has been optimised in an iterative manner and



Figure 1: H&T Presspart's eMDI powered by Cohero™.

has proven efficacy. BreatheSmart users demonstrated patient retention of 72%, a 55% increase in daily medication adherence and a 95% decline in rescue therapy. The BreatheSmart® platform also encompasses accurate clinical-grade lung function measurement via a mobile spirometer, as well as other clinically actionable digital biomarkers. The capability for data integration with other systems, such as electronic medical records (EMR) and contract research organisation (CRO) tools has been demonstrated.

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

H&T Presspart's Quantum™ dose indicator and associated app represent a potential bridge solution into more advanced connected care models in emerging markets. The off-the-shelf Quantum dose indicator is an on-can MDI indicator solution, which ensures patients don't run out of medication. This is achieved with the aid of an arrow on the bottom of the can that indicates the remaining drug level.



The Quantum dose indicator app can be used to read this arrow almost automatically and thereby track the device usage via combining the can fill-level data gathered during individual arrow readings (Figure 2). It is available for Android and iOS mobile platforms and includes dose and prescription refill reminders. Last but not least, the functionality of the Quantum dose indicator app can be incorporated into a comprehensive respiratory disease management platform, such as BreatheSmart®.<sup>16</sup>

In summary, Quantum is a significantly lower cost method of capturing some of the functionality of a fully embedded system, offering a high differentiation potential for pharma companies in emerging markets.

## CONCLUSION

The future of connected asthma and COPD care will likely unfold in a stepwise manner. Device and platform functionality, such as technique detection and patient state prediction, will probably be added over time allowing the pharmaceutical players to shape the patient interface and thus increase potential reimbursement value. With its eMDI powered by Cohero™, H&T Presspart has created a product which represents the logical next step on this journey, especially as it embeds the electronics into the device at a low cost.

Furthermore, H&T Presspart's Quantum dose indicator and its companion app can be implemented as a meaningful bridge solution to these advanced connected care models in emerging markets.

*The eMDI and Quantum logos are registered trademarks of Presspart Manufacturing Limited.*

*Cohero Health, HeroTracker, mSpirometer, BreatheSmart, and Breathe Smarter are*

*trademarks of Cohero Health, Inc.*

## ABOUT THE COMPANY

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

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**Figure 2:**  
H&T Presspart's  
Quantum app.





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to allow real-time tracking  
and care management



Mechanical  
Dose Counter



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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.

# LISTEN TO YOUR INHALER, IT MIGHT BE TELLING YOU SOMETHING

In this article, Kian Min Lim, PhD, Data Scientist, and David Harris, Head of Respiratory Drug Delivery, both of PA Consulting Group, discuss how tailored algorithms can accurately detect inhalers' acoustic signatures, effectively adding connectivity without having to add a chip to the inhaler or, indeed, modify it in any way.

Machine learning technology has advanced in leaps and bounds, spearheaded by the rapid progression of deep learning. Deep learning – widely considered as narrow artificial intelligence (AI) – has been shown to perform a well-defined task at, or beyond, the human expert level.<sup>1</sup> The deep learning algorithm can be designed to perform a singular well-defined scope or task effectively and accurately. In fact, there are many deep learning algorithm implementations in the consumer sector, for example, Apple's Siri, Samsung's face unlock, Google's voice assistant, and many others.

Leveraging these advancements, we can transfer some of these deep learning

"Our group has demonstrated that an image recognition algorithm can be adapted to listen to an inhaler during normal use, and produce a remarkable 98% confidence level of correctly identifying the inhaler's acoustic signature."

techniques to innovate current inhaler offerings. Our group has demonstrated that an image recognition algorithm can be adapted to listen to an inhaler during normal use, and produce a remarkable 98% confidence level of correctly identifying the inhaler's acoustic signature.<sup>2</sup>

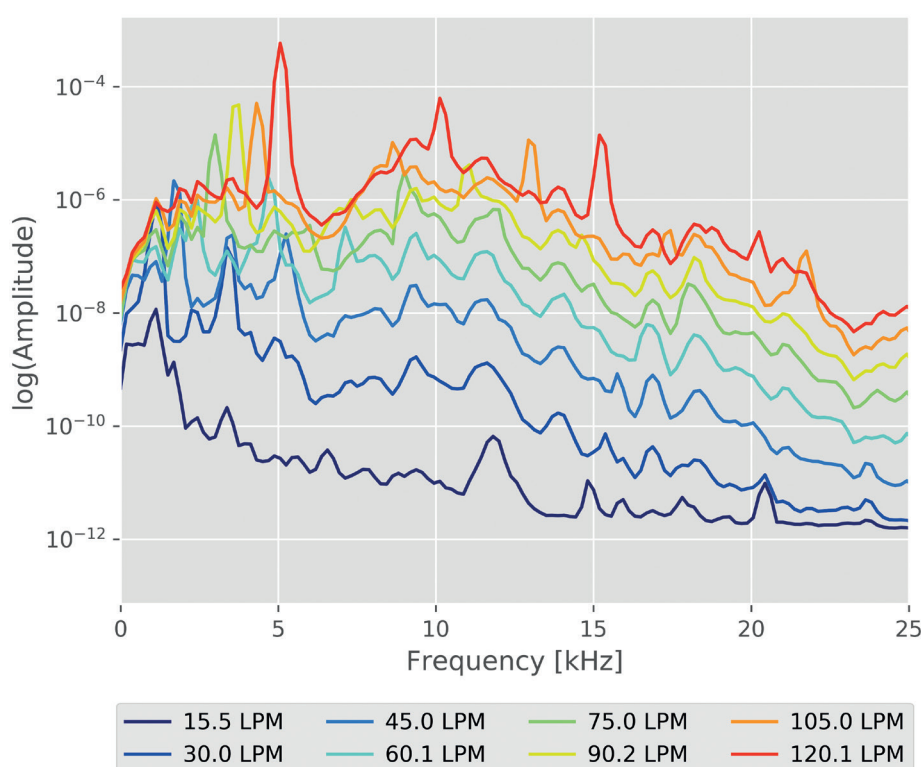


Figure 1: Frequency response plots for Sun Pharma's Starhaler DPI.



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## SOUND EMISSION FROM THE INHALER

An airflow impingement will inevitably generate noise, and each small impingement or change in direction of the airflow, will contribute accumulatively to the overall acoustic signature. These flow impingements and subtle changes of direction are specific to the particular inhaler type. For example, swirl-based inhalers have a strong tonal (frequency) response to the flowrate.

Understanding the underlying physics of how the sound is generated influences the type of parameters and performance metrics that can be derived from the emitted sound data. In a swirl-dominated flow regime, common in many different dry powder inhalers, swirl number will be a function of flowrate, with higher swirl numbers producing higher dominant frequencies (Figure 1). Thus, by listening to the sound produced and analysing the frequency spectrum, we can infer the flowrate with high confidence.

## DEEP LEARNING CAN DETECT PERCEPTUAL DIFFERENCES... & MORE

The wealth of information that is contained within the emitted sound can be used to infer various characteristics of the inhalation event, including flowrate, event actuation and even drug emission. These events often require the algorithm to detect subtle acoustic differences that – to the human ear – are inaudible. The advantage of deep learning is that it allows these acoustic signature patterns to be accurately detected and recognised, even beyond what the human ear and brain is capable of perceiving (Figure 2).

A second advantage of deep learning in this application is its robustness (98% accuracy even in initial studies), which is achieved by considering the full spectrum of the acoustic event. Through a large number of data, the algorithm automatically tunes in to a set of statistically relevant signatures that lead to the desired result. This is often referred to as automatic feature detection.

## SMARTPHONES & DEEP LEARNING

Using sound recognition technology the microphone(s) contained within a smartphone can record a sound event – and the ever-increasing processing power of the smartphone means that as time goes on it is more able to perform deep

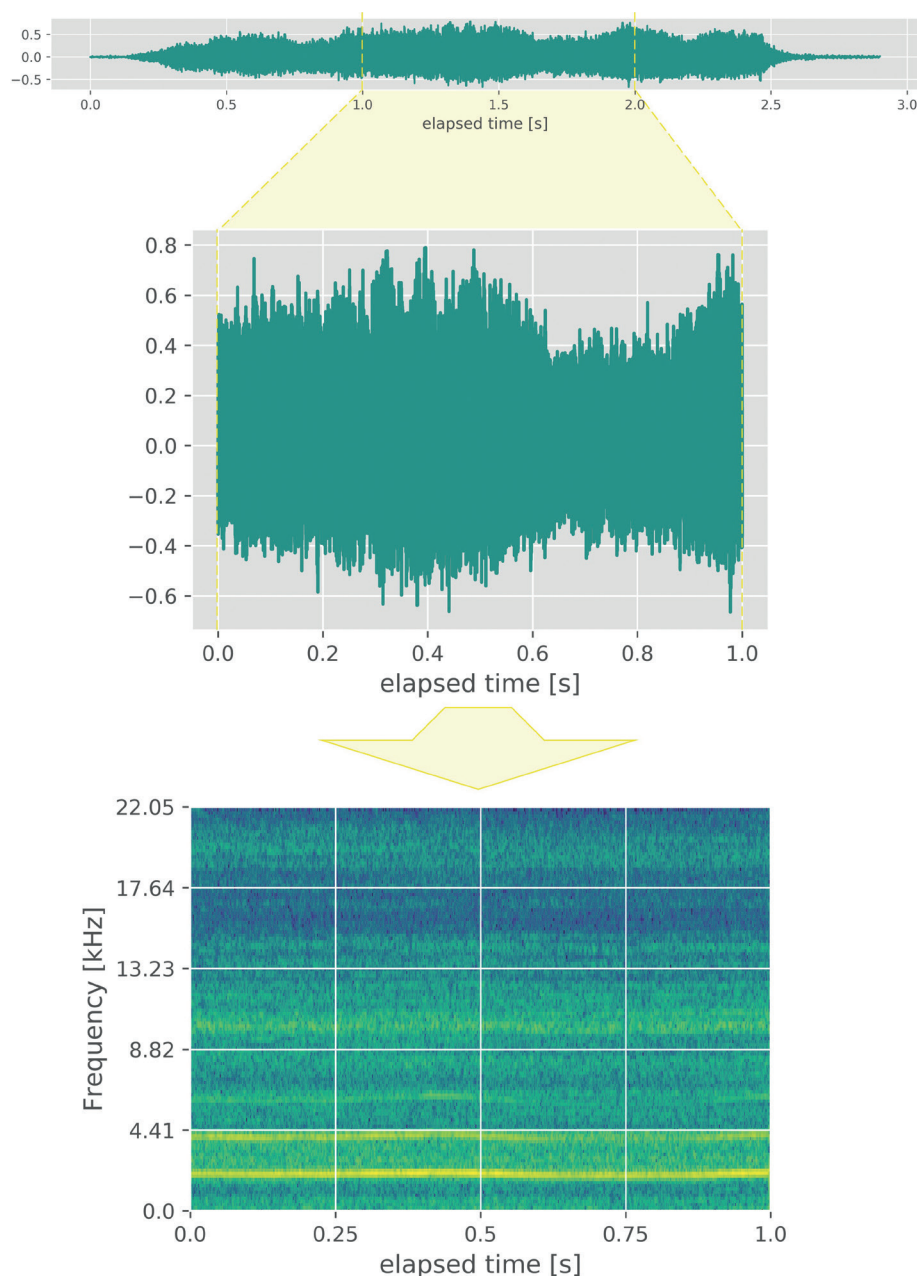


Figure 2: Audio sampling process to create spectrograms of the sound data.

learning analysis. The advancement in silicon and machine learning technology are the cornerstones of this concept becoming feasible now and their combination enables the implementation of inhaler sound recognition using a smartphone, which would not have been possible only a decade ago.

### Deep Learning Explained

Deep learning acquired its name from its architecture, in which typical deep learning algorithms encompass multiple layers of neural networks. Each layer of the neural network is composed of multiple neurons, the design of which was inspired by the human brain cell neuron. Each of these neurons is tasked to identify a single subset

or decision. Combining multiple neurons into a layer produces an algorithm that can make more complex decisions. Deep learning goes a few steps further by joining up multiple layers of neurons and other mathematical transforms together to make increasingly complex predictions possible (Figure 3).

A complex neural network (CNN) that has multiple layers of neurons and mathematical transforms enables the deep learning algorithm to be trained to predict a complex action with high accuracy. A deeper network would often be capable of producing more complex predictions, providing the information gradient across high numbers of layers has been properly addressed.<sup>3</sup>

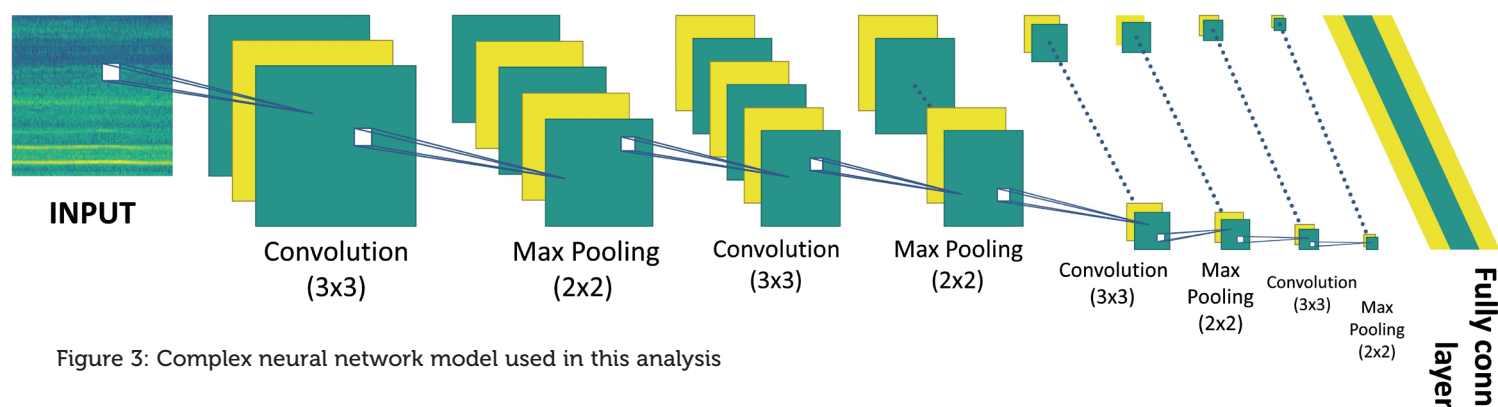


Figure 3: Complex neural network model used in this analysis

“Flowrate detection, for example, will be improved by hearing the sequence of flowrate changes, whereas intermittent events such as breath actuation or the opening and closing click of the inhaler, can be used to identify the beginning and end of the manoeuvre.”

The depth of deep learning layers is a double-edged sword because often a deeper network will require more samples and more data to be trained adequately. So it becomes a trade-off between the quantity of data versus the required level of confidence in the prediction.

### IMPROVING ALGORITHM ACCURACY

#### Synthetic Data Handles Enormous Data Requirements

One shortcoming of using a deep learning algorithm is that it can require a large number of samples to achieve the statistical significance that leads to robust predictions. In fact, a deep learning algorithm trained using only small samples sizes (say hundreds to low thousands), is likely to have limited effectiveness and accuracy.

One method to address the necessity for large datasets is to augment the original data with additional reconditioned data. Data augmentation has frequently been used in the deep learning community to generate additional data through data reconditioning. For example, an image can be flipped to generate additional mirrored data for image recognition training.

Another method to increase the

quantity of data available to train the deep learning algorithm is to use synthetic data. These are data that have been generated through artificial synthesis based upon an underlying model. This technique requires understanding of the underlying algorithm and architecture. Both augmentation methods are useful to close the gap on the data requirement rapidly. Care must be taken with the method of augmentation and synthesis given that deep learning is essentially a pattern recognition algorithm. The augmentation and synthesis of data should be generated to represent the actual event in a way that is statistically relevant and acceptable. Nonetheless, when performed properly, this technique enables the production of a highly accurate and robust deep learning algorithm.

In the context of inhaler sound data, an example of data augmentation would be intentionally to superimpose various background noises onto a cleanly recorded inhaler sound. Background noises, such as a coffee shop or noisy canteen, will help the deep learning algorithm to be more robust in a real-world environment.

The robustness is achieved by feeding the deep learning training with additional “unexpected” data, containing an underlying actual inhaler flow noise. This will prepare the algorithm to anticipate these corruptions, and make the algorithm robust across different acoustic background environments.

#### Using Sequence to Improve Accuracy

The unique sequence of events that is observed during an inhalation manoeuvre can be used to reinforce the deep learning algorithm. Flowrate detection, for example, will be improved by hearing the sequence of flowrate changes,

whereas intermittent events such as breath actuation or the opening and closing click of the inhaler, can be used to identify the beginning and end of the manoeuvre.

### ECONOMICS: SOUND COMPARED WITH CHIP-ON-INHALER

The elegance of simply listening to the sound is that it does not require any modifications to the inhaler whatsoever. Given that each type of inhaler produces a unique acoustic signature, which results from its physical design, this technology will be able detect and identify that signature, and infer useful information about the way in which an inhaler was used through analysis of the sound data.

The primary advantages of this technique are that:

1. There is zero additional cost to the device
2. There are no modifications to the device

It effectively achieves connectivity for free. Thus, the general principle of using a microphone to listen to the sound of an inhaler opens up the benefits of connectivity in drug delivery to a wider market, specifically low income economy countries where adding a chip to an inhaler is simply too expensive. Using only a smartphone, with its built-in microphone as the primary sensor, provides previously impossible access to connected delivery device technology, potentially improving drug efficacy, adherence and inhalation technique.

“There is zero additional cost to the device. There are no modifications to the device. It effectively achieves connectivity for free.”



## CLOSING REMARKS

The acoustic signature emitted from an inhaler provides a tremendous quantity of information. Flowrate and device actuation, for example, can be inferred through the deep learning algorithm.

The deep learning algorithm can robustly detect subtle differences in the

sound data, as well as producing an accurate prediction of flowrate profile based upon the sequence within the recording.

Combining the deep learning flowrate detection and the metadata that is readily available from the smartphone, a training program can be developed to improve patient inhalation technique, inhalation

effectiveness and adherence through a well-designed application that provides visual feedback that is appropriate for the target patient group.

Importantly, once the algorithm has been developed it adds zero additional cost, meaning the associated training program can be made widely available, even in developing countries.

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## ABOUT THE AUTHORS

**Kian Min Lim** is a Data Scientist and machine learning specialist at PA Consulting. He is passionate about innovation through cross-discipline technology implementation, such as developing continuous optimisation algorithms on pharmaceutical processes, implementing deep learning on consumer and medical devices and supporting medical device research using patient data. Dr Lim holds a PhD in Engineering from the University of Cambridge, UK.

**David Harris** leads the Respiratory Drug Delivery sector at PA Consulting. He is a physicist and has been working in the field of medical device development since 1994, where he started his career in the Respiratory Physics group at Fisons. He specialises in respiratory drug delivery and enjoys applying solid aerosol science and fluid dynamics to improve the efficacy of inhaler technology. Mr Harris has numerous patents and publications in this area and regularly presents at conferences.



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## ENHANCING ADHERENCE TO SELF-INJECTION REGIMENS BY CONNECTED DEVICES

Many patients do not stick to their autoinjector regimens, which can lead to poor health outcomes. As Craig Baker, Executive Vice-President at Noble, explains, there are many reasons why this is the case such as patients forgetting or insufficient communication during the training sessions. To tackle the problem, Noble has recently launched the AdhereIT platform for autoinjector training and injections, which has benefits for patients, healthcare practitioners and the pharmaceutical industry.

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

With that understood, the importance of improving adherence rates is self-evident. In practice, doing so entails two tasks. First, it is necessary to understand the nature and scope of non-adherence among patients who self-administer their medicine, in particular those whose therapy requires the use of specific devices, autoinjectors being a perfect example. This then leads to the second task, which involves focusing on possible solutions, perhaps considering the potential of new technologies to be commercialised for the benefit of patients, healthcare providers and pharmaceutical companies.

Among the technologies proposed to enhance adherence rates, connected devices have shown a great deal of promise. These devices can be utilised to capture information about patient usage which can subsequently be analysed to gain a better

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

understanding of how patients are using or interacting with their therapies. Noble® has recently developed one such device to help pharmaceutical companies lower non-adherence rates called the AdhereIT™ platform for autoinjector training and injections (Figure 1).

### FACTORS CONTRIBUTING TO NON-ADHERENCE

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

Aside from these factors, however, it has also been estimated that 46% of cases



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Figure 1: AdhereIT™ can be customised to fit a variety of autoinjector platforms.

of non-adherence result from patients' misunderstanding of prescription-dosing instructions.<sup>4</sup> This can result from:

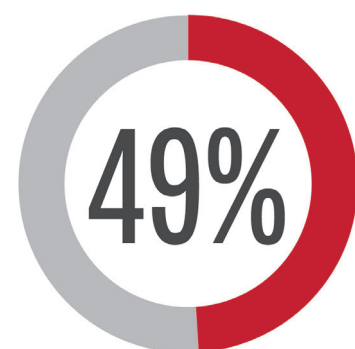
- An unsatisfactory relationship between the healthcare practitioner and the patient, including an inadequate amount of time spent training the patient
- A less-than-adequate quality of instruction received
- An inability to properly understand the Instructions for Use (IFU)
- An inadequate appreciation on the healthcare practitioner's part of the challenges of adherence following the period of initial instruction of the patient on their device (Figure 2).

A review article in *The New England Journal of Medicine* suggests that the increasing demands placed on healthcare provider's time is altering how they interact with patients. Specifically, the pressure on physicians to treat quickly and accomplish multiple goals during a visit has intensified, and in surveys many patients have described their doctors as relatively hurried and unresponsive. The article suggests various factors have also led to a decrease in face-to-face interactions between doctors and patients. While there

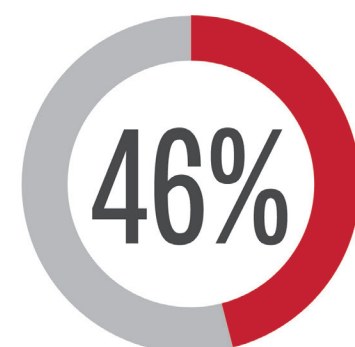
has been a narrowing in the scope of how doctors interface with patients, there has been a simultaneous growth in team-based instruction to the patient involving other professionals.<sup>5</sup> For those responsible for training patients on the proper use of autoinjectors, accuracy and professional expertise are clearly vital.

This first 30 to 90 days after diagnosis – the “onboarding” period, in which the patient is introduced to and trained on their autoinjector – is crucial for ensuring long-term adherence. However, some studies have shown that patients often have difficulty recalling the exact process of self-administration with an autoinjector following training. This reflects a study that concluded that 40–80% of all medical information supplied by a healthcare practitioner is forgotten immediately.<sup>6</sup>

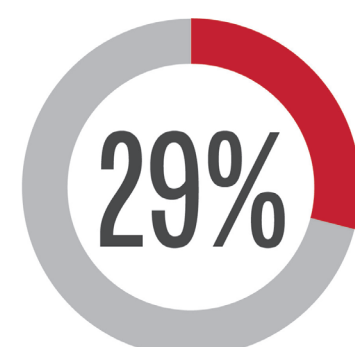
Supplementary to this finding, it has also been suggested that 19% of patients have a higher risk of non-adherence in the wake of poor physician/patient communication.<sup>7</sup> When patient training is incomplete or patients recall their training in a faulty manner, the results can include patient error, injury and adverse events – all of which, in turn, may influence these patients to curtail use of their device.



of patients admit to forgetting a prescribed medicine



of patients don't understand dosing instructions



of patients stopped taking medication before the supply ran out

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



## NON-ADHERENCE FACTORS FOR AUTOINJECTOR USERS

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

The mistakes that patients were observed making included:

- Failing to hold the autoinjector in place for the required amount of time – 76% of patients failed to hold the unit in place for at least 10 seconds after triggering
- Not pressing the device hard enough to trigger the release of the drug
- Not choosing a suitable injection site on the body
- Improper safety cap removal
- Holding the device in the palm incorrectly
- Using a swinging motion to place the tip of the autoinjector on the outer thigh.

The study found that, despite a redesign of the autoinjector for easier use, most patients continued to make at least one mistake with the device. In fact, most patients continued to make multiple mistakes.

The poor outcomes resulting from such errors can lead those using autoinjectors to respond negatively to their course of treatment, which is likely to play a role in increasing their rates of non-adherence.

“...the use of these devices can provide the informative feedback that encourages them to adhere to their prescribed dosing regimens for longer periods of time.”

## USE OF CONNECTED DEVICES TO PROMOTE ADHERENCE

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

From this vision, AdhereIT™ was born. This device offers various features that can make it appealing for patients, healthcare providers and drug companies alike.

The first of these features involves its flexible form factor: AdhereIT can fit onto a trainer that closely mimics an autoinjector as well as onto a prescribed device itself. Drug companies may decide whether to adapt AdhereIT to one or both of these. AdhereIT can also easily fit onto a variety of autoinjectors created by different companies (Figure 3).

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

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

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



Figure 3: Example of how AdhereIT™ can be used with an autoinjector.

## BENEFITS OF CONNECTED DEVICES

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

For healthcare practitioners, the device means they have a tool that enables them to check that self-injection is being performed properly, particularly by patients new to autoinjectors, both during the training phase as well as when the prescribed device is being used. Data collected by the connected device can be shared with the practitioner and reviewed for any irregularities that need to be discussed with the patient.

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

## CONCLUSION

Given their potential for enhancing rates of adherence, connected devices such as AdhereIT are likely to play an increasingly important role for patients, their healthcare

practitioners and pharmaceutical companies as rates of self-administration rise steadily.

## ABOUT THE COMPANY

Noble® works closely with the world's leading pharmaceutical and biotechnology companies to develop medical device training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes. The company's cross-disciplinary team of experienced designers and engineers provides fully customised solutions from the first concept sketch all the way through final production, in both regulated and non-regulated environments.

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## ABOUT THE AUTHOR

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



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# THINK BEYOND THE DEVICE: THE MANY SIDES TO CONNECTIVITY

In *ONdrugDelivery Magazine* the technical design and capabilities of connected drug delivery devices are often discussed. However, there are far more factors in bringing a product to market to consider than this alone. In this article, Alexander Dahmani, Chief Executive Officer, QuiO, sheds light on some of these considerations.

At first glance, connectivity can appear to be simply a technical issue. However, the challenges and requisite decisions extend far beyond design and engineering. In fact, let's not even touch upon the technical issues, seeing as they've been well and often covered elsewhere. This article is meant to broaden the scope that device manufacturers and pharmaceutical companies consider when it comes to connected drug delivery devices, helping stakeholders better navigate this new and exciting space.

## REGULATORY FACTORS

One of the greatest concerns echoed by various industry stakeholders is the perceived regulatory challenges associated with connected drug delivery devices. No pharmaceutical company wants to take on additional regulatory burdens, above and beyond what is already required for their combination product. However, having a deep regulatory understanding can inform strategic product decisions and greatly alleviate or even avoid additional regulatory hurdles when adopting connectivity. This section is not intended as regulatory advice, but rather a summary of recent regulatory guidance and how it might impact

connected drug delivery devices, companion software and associated medications.

One of the major impacts that regulation has on connected drug delivery devices is the inherent conflict between long regulatory timelines (associated with medical devices and combination products) and the pace of technological change (in electronics and software). By the time you launch a connected drug delivery device, the technology incorporated in it is likely out of date. That's why it's important to consider future-proofing the design of the device to benefit from the pace of technological innovation.

According to guidance issued by the US FDA on 25th, October 2017,<sup>1</sup> significant changes can be made to a medical device without the need for regulatory submission in many instances. The regulatory threshold for submission defined in the guidance applies to device changes that significantly affect the safety, effectiveness, or intended use of the device. Therefore, future-proofing a connected drug delivery device can be achieved by designing the embedded systems in a way that does not impact the safety or effectiveness of the device. In other words, incorporating the sensors and connectivity to exclusively and passively collect data, instead of actively impacting the core functionality (i.e. drug delivery) or overall usability of the device. This allows more rapid incorporation of new sensors, wireless modules, antennas, processors, batteries, etc. The FDA also specifies how the above guidance affects combination products:

"This guidance does not specifically address combination products, such as drug/device or biologic/device combinations; however, the general principles and concepts described herein may be helpful to manufacturers in determining whether submission of a 510(k) is required for changes to device constituent parts of combination products."

For certain types of devices, a future-proof design just isn't possible. For



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"One of the major impacts that regulation has on connected drug delivery devices is the inherent conflict between long regulatory timelines (associated with medical devices and combination products) and the pace of technological change (in electronics and software)."

“Translating device data into dosing data can be more complex and nuanced than it may seem.”

example, a closed-loop insulin delivery system will rely on the sensors and wireless connectivity to actively control the delivery of insulin, by communicating with a glucose monitoring device (and potentially a companion software application). However, if the intended use of the drug delivery device does not depend on the sensors and connectivity, then it is advisable to keep these subsystems completely isolated from the core functionality. Following this strategy has further benefits when it comes to firmware and companion software. Applying a similar risk management-based approach, there should be no issue updating the firmware to comply with changes in wireless standards (e.g. cellular carrier requirements) or to benefit from advances in wireless technologies.

Regulatory bodies have also recently clarified their view on companion software for connected devices, allowing device designers to further isolate the software from the core functionality of the device. According to the 21st Century Cures Act Section 3060(a)<sup>2</sup> which amended the Food Drugs & Cosmetics Act Section 502: “The term device, as defined in section 201(h), shall not include a software function that is intended ... for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a health care professional with respect to such data and results, general information about such findings, and general background information about such laboratory test or other device, unless such function is intended to interpret or analyse clinical laboratory test or other device data, results, and findings.”

This means connected drug delivery devices may be developed, tested and approved independently from a companion software application, if the software application only interacts with the device to collect data and mark a dose as taken. This regulatory separation of connected device and companion software enables rapid software innovation, in addition to broader device integration across various software platforms. The next section goes into more detail regarding the companion software space and factors to consider in relation to connected drug delivery devices.

## COMPANION SOFTWARE

The core relationship between a connected drug delivery device and companion software is the automated dose logging feature. Translating device data into dosing data can be more complex and nuanced than it may seem. It usually involves taking one or more data points indirectly related to the drug delivery event and making a determination as to whether the dose was consumed. In some instances, it even involves estimating how much of the dose was consumed. It’s important to be rigorous in how the device classifies a dosing event because improper classification can confuse the user and lead to unfavourable events after the fact. It’s also advisable to have the firmware on the device make the classification decision, in order to separate the functionality from the companion software. If the companion software is receiving raw sensor data and transforming it into dosing data, a regulated relationship with the connected drug delivery device may have been formed (depending on the nature and level of the data transformation). This isn’t a problem if the device and software are designed to perform additional regulated features, such as a dose calculation (e.g. bolus calculator) or dose titration system.

While the relationship between connected drug delivery devices and the companion software is largely limited to medication tracking, the overall functionality of the companion software shouldn’t be. Engagement with the app will most certainly be lower if the patient is required to use additional apps to serve their needs. Many patients may be on multiple medications, and may be interested in tracking additional metrics such as symptoms, mood, activity, nutrition, etc. A companion app shouldn’t be viewed simply as an interface for the patient to view device data or a portal to transmit device data to the cloud. Companion software should be viewed as an opportunity to enhance the patient experience and an important contributor to medication and disease management.

Data security and privacy can’t be overlooked either. It’s important to position the connected device and companion

software as a valuable tool designed to help the patient, not as a monitoring tool designed to spy on the patient.

User consent for sharing the data is required and more users are likely to consent when they see value. One strategy that may help improve patient opt-in is to link data sharing to a free support service, that way they don’t view the flow of data as a one-way agreement with no value in return. Sharing data can enable the delivery of more relevant and personalised content and support. Another strategy that may improve opt-in is to frame data sharing as a philanthropic effort, leading to insights that will help improve existing therapies or design better therapies for fellow patients in the future. Building a more productive and continuous relationship between the patient and their healthcare provider is another valuable outcome associated with data sharing.

## MARKETING AND DISTRIBUTION

Even after spending the time and effort ensuring you have the right connected offering (drug delivery device + companion software), there still needs to be a scalable way to deploy it. This can be a challenge for widely distributed products, the sort that pharmaceutical companies lose control over as they travel through multiple channels. Independent of the distribution channels and networks, the healthcare provider is an important stakeholder in the adoption of a connected offering. Even if the connected device doesn’t require a prescription, patients trust their healthcare provider’s advice and will most likely follow their recommendation in terms of using such a device. Therefore, marketing the connected offering to the physician in order to generate awareness and demand is an important first step. Making it easy for the patient to share their data with the healthcare provider can help improve demand.

Patient support programmes may be another way to generate awareness and demand, by interacting with the patient directly. Connected offerings can be incorporated as part of such a programme; a welcome kit containing the device and app instructions can be distributed to the patient after they enrol. Patient support services also represent a scalable way to help onboard patients, including training the patients how to set up the device, sync it to the app and use the different features of the app. This can occur over the phone

“For some therapeutic categories and indications, in particular those where the medication is affordable and the medical consequences of poor adherence are expensive, payers may be willing to cover some of the costs.”

or in-person, depending on the level of service offered with the pharmaceutical product and complexity of the connected offering. In certain instances, a reusable device can replace the training device and automate some of the onboarding process. The connected device can report back training results, perhaps even having periodic training modes to keep the patient's technique honed.

### BUSINESS MODEL

For some therapeutic categories and indications, in particular those where the medication is affordable and the medical consequences of poor adherence are expensive, payers may be willing to cover some of the costs. Diabetes is a good example of where payers have a strong financial incentive to improve medication adherence in order to reduce hospitalisations and prevent medical complications. However, for biologics and other speciality drugs, where the dominant administration paradigm is already at-home self-administration (e.g. when, looking at US health insurance records, the annual pharmacy benefits far outweigh the medical benefits), connected offerings and patient services will need to be covered as an expense under the “gross to net” of the pharma companies. Therefore, a business case needs to exist for pharma to allocate some of its margins to cover the incremental costs associated with connectivity and companion software. Upon consideration, there are three main business cases that make connectivity worthy of adoption by pharma companies.

#### Lifecycle Management

The first business case is lifecycle management of an established brand that may be coming off patent or simply facing increased competition. A connected offering can differentiate a product by making it easier and more convenient for the patient to use. This is important from both the patient and healthcare provider perspective. However, it is the least compelling from the

payer perspective, who historically does not pay more for additional convenience.

#### Real-World Evidence

The second business case is the collection of real-world evidence. It is valuable for pharmaceutical companies to understand how their drug is being used and how it's performing in the real world. The data collected from connected devices can be used internally to inform how products are designed and developed in the future. The data can also be used externally to contract with payers by demonstrating real-world performance. This is becoming ever more important. Payers are now expecting and demanding real-world evidence, no longer accepting clinical trial data as sufficient. Also regulators are starting to consider real-world evidence as an acceptable means for expanding a product's label, without requiring additional clinical trials across each indication.<sup>2</sup>

#### Improved Drug Performance

The third and most important business case is to improve drug performance. Improving adherence, persistence and clinical outcomes should be the primary goal for connected delivery devices. By making medications easier to remember and easier to use, patients should be more able to manage their treatment regimens. In addition, connected devices provide a real-time, accurate and dose-level mechanism for targeting support efforts. Educational content and behavioural interventions can now be tailored and delivered to the right patient at the right

time. These technologies will become even more critical as pharma companies gradually take on more risk, shifting from rebates to value-based contracts.

### CONCLUSION

It's an exciting time in the pharmaceutical industry, as new technologies arrive in the face of new challenges and new business models. Device manufacturers, software developers and pharmaceutical companies must all be aligned and in close collaboration in order to see connected drug delivery devices successfully developed, deployed and used. This requires a different, expanded set of capabilities and stakeholders than traditional drug delivery devices. However, if done properly, the additional cost and complexity will be well worth it. Soon enough, “connectivity” won't even be a topic. Devices won't be “smart”. They will just be, and we will all be better off for it.

### ABOUT THE COMPANY

QuiO is a connected therapeutics company that provides software and services enabled by smart medication devices. The ConnectedRx® cloud enables leading pharmaceutical companies and healthcare organisations to measure real-world medication adherence and resulting health outcomes. QuiO then leverages the data to target and tailor interventions designed to improve medication adherence. This data-driven approach, combined with behavioural science, improves the efficacy of existing medications.

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## ABOUT THE AUTHOR

**Alexander Dahmani** is Co-Founder and Chief Executive Officer of QuiO, a connected therapeutics company. He started the company in 2014 while pursuing a PhD at Columbia University (New York, NY, US). His vision is to enhance the real-world efficacy of medications through technology and behavioral science. Prior to starting QuiO, Mr Dahmani worked in biotech (Heat Biologics, Durham, NC, US) and technology commercialisation (Columbia Technology Ventures, New York, NY, US). He holds degrees in immunology, genetics and business.

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## ERIC DESSERTENNE, BIOCORP

Eric Dessertenne holds a pharmaceutical degree from the University of Clermont Ferrand (France), an MBA from ESSEC Business School (Cergy-Pontoise, France) and is a graduate of the Therapeutic Chair of Innovation at ESSEC Business School. He began his pharmaceutical career at Servier in France in the Corporate Strategy department and then moved to the Chinese subsidiary in Beijing, where he handled positions in the marketing and sales force department. Mr Dessertenne then joined LEK Consulting where he worked as a consultant in the Life Sciences and Private Equity practices. In 2014, he joined Biocorp as Head of Business Development & Commercial Operations. He is now Biocorp's Chief Operating Officer.

Here, Mr Dessertenne talks in-depth with *ONdrugDelivery Magazine* about the ways connectivity is developing within the pharmaceutical industry, its likely future course and how Biocorp is positioned. He explores new types of partnership and the emerging ecosystem of associated apps and services within which devices have a crucial place. One of his key themes is how developing connected technologies cannot be merely technology driven but must always meet patient and customer needs.



**Q** Biocorp is now a world-leading name in the field of drug delivery device connectivity. I wondered if you could begin by describing how it reached this position and detailing its interest in connectivity?

**A** Biocorp's intention is to meet unmet needs of pharma companies and ultimately of patients, in particular their drug delivery needs. We're answering demand with our technology platforms, some of which are connected and some of which are not connected. We've built a lot of expertise in drug delivery devices over the years in terms of concept generation, device development and right up to and through the filing process in various countries – mainly in the US and Europe. We rely on our expertise in three main segments – mechanical engineering, hardware and embedded software engineering.

What I believe is unique with Biocorp is the way that we don't merely deliver a concept, but how we work design for manufacturing and industrialisation capacity into the process very early. We focus a lot of effort on ensuring that we're generating more than just a simple idea on paper but providing all the tools to our partners in order to make it real, robust and compatible with the different regulations that the technology has to comply with.

Connectivity is a big opportunity and represents a major chunk of our activity. We

started working in the area of connectivity quite early on – back in 2013 – and I believe this was before many others. We saw that the rise of connectivity was a solid trend and that it was certainly going to meet unmet needs not only for pharma, but with benefits right through the cost structure to the payers.

We were hearing from others that connectivity was somehow a kind of general option that might or might not be provided on top of an existing strategy. In contrast, our perception was and still is that connectivity needs to be thought about and designed in terms of its specific usage and with a robust business case. It requires more of a holistic approach with connectivity at the centre, not on the periphery as an afterthought or option. This sense of the potential of connectivity which we had five years ago was well founded – you can see today the level of activity and interest from pharma and payers alike.

**Q** The different types of connectivity technology for drug delivery systems can be categorised in many ways. One way is to divide them into “integrated” and “add-on”, and Biocorp has products in both of these categories. Please could you explain the two different approaches and the advantages and disadvantages of each, using Biocorp products as examples?

**A** It's good way to divide the ways of providing connectivity to devices and, as you say, at Biocorp we have integrated and add-on approaches that answer different needs from our customers.

Broadly speaking, add-ons respond to the requirement for connectivity to be made available “immediately” on an existing drug delivery device. Let's say a pharma company already has a portfolio of products on the market around the world that were filed and approved as drug-device combinations. Gaining those approvals represents a huge investment in a lot of different countries and it is not a process that a pharma company would want to repeat from scratch. But

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“It is clearly beneficial to know that the drug is being injected properly, completely and at the right time, the right dose, that it's being stored correctly under the correct conditions. All this important information can be tracked through embedded connectivity.”

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at the same time, the company wants to provide the connectivity that its customers – patients and payers – want as soon as possible, with the smallest possible impact on the existing product/existing device. The add-on is clearly the best approach here. It doesn't impact on the industrialisation and manufacturing of the product (usually a drug-device combination) and there is usually just a small impact on the regulatory status of the product.

In terms of development timeline, an add-on can achieve a timeline that is far shorter compared to a product with integrated connectivity. Within a 2–3 year timeframe from the starting point, you can have something available and potentially commercialisable.

We have a major product, Easylog® (Figure 1) which is the add-on for pen injectors that we've been working on for the last few years. This is positioned for a specific category within the pen injector market, where you have a lot of disposable pen injectors, which represent a major portion of the market, mainly in the diabetic market, which is the largest market by volume.

The diabetic field is already very well connected on the side of the blood glucose monitors (BGMs) and continuous glucose monitors, and the missing piece is the pen injector. The Easylog technology completes the circle.

We're also offering Easylog in other chronic disease indications where there's a need to know if the dose was injected, if it was a viable dose, what was the dose injected, and so on. In numerous therapeutic areas Easylog can answer an unmet need in an immediate way.

There are some drawbacks with add-ons as well. For example, you need to ask the patient to remove the add-on from the old device and put it on the new device for reuse. So the add-on concept is necessarily dependent on an additional user step, but Biocorp has spent a lot of time making sure that the process is seamless, so that it's really easy to put the add-on on the new device and that once it's on we're not asking the patient to complete any further steps to prepare or activate it. The patient simply puts the Easylog onto their device and then they use their device as normal.

Then we have the integrated approach, which is exemplified by our DataPen®

**Figure 1:**  
The Easylog® add-on brings connectivity immediately to any regular pen injector, whether disposable or reusable.



**Figure 2:**  
DataPen® is a reusable, electromechanical connected injection pen that uses standard cartridges.



**Figure 3:** OneJet®, the first motor-driven, disposable and Bluetooth connected autoinjector.



reusable pen injector (Figure 2) and the recently launched OneJet® disposable autoinjector (Figure 3). In terms of the user experience, integrated connectivity is very easy to use. It enters into a more important process of lifecycle management within pharma companies, to develop a product with a new device with connectivity features embedded. It fits mainly for chronic diseases but also for less

price-sensitive therapeutic areas.

Having connectivity is an additional cost but the point is to compensate for this by showing that there are demonstrable benefits coming from having connectivity. It's never enough to have connectivity for the sake of having connectivity. It's important to define, specifically, why it is being added. Pharma companies are willing to bear the additional cost of a connectivity-integrated device if they are getting outputs out of it, in particular for expensive drugs where it is clearly beneficial to know that the drug is being injected properly, completely and at the right time, the right dose, that it's being stored correctly under the correct conditions. All this important information can be tracked through embedded connectivity and this is where it makes a lot of sense – both for pharma and for patients.

Cost-savings are clearly important and embedded connectivity can bring cost savings. With regard to adherence, if it can be verified that the patient is getting the prescribed dose, injected properly, this is clearly attractive to the payer, whether it be the insurance company or the state which is paying. Improved disease outcomes and potential reductions in overall cost of care and treatment then follow.

It's important not to think of add-ons versus integrated/embedded connectivity, as a binary “either or” proposition. Add-ons can be used as a way to try connectivity, to bring connected versions of a product to the market for use by patients, and to gather information, including conducting pharmaco-economic studies. Add-ons are relatively cheap in terms of development cost, and very low risk in terms of the original pharma product. Having gathered

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“Several pharma companies are already convinced and clear about the direction that they wish to take, and have already initiated integrated connected device programmes. That's the reality. But for sure if companies require additional evidence before committing to integrated connectivity, add-ons can help.”

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data and proven the benefits of connectivity – including to payers – this then puts the pharma company in a strong, well-prepared position for the second step of integrated connectivity.

However, several pharma companies are already convinced and clear about the direction that they wish to take, and have already initiated integrated connected device programmes. That's the reality. But for sure if companies require additional evidence before committing to integrated connectivity, add-ons can help.

**Q Biocorp's technologies span the inhalable and parenteral areas of drug delivery. Does Biocorp have plans to develop connectivity solutions beyond the inhalation and injection routes?**

**A** Biocorp's historical expertise is in parenteral areas, we've been working in the injectable field for more than 20 years. Additionally, thanks to the Inspair® technology, an add-on for inhalation devices (Figure 4), we have moved outside the parenteral space and developed other ways to provide benefits to our customers and to patients. That's our philosophy today regarding connectivity – we will answer unmet needs, whatever the drug delivery route.

We do have plans to work on other areas, however, this would most likely be more based on a specific customer's demands. So, for example, a customer might say to us that Biocorp has demonstrated to the market that it can make connected injectors and apply connectivity in inhalation too, we believe that connectivity could apply in other therapeutic areas or other delivery routes and we believe Biocorp has the skills an expertise to help us in those areas. Biocorp would be open to that – even though as a platform technology provider injectable is really our key area and where we will be most proactive in answering most market needs.

Depending on the type of product we are working on we tackle different issues and

address different patient needs. For example with Easylog we're tracking global adherence – whether the dose has been injected and if it was the correct dose. With other devices, Inspair for example, we provide ways to train the patient in how to use the device correctly. The Inspair on a pMDI is able to track whether the patient presses the canister at the same time as they inhale – so it's working on the synchronisation of breath-hand co-ordination, which is very important for pMDIs. In that specific case we could imagine that the Inspair add-on could be prescribed at the initiation of a treatment to help ensure that the device is being used correctly and then after a couple of months if the patient is happy they are trained properly, and there's no requirement for additional data, they could potentially continue without Inspair.

Another area in which connectivity has a crucial role to play is, of course, in clinical trials – specifically, validating the data gathered during clinical trials. In the future, using connected devices during clinical trials will be key to helping ensure that the data submitted to the regulators is robust and that it is accepted without its validity being questioned.

**Q With the high-profile Facebook personal data controversy in the US earlier this year, and the recent implementation of the EU's GDPR legislation, data privacy and security is now a topic everyone is thinking about. However, the collection, transmission, storage and use of personal data is central to the entire concept of connecting drug delivery systems so the drug delivery industry has had these topics front and centre for some time. How does Biocorp approach**

**the specific challenges arising from data privacy and security considerations?**

**A** It's really important to talk about this and I believe addressing data privacy and security issues properly is key to allowing the broadest possible adoption of connected drug delivery devices. It's essential for us to gain the patient's confidence by demonstrating that we are taking their data privacy and security very seriously.

We're not talking about "normal" data here – this is highly sensitive data relating not only to health and medication but also other personal aspects of patients' lives. If these data are shared with a patient's insurance company, their bank or their employers, this could have an impact. I hear a lot that there are fears amongst patients about how their data could be used by third parties if there was a security breach or leak.

There are clear guidelines and all device manufacturers and pharma companies that might commercialise a connected product must abide by them. This has been absolutely crucial for us since the very beginning and so, for example, when first we embarked on the development of smart devices we acquired encryption technology to ensure that any data we are pushing away from Easylog are encrypted at their origin.

What we've seen over the past couple of years is that there's been a lot of movement in this area from big players. Amazon, Flex, Qualcomm – they all have an ambition to provide solutions for transmitting and storing health data, and also analytics, to pharma, payers and/or patients. These big companies have the global presence to ensure that the solutions are scalable and updated country by country according to the different regulations as they come into force and change.

We see the recent European GDPR regulation as good news not least because it harmonises all the different national regulations that we had until now.

So in terms of our approach, Biocorp has taken a decision to focus on the aspects of data privacy and security that relate to the device itself. So we want to be sure that from the moment the device begins gathering information, and then potentially storing it and sharing it to a third-party device, most often a smartphone application, that this flow of information will be highly secure. We have put a lot of effort into this – I mean, really a lot.



Figure 4: Inspair® is a smart sensor for inhalers that records each dose delivery, monitors hand-breath co-ordination and provides feedback to patients on technique.



"With Easylog in combination with a connected BGM and other elements, the app coaches the patient, and makes sure they take their medication properly, and that they don't have other issues in their life that could impact their disease. The final customer is the payer, insurance companies in the US. This is a very important new aspect of our business."

We also need to be as open as possible to pharma's requests and requirements. This is where we see the big players I mentioned just now having an influential voice. Our pharma partners are telling us that they are working with, say, Amazon and they therefore ask us to make sure that when we develop a device for them, it can transmit its data to a particular Amazon system.

**Q** You have been at Biocorp for four years now, things are moving fast and a lot has happened in the industry over this period. What are some of the most noticeable trends that you have seen unfolding?

**A** When I first arrived at Biocorp, if we were presenting our connected devices to industry, there were a lot of people saying that this would potentially be the solution of the future, it definitely could help patients – they could see the potential, there was strong interest, but the conditional "could" and "might", was used. In these large organisations it was still very much perceived as a technology driven trend and often lacked strong support from the senior management and the digital strategy that would explore where a connected device would fit in.

Now almost all of these big organisations not only have a digital strategy but it is a top priority. Digital is a broad field and can be applied in a lot of ways but for sure connected drug delivery devices form a significant part of it in some of these organisations. They have brought teams together, so you have connected device teams. Most of the big pharma companies and some insurance companies now have a clear view of what they are expecting to achieve. This was not the case four years ago.

Another thing I heard a lot four years ago was that connectivity looked interesting but who will pay for it? Today pharma knows firstly that they can pay. Secondly that they can go to payers and say thanks to this connected device we've reduced the overall cost of disease by a certain percentage so please pay us a premium or

please don't break our price by 20–30% as would normally happen if we hadn't invested in connectivity.

Connected devices are now, in fact, a reality. Products have been launched, and there are some positive outputs. For pharma especially, this really is a remarkable transformation in only four years.

**Q** Please would you describe the most recent news and progress at Biocorp?

**A** We've been very active in terms of development. At Pharmapack Europe in Paris earlier this year, we unveiled our latest device, the Onejet. It is the first motor-driven, disposable, natively connected autoinjector, and we received the Innovation Award at Pharmapack for that. Onejet is very important for us and it is not merely a technology for its own sake – it answers a need in the autoinjector space.

Just to explain how we are developing technology to meet specific needs and not for its own sake; we have worked a lot on add-ons and we saw that this worked for pen injectors. However, the use case for autoinjectors was not so good because we are looking at one shot, and it is asking patients a lot to take off the add-on and put it on another autoinjector out of the box every time. It isn't in step with a chronic treatment. So we decided that the autoinjector would be natively connected.

Onejet meets both the technical challenge of developing such a product and the user needs of getting immediate feedback on usage. It's a major accomplishment for us and we're proud of this product.

Regarding partnerships, we are working very closely with a lot of pharma companies and recently we've extended the scope of our partnerships by signing a deal with a service provider in the diabetes sector called Chronicare (Newtown, PA, US) that offers an intelligent app with embedded algorithms for diabetic patients. With Easylog, in combination with a connected BGM and other elements, the app coaches the patient, and makes sure they take their medication properly, and that they don't

have other issues in their life that could impact their disease. The final customer is the payer, insurance companies in the US. This is a very important new aspect of our business and it is a very important milestone for Biocorp. It will continue to be important. We are entering into a more holistic approach where there is the drug, the device and all of the surrounding services, and this potentially extends the scope of our partnerships and broadens the type of partners we can search for.

In terms of therapeutic area, this partnership is focused on diabetes and Easylog really completes the circle with the BGM and the app. The huge benefit in diabetes is obvious but this applies across a range of indications. In Parkinson's disease for example, where you have a need for dose titration when initiating treatment. How are you sure that the regimen is respected? With a connected pen you can be sure that you get the correct titration.

Also we are taking a great interest in the types of deals that big pharma companies are signing for companion apps. For example, the French company Voluntas partnered with Roche to develop an app for use in breast cancer. Companion applications that have a true medical effect and are considered a medical device are of real interest to pharma companies and this fits very well with a connected medical device.

**Q** And finally please tell us about some of the broader aims and objectives of Biocorp looking on into the longer-term future?

**A** At its core, Biocorp is a technology innovator and we will continue down that path – providing what we consider to be the best solutions for our partners. But I strongly believe that simply providing the technology is not enough. The technology is crucial for certain, but it has to fit properly in an ecosystem that is changing very rapidly. For example, in the future our systems might not simply track information but might guide and advise patients, going a step further.

Biocorp is very alert to these possibilities and this is where I believe we could see considerable additional value in the future. I think what we will have to do as a technology provider in the device field is perhaps comparable to what the big tech companies, such as Apple, have done in their industry – first to develop the device for patients, and then provide additional services as well. You have to be open to that ecosystem. We were saying that in four years things have changed a lot and I believe there will be even greater change in the next four years. This is where Biocorp wants to go, moving together with its partners.

#### 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 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

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# 2018/19

## EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
July 2018	Novel Oral Delivery Systems	DEADLINE PASSED
August 2018	Industrialising Drug Delivery Systems	Jul 5th 2018
September 2018	Wearable Injectors	Aug 2nd 2018
October 2018	Prefilled Syringes & Injection Devices	Sep 6th 2018
November 2018	Pulmonary & Nasal Drug Delivery	Oct 4th 2018
December 2018	Connecting Drug Delivery	Nov 1st 2018
January 2019	Ophthalmic Drug Delivery	Dec 6th 2018
February 2019	Prefilled Syringes & Injection Devices	Jan 3rd 2019
March 2019	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 7th 2019
April 2019	Pulmonary & Nasal Drug Delivery	Mar 7th 2019
May 2019	Injectable Drug Delivery: Devices Focus	Apr 4th 2019
June 2019	Connecting Drug Delivery	May 2nd 2019

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## UPGRADING RESPIRATORY CARE WITH AI-POWERED SENSORS AND TRUE ADHERENCE DATA

In this article, Martijn Grinovero, Co-Founder and Chief Commercial Officer of Amiko Digital Health, and Fabian Schütte, Business Development Manager at Sanner GmbH, describe the potential of artificial intelligence-powered sensors used in combination with standard inhalers to upgrade respiratory therapy, and introduce Respiro®, an innovative digital health platform solution for respiratory care.

Digitisation has opened entirely new ways of interacting in all areas of our lives. Even in the pharmaceutical and healthcare sector, which has a tendency to be rather conservative, we are witnessing drastic changes. Digitisation makes improvements possible across a multitude of therapeutic areas. Conventional therapy can now be upgraded significantly with connected devices. Take respiratory health for example. With more than 300 million people affected by asthma globally, and 100 million suffering from COPD, treatment costs amount to over €80 billion (£70 billion) in the US<sup>1</sup> and Europe<sup>2</sup> each. Most of these costs result from complications and hospitalisations, most

of which could be prevented through more adequate treatment.<sup>3</sup>

### CONNECTED THERAPY HELPS PATIENTS AND HEALTHCARE PROFESSIONALS ALIKE

Developing new forms of treatment is challenging enough, and there are very sophisticated methods already available. However, it is not sufficient. To achieve more adequate treatment of asthma and COPD, we need to realise that no matter how sophisticated a method is, most patients struggle to follow their treatment plans, to administer their medication correctly and to support their treatment in



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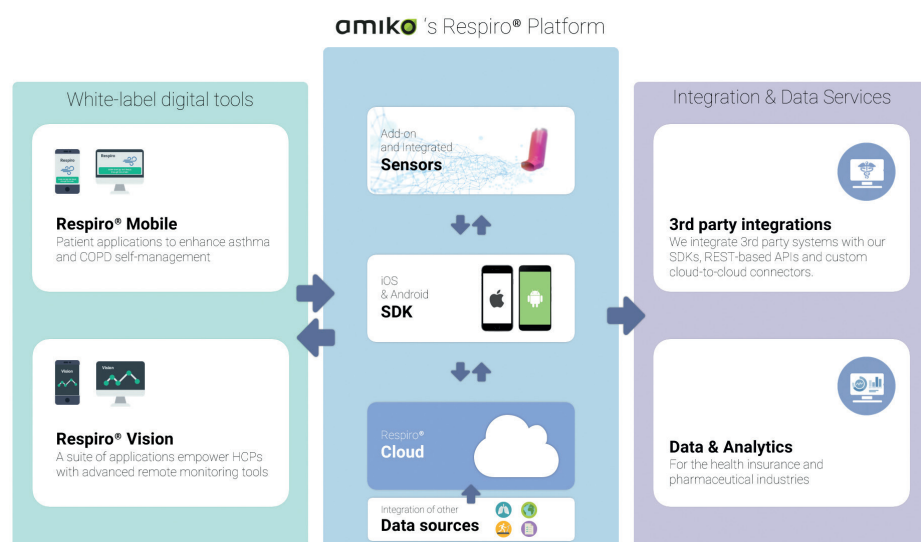


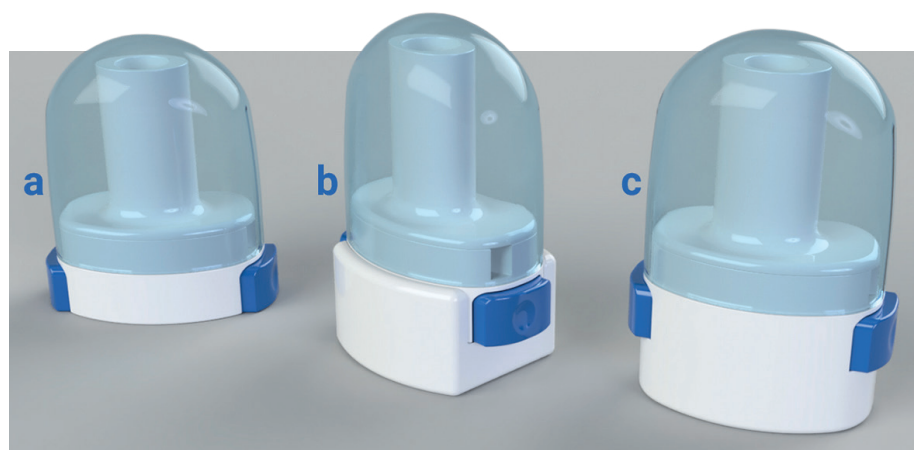
Figure 1: An overview of Amiko's Respiro platform.

everyday life. On the other hand, physicians often lack the tools and the information to understand their patients' state of health, whether they are following their treatment plan and – most importantly – whether they are taking their medication in the correct way. This hinders them in finding the best therapy for each individual patient. This scenario suggests that rather than simply offering incrementally better medicines, we need new ways of delivering and upgrading respiratory care and activating patient self-management.<sup>4</sup>

Connected therapy has the potential to tackle the most important needs in respiratory care. First, it is about engaging patients and facilitating the process of self-management, for instance with technologies that track and guide optimum medication use. Connected therapy is designed to improve the patient experience with functionalities that are aligned to patients' needs, such as reducing the burden of disease management, and to facilitate greater self-care and self-activation. Second, it is about making sure that healthcare professionals receive the right information they need to make timely, evidence-based decisions. This can be facilitated by tools that provide real-time data on medication usage and patient health. Based on advanced real-time data, treatment can be personalised to optimise individual treatments and maximise health outcomes.<sup>4</sup> Furthermore, the possibility of real-time adjustments enables the shift from reactive to preventive and predictive medicine. This will ultimately lead to better clinical and economic outcomes.

## HEADING TOWARDS TRUE ADHERENCE

Respiratory medicine is at the forefront of the digital healthcare wave. Several connected drug delivery solutions are already approved and marketed, including both add-on and embedded designs for inhalers. Some of these solutions have demonstrated the ability to increase adherence to asthma and COPD medication in clinical studies. This is a promising first step, since the success of any medication depends on the individual patient's adherence to the dosing regimen, and at least 50% of all patients do not take their daily medicine as prescribed. However, the delivery of respiratory medications is mainly achieved by inhalers, which require several, often complex, steps for administration.<sup>5</sup> Each device has specific instructions on



**Figure 2: Making inhalers smart with Respiro Sense (a), either as add-on device (b) or integrated solution (c).**

how it must be used, including pre-actuation steps (for instance removing the protective cap or pushing a lever) to ensure successful actuation and reliable drug delivery.<sup>6</sup>

Most patients make drug delivery technique errors leading to significantly decreased levels of medication efficacy, even if they take the right dosage. These technique errors compromise both drug delivery and the overall treatment effectiveness, increasing the risk of severe exacerbations and hospitalisation for patients with asthma or COPD. Hence, a solution is required that combines the measurement of both adherence and technique, in other words, a solution that provides a measurement of true adherence, reflecting the actual inhaler use. Yet currently available inhaler solutions only capture adherence information, and do not assess the way in which patients use their devices.<sup>4</sup>

## RESPIRO – LEVERAGING THE POWER OF TRUE ADHERENCE DATA

Appropriate monitoring is crucial to find out whether patients adhere to the prescribed regimen and whether they use the correct drug delivery technique. True adherence can only be achieved by monitoring both factors: correct dosing and correct inhaler technique. Detailed information about true adherence in both research and real-life settings is essential for a better understanding of the use and the effectiveness of an inhaled drug therapy. This information is also important for the development and assessment of personalised interventions promoting adherence and correct inhaler technique. With Respiro, the digital health company Amiko has developed such a solution,

“Currently available inhaler solutions only capture adherence information, and do not assess the way in which patients use their devices.”

which we will introduce in detail in the following paragraphs.

Amiko was founded in 2015 and develops solutions to enable the transition from conventional to connected therapies. The company's first commercial product is Respiro® (Figure 1), a complete, CE certified digital platform that uses proprietary sensor technology to collect true adherence data from respiratory medication use, offering both tools and analytics to maximise the value of this data, so that actionable insights can be derived for patients, healthcare providers, pharmaceutical producers and payers. Amiko's Respiro platform received the first prize at the prestigious IBM Watson AI XPRIZE's annual Milestone Awards (2017). All sensor devices and software tools are developed under Amiko's ISO 13485:2016 quality management system and are designed to meet current and future security and privacy requirements, including the 2018 EU General Data Protection Regulation (GDPR) and the US Health Insurance Portability and Accountability Act (HIPAA), of 1996.

### The Core: Sensor Technology

At the core of the platform is the patented Respiro Sense technology, which powers Amiko's sensor solutions for respiratory medications. The technology is suited for both add-on and integrated smart inhalers, where low power consumption and cost-efficiency are key factors (Figure 2).

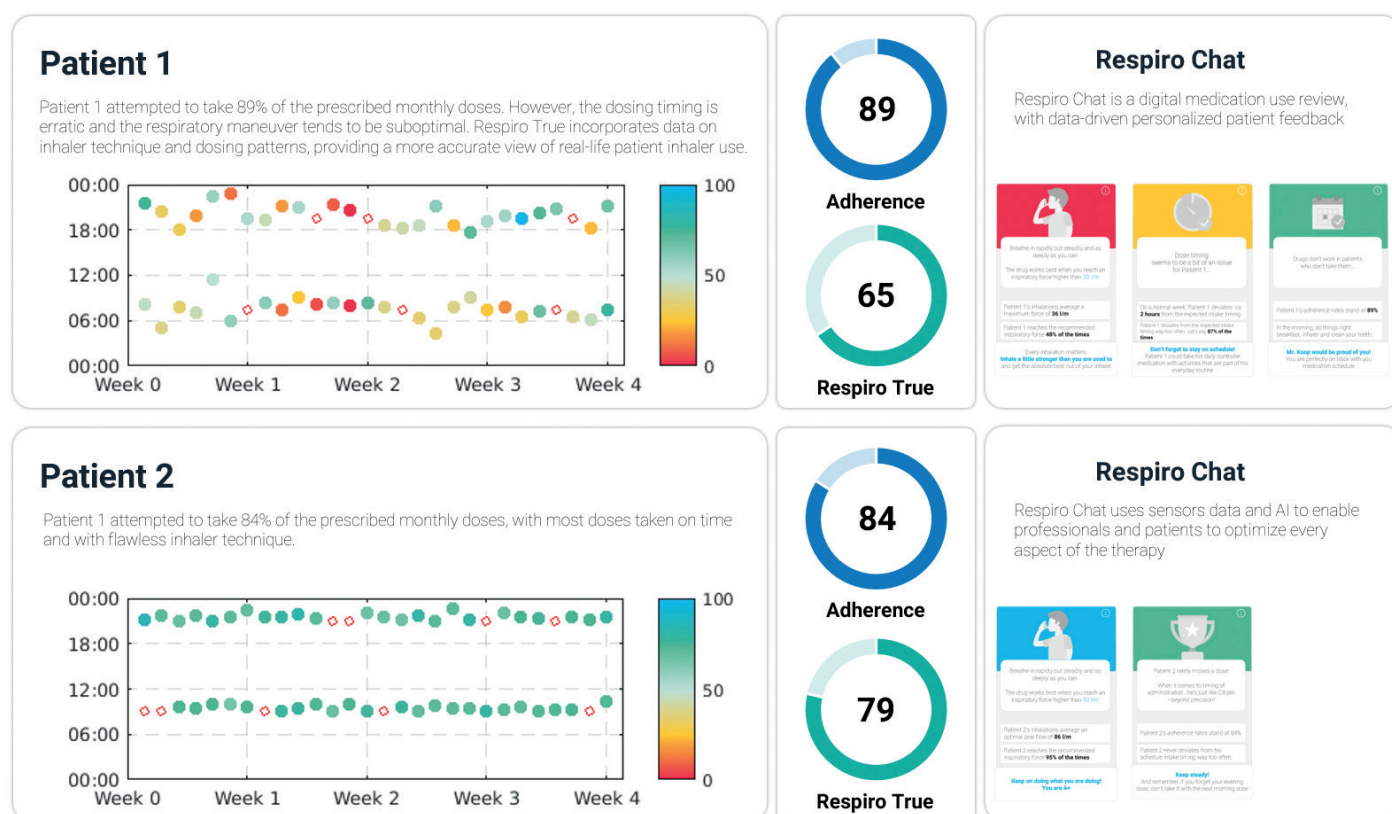


Figure 3: Respiro True is a novel adherence metric that expands the traditional measurement of adherence with data on inhaler technique and dosing patterns.

The sensors automatically track data on the entire respiratory manoeuvre, including data on inhaler technique to record when, and how well, patients use their inhalers and to help monitor lung health. Most importantly, patients do not need to change their accustomed therapy, but are supported in optimising how they use their inhalers: the same steps are used to inhale the prescribed dose, the delivery path is not interrupted, and they receive the same handling and delivery performance.

The Respiro sensors run real-time machine learning algorithms, which demonstrate the advantages of using artificial intelligence (AI) with end devices, integrated within a medical product. The collected data is processed, stored and encrypted independently on the sensor device. This approach is beneficial in terms of functionality, security, cost and power consumption. The device can offer active guidance to patients while they are using their inhaler. It can issue smart dose reminders and improve the quality of the inhalation technique. Further, the device can apply advanced cryptographic techniques without significantly impacting the power drain of the overall system, while ensuring an optimal degree of cybersecurity and data privacy. The costs associated with data persistence and storage are

minimised. Finally, battery life is extended with fast and affordable over-the-air data transfer. In a nutshell, the Respiro Sense technology delivers a solution that fulfils the requirements of optimal power consumption and low sensor production cost, with the flexibility to seamlessly add new features to deliver ever more reliable and detailed results.

### USING DATA AND AI FOR BETTER TREATMENT OUTCOMES

The Respiro platform uses data and AI to assist healthcare professionals and empower respiratory patients to achieve better treatment outcomes. The data collected and processed by the sensors flows into the Respiro cloud, which is designed to evolve continuously with therapeutics, patient-reported, behavioural, physiological and environmental data (Figure 3). The system suggests the optimum therapy path and the right level of healthcare resources for each individual, thus reducing costs and increasing therapy effectiveness. It does so by identifying and quantifying adherence and inhaler technique, and by identifying the correct choice of inhaler device. It further enables accurate, remote, real-time case prioritisation for early prediction

and prevention of disease exacerbations. Advanced insights on medication use and effectiveness are made available, too.

Interactive digital tools create a more personalised, connected care experience and simplify self-management, encouraging patients to engage in their own therapy. Amongst these digital tools is a patient diary to track different asthma and COPD medications, symptoms, triggers, peak flow measurements and flare-ups. Personalised support and data-driven feedback help improve adherence and inhaler technique, while patients receive medication reminders and have a channel for enhanced provider-patient communication available. Clients can choose to offer Amiko's Respiro end-to-end service as a white label solution or use the data services built on flexible representational state transfer (REST)-based application programming interfaces (APIs), Android and iOS software development kits (SDKs) and custom connectors for legacy system requirements (Figure 4).

### A PARTNERSHIP FOR TRUE, SMART ADHERENCE

In January 2018, Amiko and the primary packaging and device specialist Sanner announced their development and



commercial partnership to expand Amiko's Respiro portfolio. Sanner was founded in 1894 and is an established partner to global pharmaceutical companies in the design, development, industrialisation and manufacturing of custom-made drug delivery and dosing systems for powders, solids and liquids. Sanner's portfolio and expertise ranges from primary packaging solutions to mixing devices, injection and application systems. For the respiratory care sector, Sanner develops and manufactures nicotine substitute inhalers, metered-dose inhaler (MDI) actuators with counters and dry-powder inhalers (DPIs). Moreover, Sanner is an industry partner for integrated and drop-in desiccant solutions, as well as consumable add-ons such as moisture-tight drug storage cartridges or mouthpieces with integrated filters. Besides increasing drug stability and ensuring the accurate performance of drug delivery devices, Sanner provides solutions that help improve medication adherence and compliance.

The two companies are working closely together to incorporate Amiko's Respiro Sense into custom add-on or integrated device solutions for respiratory device or drug producers who are looking for new connected solutions. As a start-up, Amiko offers a quick development process for the development of fully functioning, CE marked devices, which clients can use and test in low-volume strategic projects. As a fully integrated contract manufacturer, Sanner supports Amiko with its deep knowledge in all activities leading up to and including design, engineering and scale-up manufacturing. Bringing connectivity to respiratory care is the first step in marketing this novel technology. In the future, other respiratory delivery systems including nasal

**Figure 4: Respiro offers advanced inhaler sensors and data analytics.**



sprays and nebulisers, as well as injectables, applicator systems or pharmaceutical primary packaging for further therapeutic areas, will follow.

## ABOUT THE COMPANIES

### Amiko

Amiko develops advanced sensor technologies and digital health solutions to assist healthcare professionals and empower patients to achieve better outcomes. Founded in 2015, Amiko has headquarters in London, UK, and ISO 13485:2016 certified R&D laboratories in Milan, Italy. Amiko serves commercial, institutional and individual customers all over the world, and is growing to become a global provider of advanced medication sensor and data analytics technologies.

### Sanner

Based in Bensheim, Germany, the Sanner Group was founded in 1894 and is now in its fourth generation as a family-owned enterprise. Sanner develops and produces high-quality plastic packaging and drug delivery systems for pharmaceutical, medical and healthcare customers. The group gained

international recognition for its desiccant know-how and moisture protection solutions. With more than 500 employees, Sanner is present all over the world, amongst others in Germany, China, India and the US. The company produces over two billion plastic units each year for standard and customised packaging and drug delivery solutions.

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## ABOUT THE AUTHORS

**Martijn Grinovero** is the Chief Commercial Officer and Co-Founder of Amiko. He is responsible for leading Amiko's commercial go-to-market teams, including sales, marketing, commercial relationships and business growth. Mr Grinovero has an MSc in Strategic Management from the Rotterdam School of Management (the Netherlands). Prior to joining Amiko, he worked at Alpha Founders Capital (Bangkok, Thailand) where he was responsible for the marketing strategy of the fastest-growing start-up in the company's portfolio.

**Fabian Schütte** is Business Development Manager at Sanner, responsible for the product segment Engineered Packaging Solutions, with a focus on customised primary packaging systems and devices. Before taking on this position at Sanner two and a half years ago, Mr Schütte worked in the segment of glass primary packaging systems and injection devices at Gerresheimer Bünde (Bünde, Germany).

# 9TH ANNUAL GLOBAL DRUG DELIVERY & FORMULATION SUMMIT

Berlin, Germany, March 12–14, 2018



By James Arnold, Assistant Editor, *ONdrugDelivery Magazine*

March 2018 saw Berlin play host to the 9th Annual Global Drug Delivery & Formulation Summit (DDF), organised by Mark Allen Group. The three-day conference hosted 227 delegates, 64 speakers and 125 commercial partner attendees, split across pharmaceuticals, 60%, delivery/formulation services, 31%, and universities, 9%.

The agenda featured four streams of presentations – Small Molecules, Biologics, Technology & Innovation and, a new addition, Device Development. Given that the topic of this issue of *ONdrugDelivery Magazine* is “Connecting Drug Delivery”, this review will focus on the Device Development stream and emphasise the talks that focused on connectivity.

The first talk of the new Device Development stream, given by Martin McLoughlin, Head of Device Development, Bristol-Myers Squibb, on the use of decision analytics to provide a rigorous approach to device selection and development gave insights into a methodical approach to this key issue. The rest of day one in the stream featured a strong emphasis on the evolving regulatory concerns of the combination product market. Of particular interest was the talk given by Richard

Wedge, Director Design Control Implementation, Pfizer, covering strategy for combination product post-launch risk management, an area of increasing importance given the post-market surveillance requirements of the new EU Regulations for Medical Devices (MDR) published last year. In addition, the stream

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“The conference featured a strong line of talks on the topic of connectivity. The Device Development stream kicked off day two with a lively panel discussion titled “Challenges and Opportunities in Combination Product Design, Development and Use.”

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featured talks on specific technologies and areas, including an excellent overview and outlook of the respiratory sector given by Gunilla Petersson, Science & Innovation Director, AstraZeneca.

The conference featured a strong line of talks on the topic of connectivity. The Device Development stream kicked off day two with a lively panel discussion titled “Challenges and Opportunities in Combination Product Design, Development and Use”, moderated by Bastiaan de Leeuw, Head of Business Development, Cambridge Design Partnership (Cambridge, UK), featuring Muriel Didier, Human Factors Team Head, Novartis, and Richard Wedge. The discussion quickly brought in the promise of connectivity and its potential applications, which remained a theme for the duration.

The devices stream also had an excellent talk on the subject of connectivity given by Tom Lawrie-Fussey, Digital Services Specialist, Cambridge Design Partnership, highlighting how connected technology can enhance the design process by revealing the actual behaviour of users, allowing for smarter design and better outcomes overall.

Continuing in the vein of connectivity, of particular interest was the closing keynote session of day two, a panel discussion moderated by conference chair Olaf Queckenburg, Head of Global Chemical & Pharmaceutical Development, Bayer, titled “How Big Data and Artificial Intelligence Can Revolutionise R&D”. The panel featured Brian Henry, Vice-President, Drug Product Design, Pfizer; Hannah Batchelor, Senior Lecturer in Pharmaceutics, Formulation and Drug Delivery, Director of Research, School of Pharmacy, University of Birmingham (UK); Patrick Garidel, Associate Director of Protein Science, Boehringer Ingelheim; and Prof Clive Wilson, JP Todd Professor of Pharmaceutics, University of Strathclyde (UK).

The discussion covered a wide range of topics and tones, from the highly optimistic outlook for the impact big data and AI will have on manufacturing and industry and how connectivity will enable closer co-operation between academia and industry, to more reserved considerations on the capacity, or lack thereof, of hi-tech solutions like big data and connected healthcare to take root in less developed parts of the world, as well as concerns surrounding cybersecurity and hacking.

The panel deliberated the practicalities of implementation and how to use the data gathered by this new technology,



“The discussion covered a wide range of topics and tones, from the highly optimistic outlook for the impact big data and AI will have on manufacturing and industry and how connectivity will enable closer co-operation between academia and industry, to more reserved considerations on the capacity, or lack thereof, of hi-tech solutions like big data and connected healthcare to take root in less developed parts of the world, as well as concerns surrounding cybersecurity and hacking.”

concluding that patience will be required and it is better to take a slower, right-first-time approach than to rush ahead without due consideration. The overall message was a positive one, the information age has much to offer the world of healthcare, but there remain risks and concerns that

still need to be thoroughly examined and duly addressed.

The last major theme to run through the Device Development stream was human factors. Patient-centricity and human factors engineering is a regular topic of discussion in modern delivery device development and,

as such, was mentioned in several talks. A particular focus was given to the subject in the talks by Muriel Didier, with a focus on autoinjector design, Tom Lawrie-Fussey, with insights as to using technology and data science to observe user behaviours, and Richard Featherstone, Managing Director, Medical Device Usability (Cambridge, UK), presenting the results of research into the





underlying motivations behind patient preferences. The discussion of human factors was, unsurprisingly, not limited to the device development stream, and was the subject of two detailed talks focussing on the oral delivery route, given by Prof Dr Sven Stegemann, Director Pharmaceutical Business Development, Lonza, and Prof Wilson.

Though device development is of key interest in this issue of ONdrugDelivery, it was but one of four streams. Some highlights from the rest of the conference include Patrick Garidel's talk considering the practicalities and feasibility of high viscosity biologic formulations, Robert Meyer, Principal Scientist, Innovation and New Technology Development, MSD, discussing the values and ethos of investing in innovation in manufacturing (which also expressed the theme of excitement about the possibilities offered by smaller scale continuous manufacturing, enabled by innovation and data, which ran through many of the industrial talks), and the final keynote talk of the conference by Christophe Tistaert, Senior Scientist, Janssen, on developing a child-friendly chewable formulation of mebendazole for use in the developing world.

Naturally, networking is as much a part of a successful conference as the presentations and DDF did not disappoint, with long networking breaks and lunches to meet and discuss with fellow delegates. DDF features iSolve, its intelligent networking system for matching "buyers and sellers" with the same priorities and providing a scheduled private meeting. According to the DDF post event report, 77% of attendees "met somebody who could help with their current challenges" and 98% "learned something new and useful that can apply to their work".

This DDF featured the conference's first poster competition, with the winner selected by the delegates, which was won by "Polymeric Nanocarriers for Ocular Drug Delivery" by Vijayabaskarreddy Junnuthula et al of the University of Helsinki (Finland).



Overall the conference was a resounding success, with a solid mix of representatives from academia and industry, and strong showings from pharma, manufacturing and device design. The 8th Annual American Drug Delivery & Formulation Summit will take place in San Francisco, CA, US, on October 10–11, 2018, and DDF returns to Berlin for the 10th Annual Global Drug Delivery & Formulation Summit on March 11–13, 2019, with topics being researched including "bringing device development closer to drug formulation" and "developing medical devices for wider eHealth integration".

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# INNOVATION ZED

## INSULCHECK CONNECT: ADDRESSING ADHERENCE WITH A CLOSED-LOOP SOLUTION

In this article, John Hughes, Chief Executive Officer, Innovation Zed, and Alina Smotrova, Business Development Manager, SHL Group, discuss the success of the InsulCheck Classic, an add-on device to help patients with diabetes improve adherence to their medication, and how user feedback and modern technology has led to the development of its second generation, InsulCheck Connect.

It is well documented that non-adherence to medication is a public health problem worldwide. With the increasing prevalence of chronic diseases and the growing list of conditions that require self-injection, such as diabetes, Parkinson's disease, multiple sclerosis, rheumatoid arthritis and migraine, ever more patients are demanding a simple solution that can help them manage their conditions more efficiently without disrupting their daily routines.

Having been diagnosed with diabetes more than 25 years ago, John Hughes, Chief Executive Officer of Innovation Zed, is no stranger to the complexities associated with the management of chronic conditions. When he noticed his own behaviour falling short of optimal, he saw a need for a technology that could help him close this gap. That is why John and his colleagues at Innovation Zed, an SHL partner company, officially launched InsulCheck Classic in 2016, an add-on device for existing insulin pens. Since then, thanks to its intuitive features and compatibility with the majority

of insulin pens on the market, the device has benefited a number of users across the globe.

Now in 2018, on the eve of the next generation, InsulCheck Connect, hitting the market, the team behind this patient-proven product takes a look back at its journey, discusses the key learnings that led to InsulCheck Connect, and talks about what lies ahead for the platform.

### THE CHALLENGE OF NON-ADHERENCE

The impact poor adherence has on diabetes treatment can range from below optimal health outcomes to extremely dire consequences, such as heart disease, stroke, kidney failure, lower limb amputations and blindness.<sup>1</sup> Poor outcomes can, in turn, lead to increased healthcare service usage, ultimately resulting in the escalation of healthcare costs. The financial pressure is sometimes even passed onto patients by payers through higher co-payments or via higher costs of coverage per employee.<sup>2</sup>

In light of these challenges, a multitude of studies have been carried out to understand the determinants of non-adherence and identify methods of improvement. When studying diabetes, for example, one common method is to have patients keep what is known as a

"The results of poor adherence to diabetes treatment can range from below optimal health outcomes to extremely dire consequences, such as heart disease, stroke, kidney failure, lower limb amputations and blindness."



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“diabetes diary”, where patients produce a written account of when they took their medication and what their glucose levels were like every few hours. This type of subjective approach where patients are asked to define their own adherence, either using pen and paper or through personal interviews with healthcare providers, is often time-consuming and can result in unreliable reports. For example, a study where patients were asked to provide their subjective ratings of adherence found that those admitting to non-adherence were able to describe their behaviour accurately,<sup>3</sup> whereas patients who denied non-adherence were unable to accurately recount their activities.

On the other hand, traditional objective strategies, such as counting remaining dosage units (e.g. tablets) during clinic visits or using pharmacy databases to track when prescriptions are filled, have their own set of limitations. This is in part because obtaining medicine by itself does not ensure its use. Such information can also be incomplete because patients may use more than one pharmacy, or data may not be routinely captured. In addition, implementing a comprehensive information technology infrastructure involving multiple parties can be complicated, time-consuming and potentially very costly.

### ADDRESSING ADHERENCE WITH TECHNOLOGY

Recent developments in modern technology have made it possible to monitor adherence more easily and objectively, without adding burden to the patient. For example, the creation of devices that automatically record details about oral and inhalation therapy can provide evidence-based records of the patient’s behaviour. Yet when it comes to combination products, introducing a new feature is often a lengthy process, complicated by regulatory hurdles, costs and time-to-market considerations.

First introduced to the market in 2016, InsulCheck is a snap-on accessory for a wide range of existing insulin pens (Figure 1). Providing patients

with the benefits of technology, the device enables straightforward insulin management for diabetics. Its first generation, the Classic, reliably displays the time since the last injection on a large and easy-to-read display panel that ensures the information is easily accessible to the user.

Since its launch, users of this intuitive device have first and foremost praised its ease of use – there is no need to adapt to new regimens as the device can be used with existing pens. They have also reported significantly improved confidence in managing their injections, no longer needing to worry about double injections and opportunities to catch up on forgotten injections, which in turn leads to improved safety and better health outcomes. More importantly, reports have suggested that many patients now see the device as an essential, even indispensable, complement of their pens, adding that they will continue to use it when they move to new pens.

### LEARNING FROM EXPERIENCE

Whilst InsulCheck Classic was widely praised among its users for its ability to support adherence, user feedback, gathered by telephone, surveys, traditional mail and online, revealed that patients wanted more information that could help them save time and effort. This could be achieved through the automatic recording of injection data, which could be logged in digital diaries and passed to clinicians for evidence of treatment. Users also wanted the ability to enable auto-correlation via intuitive pictorial representations where data related to glucose readings and insulin intake is presented on their mobile devices.

This user feedback led to the creation of InsulCheck Connect, the second-generation iteration where data recording and connection capabilities have been implemented to support the analysis of injection behaviour. The connected device can record the time and frequency of injection and send this data to the patient’s mobile device. From there, the data can be integrated into diabetes management algorithms to support condition management.

“User feedback led to the creation of InsulCheck Connect, the second-generation iteration where data recording and connection capabilities have been implemented to support the analysis of injection behaviour.”

In order to capture a more accurate account of device acceptance and functionality, the team created a connected version of the add-on device to undergo intensive trials in the UK NHS. Initial findings revealed that not only is the collection of data important, but the presentation and format for user and clinician interpretation is also key. The trial also reinforced the premise that there is value in having a one-size-fits-all solution readily accessible across a range of existing injection pens, covering over 100 million users worldwide.

### ENHANCED FEATURES FOR BETTER CONNECTIVITY

Since the NHS trial, InsulCheck Connect has undergone a series of design enhancements to improve its usability and capabilities. For example, besides recording injection time and frequency, a sensor that detects device mounting and dismounting activities was added so as to track pen usage and potentially highlight anomalous behaviour – crucial information which can be used to give feedback on best practices. Because insulin needs to be stored under certain temperatures to maintain safety and efficacy, the device can now also measure and track ambient temperature, giving warnings when necessary. The industrial design was also improved to support a larger display area and to make space for an upgrade to the battery component, which can now be recharged via a USB cable.

With InsulCheck Connect, each and every data point is automatically recorded and sent to the user’s mobile device wirelessly via Bluetooth. Paired with a mobile application, the data becomes an invaluable asset for clinicians and health professionals who need accurate evidence of user behaviour, to support treatment adjustments.

**Figure 1: InsulCheck can be easily mounted onto a majority of existing insulin pens.**



Understanding that quality and safety are at the core of any medical treatment, the InsulCheck Connect has attained a CE marking approval in Europe and has been certified by the US FDA as a Class I medical device.

### CLOSING THE LOOP FOR THE VALUE CHAIN

Once InsulCheck is attached to a pen and connected to a mobile phone, patients can enjoy the benefits of data monitoring and condition management without the need to change their routines, an important characteristic that is at the heart of InsulCheck's add-on approach.

With reliable injection data at hand, patients know the exact details of their previous injection, which helps them avoid dose miscalculations and miss fewer injections. Caregivers are also provided with peace of mind by the integration of functions such as remote monitoring and instantaneous alerts.

For healthcare professionals, including nurses and physicians, a significant amount of time can be saved over manually gathering and logging adherence data, with the added benefit of improved reliability over traditional manual methods. The time saved can then be focused on addressing the situations at hand, whether it is on improving adherence or laying out plans for optimal treatments.

For pharmaceutical companies seeking to utilise connectivity to support adherence and create market differentiation for their products, InsulCheck's add-on approach lowers the barriers to entry. This is because integrated pens are expensive to create and require extra time to attain regulatory approvals. In addition, patients will be required to adapt to new practices and habits, thereby increasing the potential for resistance.

For pharmacies, the collected data can be incorporated with a customer database to provide personalised services, which can help enhance user experience, drive loyalty and also improve customer retention and penetration.

Last but not least, payers can gain real-world insight into understanding if prescriptions are not only filled, but properly adhered to. These insights help payers identify the patients who achieve optimal treatment and the best health outcomes, which in turn can translate into lower healthcare costs that can go back into



Figure 2: InsulCheck Connect's closed-loop system.

rewarding the patient. The data also allows payers to more effectively help patients who have not achieved optimal treatment.

In summary, with each member of the value chain benefiting from the data captured, the Connect presents a closed-loop solution that helps patients achieve better health outcomes (Figure 2).

### BEYOND ADHERENCE

When recommending strategies to improve adherence, the WHO advises using a multi-disciplinary approach that combines feasible self-reporting and reasonable objective measures.<sup>4</sup> InsulCheck Connect supports this multi-disciplinary approach by making the sharing of objective, real-world data possible across multiple conditions, devices and platforms.

To support this aim further, Innovation Zed has launched a number of initiatives within the digital space to provide its software partners with market-tested expertise and knowledge in the

form of a certified medical device with an open application programming interface (API), through which data is easily available for integration. The data, which can be

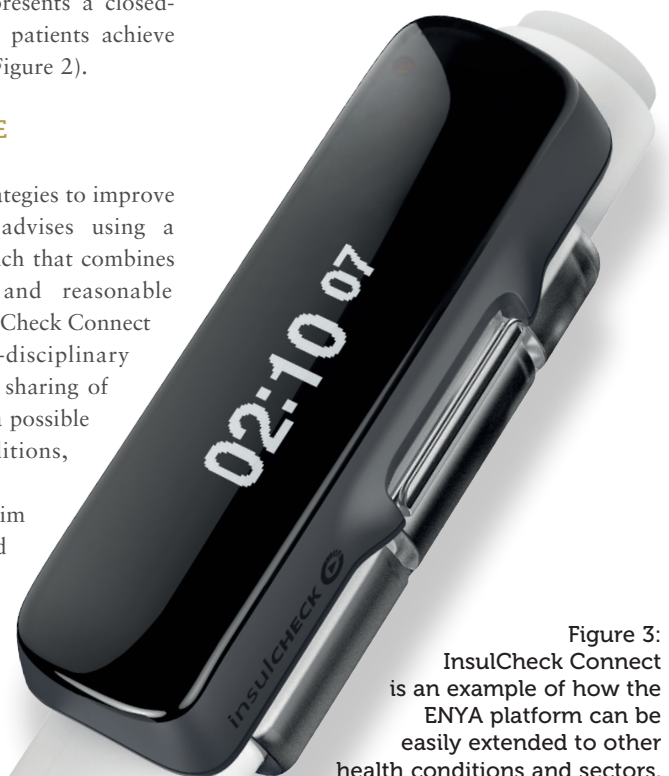


Figure 3: InsulCheck Connect is an example of how the ENYA platform can be easily extended to other health conditions and sectors.

used for condition insight and analysis, can be transformed into invaluable statistics that will enhance their existing offerings.

With the ongoing increase in injectable therapies for the treatment of chronic conditions, Innovation Zed is expanding this approach to be easily extended to other health conditions and sectors in the form of a condition-agnostic hardware platform – ENYA. The ENYA Platform is completely injection-device independent and can work across multiple injectable conditions. This makes it possible for pharmaceutical companies to support their patients with the benefits of connectivity without recertifying their injection devices (Figure 3).

As the industry is focusing more and more on patient-centricity, the add-on platform provides an excellent opportunity to improve patients' user experience. This can be done without changing the injection process that they are accustomed to. The data captured by the add-on device can be used to introduce a focus on adherence, which will help the patient manage their therapy and, with their consent, be shared with caregivers, doctors, payers and pharma companies.

#### ABOUT THE PARTNERSHIP

SHL is a world-leading solutions provider in advanced drug delivery systems, such as autoinjectors and pen injectors. Its pioneering products for major pharmaceutical customers are based on human-centric designs and market-proven functionalities. Combining SHL's broad knowledge base with Innovation Zed's condition management expertise, the partnership offers a flexible, robust and risk-proof approach to supporting pharma's first steps into connected devices and digital health.

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#### ABOUT THE AUTHORS

**John Hughes** is the Co-Founder and Managing Director of Innovation Zed. As a computer scientist and entrepreneur with over 30 years of experience in business development, Mr Hughes dedicated his career to developing digital solutions that create better health outcomes for patients.

**Alina Smotrova** is a Business Development Manager at SHL Group responsible for the expansion into new markets and exploration of new technologies and business models. She works with SHL's customers and partners to provide advice on business model innovation, market insight and growth strategies with a particularly focus on digital health.

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# NORMALISING CONNECTIVITY – COULD UNCONNECTED DEVICES BECOME THE EXCEPTION?

When discussing the future of drug delivery, the rise of connected technology frequently dominates the discourse. Looking at the next generation of technologies in this area, Charlotte Harvey, Consultant Mechanical Engineer, Sagentia, ponders the prospect of connectivity becoming the baseline – at what point will drug delivery devices without connectivity become the exception?

Consider the question: “Why should I add connectivity to my drug delivery device?” As connected technology becomes ever more mainstream across all aspects of modern life, that question is likely to change to “Why should I not?”

Connected devices are a growing trend within the drug delivery space. Not only does connectivity enhance existing devices, advancing technologies give rise to opportunities for new use cases which further the ambition of moving healthcare

away from the hospital and into the home. With the increased dominance of connected devices in the consumer sector, users’ expectations and behaviours have changed. Emerging technologies promise ubiquitous, reliable and effective connectivity, leading to the conclusion that adding it to drug delivery devices will ultimately become a no-brainer.

## WHY ADD CONNECTIVITY?

Historically, the main drivers for designing a connected drug delivery device have been to:

- Improve patient outcomes
- Reduce healthcare costs
- Improve usability
- Differentiate the product on the market.

The first two of these drivers are addressed by focusing on improving medication adherence, which is therefore becoming

“A June 2017 industry insight report from Ericsson Consumerlab showed that 39% of chronic patients prefer online consultations to face-to-face meetings.”

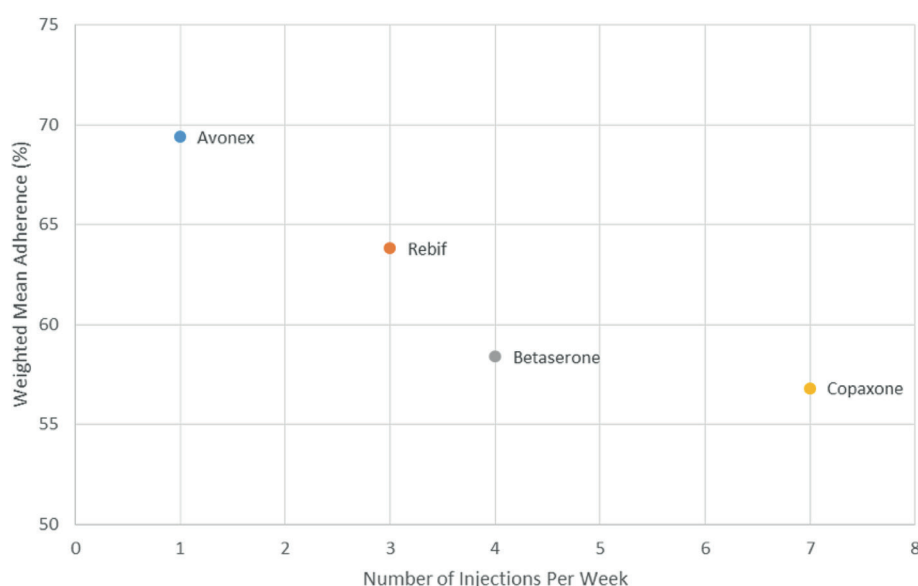


Figure 1: Weighted mean adherence rates plotted against the number of injections per week for four disease modifying drugs for multiple sclerosis.<sup>1</sup> Note that Avonex is an intramuscular injection whereas the rest are subcutaneous.



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an important goal for pharmaceutical companies and healthcare professionals (HCPs). A 2013 literature review<sup>1</sup> (Figure 1) showed how adherence is an issue for some multiple sclerosis (MS) drugs, with weighted mean adherence rates below 70%. Clearly the medical profession wants to see this percentage increase and so improve outcomes for their patients.

Connected devices give HCPs the opportunity to monitor patients more closely in order to make sure that not only are they using their devices, but also that the way they are using them is correct and efficacious. HCPs can then work with patients who are not taking their drugs or who are taking them incorrectly. On a larger scale, this information can be fed back to device manufacturers so they can improve adherence in their redesigns. Any data which can be gathered that explain why the adherence levels are low for certain populations is even better. For instance, the literature review<sup>1</sup> found a correlation between adherence rates and number of injections per week.

From a healthcare perspective, treating patients in hospital increases costs, using up resources such as HCPs and bed space. In parallel, there is also a growing number of patients who would like to see healthcare moving away from the hospital and into the home. For example, a June 2017 industry insight report from Ericsson Consumerlab showed that 39% of chronic patients prefer online consultations to face-to-face meetings.<sup>2</sup> This is because these patients tend to prefer managing their treatment in a familiar environment, without the need to make appointments and travel frequently. Connectivity allows for remote care and reduced physical contact between physicians and patients.

### IDENTIFYING BARRIERS TO ADDING CONNECTIVITY

The decision to add connectivity to a device is significant because doing so can be complex. It is not entirely straightforward to add Bluetooth or Wi-Fi features to a device, particularly one which was previously fully mechanical. Additionally, new sensing technologies may need to be added to collect data, for example, injection force, time between drug readiness and injection, and inhalation profile. There are trade-offs between the need for the data and other factors (development time, device size, safety, etc), and so not every reason for a connected device is sufficient to build a

compelling business case.

When designing connectivity into drug delivery devices, it is also important to ensure that cybersecurity risks are addressed so that the vulnerability of a device, to hacking or malware, for example, is minimised. Only when it meets a user or business need should connectivity be added to a device. However, in the future the changing technology landscape could make the decision to connect much simpler.

### HARNESSING THE AVAILABLE CONSUMER TECHNOLOGIES

There are technologies already being used in the consumer market which can be applied to the medical industry generally, including drug delivery. The most commonly used technologies include Wi-Fi, Bluetooth, cellular and NFC (near-field communication). However, there are limitations to these technologies in their current form which have prevented wider use within drug delivery devices. For instance, wireless technologies require the device to be in range of a particular location or other device, and NFC requires a particularly close range. Bluetooth requires a hub to send data to (and so works best with a companion device). Cellular technologies need a SIM and are pay-to-use. Most technologies require some sort of set-up, either by the user or HCP.

Despite these issues, technologies are widely available in the home which could be harnessed to develop new drug delivery use cases:

- The user interface (UI) for a drug delivery device is central to ensuring that it is being used correctly, so there are always opportunities for improvement and to cater better for those less able to use standard UIs (for instance, those with visual impairments or dexterity issues). Voice recognition provides an opportunity to be more inclusive and is already widely used in the consumer market.

“The medical device industry is generally slower to take on new technologies than the consumer industry. This is understandable due to the increased regulation and safety considerations. Therefore, emerging technologies often take longer to appear.”

- User expectations could lead drug delivery devices to become a part of the Internet of Things (IoT) for those managing chronic conditions. Home assistants could be key in enabling this, as they could provide updates on device status (for instance, if a drug needs reconstituting or warming) and potentially pass instructions to the device from the user (when functions are not safety critical). More simply, they could provide patient reminders, particularly useful for elderly patients who need to take enteral medication at a particular time of day.
- Bluetooth beacons can help to remind users to use their device once they are in a particular location, such as their home (more on beacons later). For those with multiple, complicated therapies, such as elderly patients, this could provide a real opportunity to make their therapy more manageable.
- An augmented reality device (like Google Glass) could provide instructions during use to a novice user. This could even be tailored to individual devices and their patients. Augmented reality could also help those who need more training and assistance in using their devices, such as children or those with learning difficulties.

“Unfortunately, Bluetooth is not as versatile as cellular technology as it requires a data hub, such as a smartphone, enabled with the correct Bluetooth version. However, these devices continue to become more prevalent and it will not be long until all smart devices are Bluetooth 5 enabled.”

These scenarios rely on technologies consumers are familiar with (although in the case of augmented reality, still not widespread). These technologies are not available to all users, however, and this has been a major stumbling block to creating devices with connectivity as a major feature. Where the consumer sector can allow users to self-select through access to technology, the medical industry has to ensure coverage for the entire patient population (for most devices). However, should an environment of ubiquitous and reliable connectivity arise, this could be a game-changer.

### EVALUATING EMERGING TECHNOLOGIES

The medical device industry is generally slower to take on new technologies than the consumer industry. This is understandable due to the increased regulation and safety considerations. Therefore, emerging technologies often take longer to appear. Such is the case with Bluetooth 5 – the newest version of Bluetooth which (for context) is in only the Samsung S8 smartphone onwards.

Up until recently Bluetooth came in two distinct flavours: Bluetooth and Bluetooth Low Energy (BLE). Bluetooth was used for wireless keyboards and mice, wireless headsets and speakers. BLE uses a lot less power and was designed for areas like healthcare, fitness and beacons. An example is wearables which use BLE rather than Bluetooth. In the summer of 2016 the Bluetooth Special Interest Group (Bluetooth SIG) announced Bluetooth 5, which will likely become the *de facto* version of

Bluetooth over the next few years. It has twice the speed and four times the range of Bluetooth 4.2. Bluetooth 5 has the ability to replace BLE in low-power devices as the increased communication throughput means communication time is reduced. This means less compromise in drug delivery devices when it comes to how the connectivity feature is utilised.

Bluetooth 5 allows devices which are already connected to transmit even more data. Since there is less need to worry about energy consumption or data volumes, it's now possible to collect all the data you may possibly want and broadcast it back to a smartphone or other hub, even if there is no current use for it. For example, if using a patch pump, more than just the delivery time can be logged. An entire profile of the delivery can be recorded, including varying flow rates and any pauses to be sent for analysis. There is usually also a concern about when Bluetooth can broadcast and for how long – with a longer range and faster communication this would no longer be an issue.

Beacons are also being given a boost with the introduction of Bluetooth 5, and they have applications in the drug delivery space as part of the IoT. Beacons are small Bluetooth radio transmitters which are visible to Bluetooth-enabled devices once in range. If the device recognises the beacon's ID it will then trigger a pre-set event, such as in the example given earlier where a reminder is triggered when a user gets home.

As the amount of data which can be transferred with a beacon is larger (with Bluetooth 5) than just the beacon's ID, it can also transmit sensor data such as temperature. This could be used to track the temperature of a drug and keep users informed of time left before their injection can be performed. Beacons could potentially be used alongside a drug right from dispensing, enabling a batch of drugs to be tracked from the filling line to the patient as an anti-counterfeiting measure. Information on the drug, such as dose, could be conveyed to the device itself, which could automatically set the injection profile for that user. The use of beacons also goes beyond the home environment – tracking drugs' movement through a hospital is

already happening with barcode readers, but beacons would be a more time-efficient, less manual solution.

When it comes to tracking drugs, particularly when there are concerns about counterfeiting, NFC has been the go-to technology to date. Various drug packages have been supplied with RFID tags which either allow the user to track their therapy or allow devices to authenticate the drug prior to use. Beacons perform this task automatically, in that they require no user interaction once set up. Therefore, the authentication step would become more user-friendly if beacons replaced NFC in these cases.

Unfortunately, Bluetooth is not as versatile as cellular technology because it requires a data hub, such as a smartphone, enabled with the correct Bluetooth version. However, these devices continue to become more prevalent and it will not be long until all smart devices are Bluetooth 5 enabled. Additionally, Bluetooth 5 continues to be the lower energy option, perfect for use in a hand-held device to keep battery use to a minimum.

### ASSESSING FUTURE TECHNOLOGIES

The connectivity industry is likely to move from a relatively disparate set of technologies to a landscape mapped by one or two. The key technology to watch is 5G. Its benefits should lead to increased coverage compared to 4G as users may start favouring a cellular connection over Wi-Fi. 5G would then be the focus of most efforts to connect those devices which warrant connectivity. From the perspective of designing a device, cellular technologies are already the preferred option as the only way to create a device that can be used anywhere. Additionally, Wi-Fi requires more reliance on the user (or HCP) to set up the device with the network.

5G is estimated to be introduced between 2020 and 2025. Given that it is still some way into the future, there are loose definitions on what it will look like and the benefits it will provide. However, the mobile operators interest group, GSMA, has outlined a number of objectives,<sup>3</sup> and

“Approximately one third of the world's population is projected to be covered by 5G by 2025, and will therefore be in a position to transfer data continuously given the high speeds and reliable connection.”



there are industry expectations on what 5G has to look like. For example, the speed of 5G is anticipated to be 1 Gbit/s, with some estimates as high as 10–50 Gbit/s compared with the average 4G speed of 15 Mbit/s. It is for this reason that we can expect cellular connections to start replacing Wi-Fi (for context, an HD film could be downloaded in seconds over a 5G network). These features will help enhance the use cases discussed earlier as well as create the opportunity for new ones, for example:

- Where an elderly patient has a complicated treatment regimen to manage, it would be beneficial for a carer to be able to monitor the patient's drug delivery activity live. The lower latency of 5G will make this easier.
- Where patient data is being collected to help understand adherence across a patient population, larger volumes of data could be collected and processed. With faster upload and download speeds, each use of an inhaler (for instance, the inhalation profile) could be analysed away from the device with the user or HCP alerted to potential issues.
- It will be easier to integrate drug delivery devices into the IoT. With smoother operation they will meet the demanding ease-of-use requirements of the consumer market, potentially merging with health monitors.
- Wearable drug delivery devices are often connected to allow better management of what is often a complicated treatment. Using 5G, a system can be designed with the expectation that the user will be able to upload or download data continuously as needed.

The spread of 5G among mobile devices (5G is intended to be usable with existing 4G networks) can be combined with the spread of mobile devices themselves to create an image of a highly connected world. Approximately one third of the world's population is projected to be covered by 5G

by 2025, and will therefore be in a position to transfer data continuously given the high speeds and reliable connection. This continuous guaranteed connection will help with the rise of autonomous cars, drone delivery systems and widespread adoption within the healthcare industry. What this means in practice for drug delivery is much more frequent uploading and downloading of data, given that the faster speeds of 5G will permit less energy usage for the same or greater data transmission.

It should be noted that the wider reliance of the healthcare industry on a connected world will have a significant impact on how conditions are diagnosed and treated, even when the devices themselves are not connected. Remote appointments with doctors are likely to become more prevalent. Wearable health monitors have the potential to flag early indicators of illness to users and doctors. Where drug delivery devices are connected, it will become important to fit into this new ecosystem, streamlining treatment and improving outcomes for patients. Demand for drug delivery devices to contribute positively to this trend will increase and device designers will have to determine where this fits into their user and business needs. 5G is the key technology which will enable this ecosystem and the industry to keep up with demand.

## CONCLUSION

The advancement of connectivity technologies is not slowing down, and many industries are excited about the possibilities that are opening up. Within drug delivery devices, the ability to transmit data faster and more reliably will make it easier for device designers to meet challenging user and business needs. And the spread of coverage among more users, to more distant regions will make it possible to integrate the connectivity function fully with the use of the device.

Healthcare is transitioning out of hospitals, and user expectations and

behaviour are changing as they become accustomed to the IoT. Drug delivery devices will need connectivity in order to keep up with these changes and we expect these connected devices to become the new norm. Of course, the implementation of connectivity will require extensive human factors engineering studies to investigate and validate new use cases. Manufacturers need to plan ahead for the changing technology landscapes, taking account of the new use cases enabled by emerging and future technologies.

## ABOUT THE COMPANY

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

Sagentia employs over 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has 16 European and North American offices, two UK-based dedicated R&D innovation centres and more than 400 employees. Other Science Group companies include OTM Consulting, Oakland Innovation, Leatherhead Food Research and TSG Consulting.

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## ABOUT THE AUTHOR

**Charlotte Harvey** is a consultant mechanical engineer within Sagentia Ltd. Her experience lies predominantly in managing medical product developments, specifically those in the surgical and injectable drug delivery fields. Recent projects have included front-end innovation in the drug delivery space, user interviewing for human factors, and several instances of developing reconstitution-based autoinjectors. Charlotte graduated from the University of Cambridge with a Masters in Mechanical Engineering.



**Economy Spring**

## PRECISION METAL COMPONENTS IMPROVE CONNECTED MEDICAL DEVICE PERFORMANCE

In this article, David Philbrick, Business Development Manager, Economy Spring (MW Industries), discusses the critical role a variety of metal springs and components play in a connected drug delivery device and presents an example of how failure to consider them properly can send a successful commercialisation sideways.

*This article is based on an MW Industries white paper: "Precision Metal Components Improve Connected Medical Device Performance".*

Extensive technological inroads in drug delivery devices and surgical platforms are enabling significant improvement in the quality of patient care. One of the major ways in which this is happening is through the incorporation of connectivity. While a significant amount of technology goes into the development of connected devices, sometimes the smallest components, such as springs, wire-forms, stampings and bellows, can enhance the performance of the electrical circuitry in the device and reduce its size.

Take autoinjectors as an example. In the early days of these devices, a spring was used to perform a mechanical function, by way of storing and releasing energy. Today's electronic, connectivity enabled devices require much more sophisticated components such as battery or timing

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"Today's electronic, connectivity enabled devices require much more sophisticated components such as battery or timing contacts that assist in triggering device circuitry."

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contacts that assist in triggering device circuitry. These components are crucial parts of the internal circuitry that facilitates the advanced features of an electronically upgraded device and, whilst they are seemingly simple, it requires expertise to get the most out of them.

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"The battery, circuit timing contacts, circuit routing, component coatings and non-magnetic metal alloy integration are just a few of the components whose characteristics need to be carefully designed to ensure that the device will work properly."

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## BOX 1: CONNECTED DEVICES

Connected devices feed information back to physicians and help ensure that they are being properly utilised by the patient. As a result, it is increasingly critical to make sure component design will support this desired functionality in electronic systems.

In the field of drug delivery, the specific areas where this technology is making significant progress are inhalers and autoinjectors. However, in the broader context of the healthcare world, connectivity is making its way into hand-held laparoscopic/endoscopic devices and powered electrosurgical/robotic surgical platforms as well.

With pharmaceutical applications, patients are now able to administer their own drug treatments in a more controlled manner. Improvements in device functionality have resulted in automatic dose tracking, as well as tracking the timing and frequency of therapy. Physicians can effectively monitor patient care automatically through data analysis, which will tell them if the device is being used properly. Pharma companies can also harvest data on device usage to develop more effective devices and therapies in the future. Further, the integration of Bluetooth and near field communications (NFC) enables self-administered drug devices to communicate via the internet and mobile apps.

Surgical devices also are taking advantage of the latest in connected technology. Examples include monitoring the physician's use of the device during procedures and determining effectiveness of device utilisation. Additional capabilities include automatic activation of device safety features, as well as autonomous data output to a clinical repository or patient files. This data harvesting can be used to enhance surgical procedures, create next generation devices and improve patient care.

"If the gold coating technique, spring characteristic and proper metal alloy have not been designed effectively in a connected device product, the chances that the device will not function properly are exponentially higher."

### THE PATHWAY TO CONNECTIVITY

Many next generation pharmaceutical and surgical devices will share one thing – the ability to gather and disseminate data (see Box 1). The battery, circuit timing contacts, circuit routing, component coatings and non-magnetic metal alloy integration

are just a few of the components whose characteristics need to be carefully designed to ensure that the device will work properly. Part of that decision-making process requires that you are working with a supplier who has the knowledge, capability and reputation of delivering high quality, precision components.

Here follow some examples of battery and device timing contacts that may be utilised in a connected device.

#### Gold-Plated Bellows

Microscopic bellows components (Figure 1) can be designed for use in creating electrical circuit contacts in wearable devices, autoinjectors and inhalers. They are ideal for "noisy" electrical environments where the traditional "pogo" style pins are too rigid in the circuit design, or where there is excessive motion or vibration that results in

damaged pins or connections. The bellows are designed to absorb shock and able to withstand sudden jarring motions at a circuit connection (similar to a spring) and dampen vibrations, enabling reliable continuity of the circuit.

#### Coiled Wire-Forms and Springs

These components (Figure 2) come in a variety of sizes and shapes and are ideal for battery contacts where the spring force creates positive pressure to the power source. They can also facilitate complex routing in a moulded housing or a circuit path through a device. Wire-forms can also be gold plated for improved electrical and corrosion resistance resulting in reduced metal oxidation.



Figure 2: An example coiled wire-form.

#### Leaf Springs or Stampings

The spring characteristics of these components (Figure 3) can assist with battery and circuit board design while generating positive spring pressure to maintain connectivity. The leaf springs can also be designed as finger contacts for various timing events in the device motion, deflection or actuation of the device. The result is enhanced device functionality based on contact motion and spring recovery within the moulded device housings. These components also can be designed to utilise selective gold-plated or banded strip material to reduce the gold coverage on the entire component. This technique results in significantly reduced part costs with gold plated at the exact contact points.

In addition to battery and timing contacts, there are also metal components that can be used in an electrical circuit function where magnetism helps to trigger the circuit connection. In this instance, a non-magnetic metal alloy integration may be required to minimise any undue



Figure 1: Gold-plated bellows.



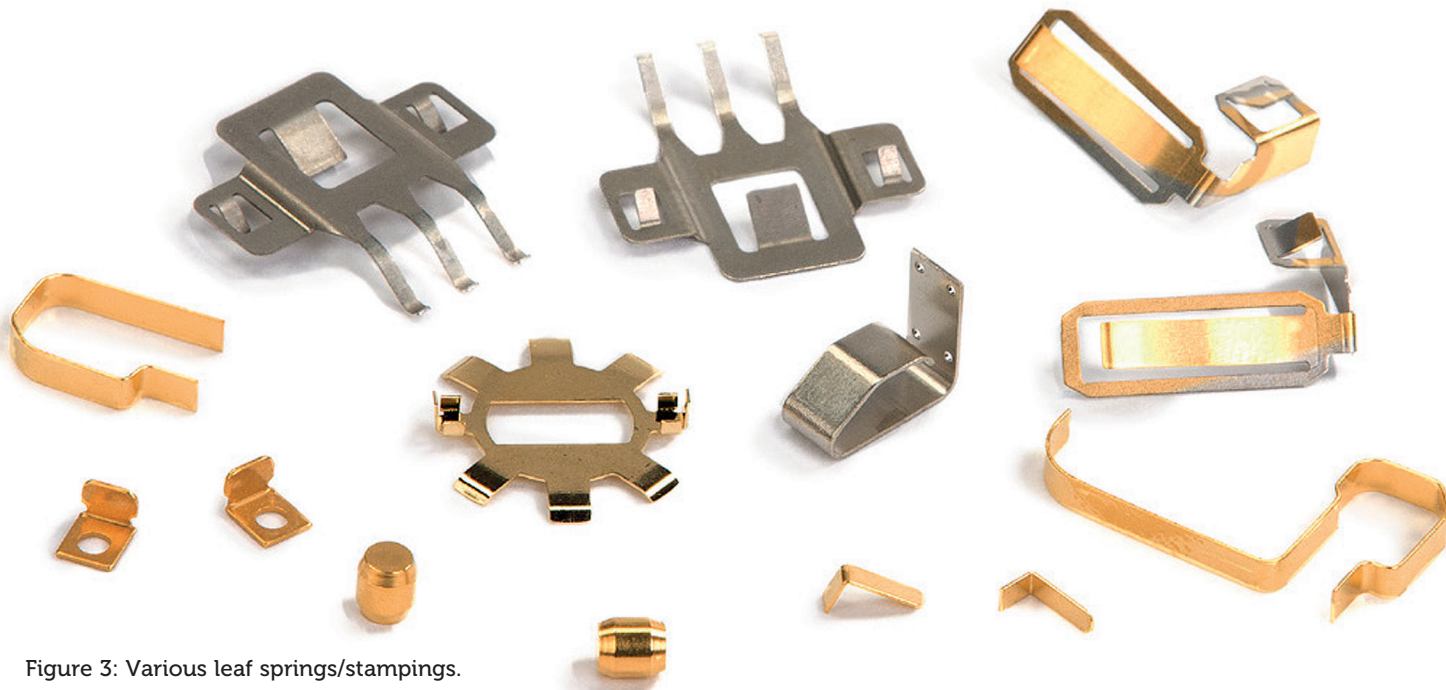


Figure 3: Various leaf springs/stampings.

“The resulting actions eliminated the voltage/current variation experienced in the finished product, which led to consistent circuit functions and timing in the device.”

magnetic signature that would influence the circuit timing by energising the leaf spring and thus inappropriately influencing the circuit timing.

### THE IMPACT OF FAILURE

If the gold coating technique, spring characteristic and proper metal alloy have not been designed effectively in a connected device product, the chances that the device will not function properly are exponentially higher. In practice, this could mean that the device does not administer the medication dose correctly, thus negatively impacting patient care, or corrupts the data collection process, supplying incorrect data to the end-user (e.g. healthcare professional, data analyst). At the very least, such outcomes are undesirable and will have a serious negative impact on perceptions of the device's quality and reliability. In a worst-case scenario, there is a significant adverse effect on patient health, due to device malfunction or a physician unwittingly prescribing a flawed treatment due to inaccurate data. As a real-world example, below is a scenario of how an incorrectly defined coil spring drawing was adversely affecting a connected device.

#### Situation

A large contract manufacturing organisation (CMO) was having problems with maintaining consistent voltage/current

levels on a circuit in a connected drug delivery device it manufactures. The resistance level of the coil spring was becoming an issue as commercialisation activity ramped up. Spurred by experiencing higher instances of electrical performance variability, upon investigation they discovered that their spring supplier could not hold the required tolerance of the spring's free length defined on the part drawing. During incoming inspection, the existing spring design experienced a very high rejection frequency. The fallout due to the free length was, on average, 40%.

#### Problem

At the time, it was unknown to the CMO that the variation in free length was the primary contributor to vast differences in the spring's resistance level. The spring was very long, coupled with a large coil count (70 inactive coils) and a poorly-dimensioned free length tolerance defined by the part drawing. Initially, the free length tolerance was designed to help control the amount of wire in the spring. As a result, it would control the resistance level needed to trigger the circuit in the finished product.

Unfortunately, the part drawing focused on the free length rather than establishing a measurement for the resistance level of the spring itself. To make matters worse, the spring supplier was also rejecting a very high volume of springs on the

manufacturing line resulting in high internal scrap. Since they could not meet 100% of the free length tolerance as noted on the part drawing, the supplier was forced to ship a small percentage of “long springs” to keep up with the increase in demand. These conditions led to the variation of the voltage/current levels in the device.

#### Solution

Upon a thorough investigation by the Economy Spring team, it was discovered that the resistance measurement was required on the part drawing and in-process resistance checks were needed to control the amount of material in the finished spring. By incorporating this measurement technique, a new spring was designed to minimise the voltage/current variation, resulting in an increased free length tolerance.

The recommendation of these print changes reduced internal scrap at the spring supplier, increased throughput on the CMO manufacturing line and reduced fallout at incoming inspection. The resulting actions eliminated the voltage/current variation experienced in the finished product, which led to consistent circuit functions and timing in the device.

### CHOOSING YOUR SUPPLIER

It's important to do your homework so that the suppliers you select to be part of your journey can help you race to the finish line, instead of creating problems and obstacles along the way. Choosing the right supplier will have a positive impact on the all-important speed-to-market timeline. A wrong supplier will not only prevent you from reaching your commercialisation goals

quickly, but it could also negatively impact the functionality of your device.

### Robust Quality Control System

Having a robust quality system is critical to ensure the life of the project and its commercialisation success. Product failure is not an option – particularly for a product that should create improved patient therapies and be the centre of a developing smart device platform.

The supplier's ISO 9001 and ISO 13485 certifications should be evident. Plus, a supplier who can demonstrate US FDA Medical Device Establishment Registration and Device Listing capabilities as well as GMP illustrates their commitment to consumer safety and product reliability.

You want to make sure that your

## ABOUT THE AUTHOR

**Dave Philbrick** is Business Development Manager & Lead Product Engineer for Economy Spring, an MW Industries Company. For more than 38 years he has been involved in supporting new product development for medical instrumentation & drug delivery systems for Medical / Pharma OEM's. He is a specialist in metal component development, design and integration.

component supplier is more than capable of providing the appropriate quality planning. Control plans, process flow diagrams and Process Failure Mode and Effects Analysis (PFMEA) need to be in place so that a change is not made after validation approvals. Emphasis on the PFMEA design in your supplier's environment will help understand the weakest part of their process and make sure adequate controls are in place to address ongoing issues.

### Metrology Capability

Ideally, a supplier will have state-of-the-art, in-house metrology capabilities. Components need to be accurately measured and data needs to be supplied to meet statistical requirements. Automated measurement systems and the ability to collect data without human interpretation has become more prevalent. This level of activity helps the original equipment manufacturer (OEM) build the bridge needed to support the FDA submission on the device or project. The supplier's ability to provide supporting measurements helps the OEM to meet statistical protocols and verify quality expectations.

### CONCLUSION

In addition to the attributes listed above, it's important for a supplier to have a competent level of experience working with design of electrical contacts and circuit connectivity

required of emerging smart medical devices. It is also desirable for a supplier to have a broad geographic footprint so that solutions are located in close proximity to your manufacturing location. Lastly, but equally as important, look for a supplier with a strong engineering staff that can address all of the twists and turns that are likely to take place through the product development lifecycle.

When these attributes are in place, drug and surgical device OEMs stand a greater chance of launching commercially-successful products, which provide both the patient and physician with smart device experiences that can deliver powerful results.

### ABOUT THE COMPANY

Economy Spring, a division of MW Industries, is a manufacturer of advanced medical device components, including highly-engineered, precision metal components and assemblies such as springs, surgical sharps, needles, laser machined tubing, staples, titanium clips and complex assemblies. The company deploys its end-to-end product lifecycle know-how and design expertise to shorten product development time and lower costs. Economy Spring's >40-year track record helps deliver product reliability and performance in demanding surgical and drug delivery applications. The company is registered with the US FDA and has ISO9001 certified and ISO13485 compliant quality processes.



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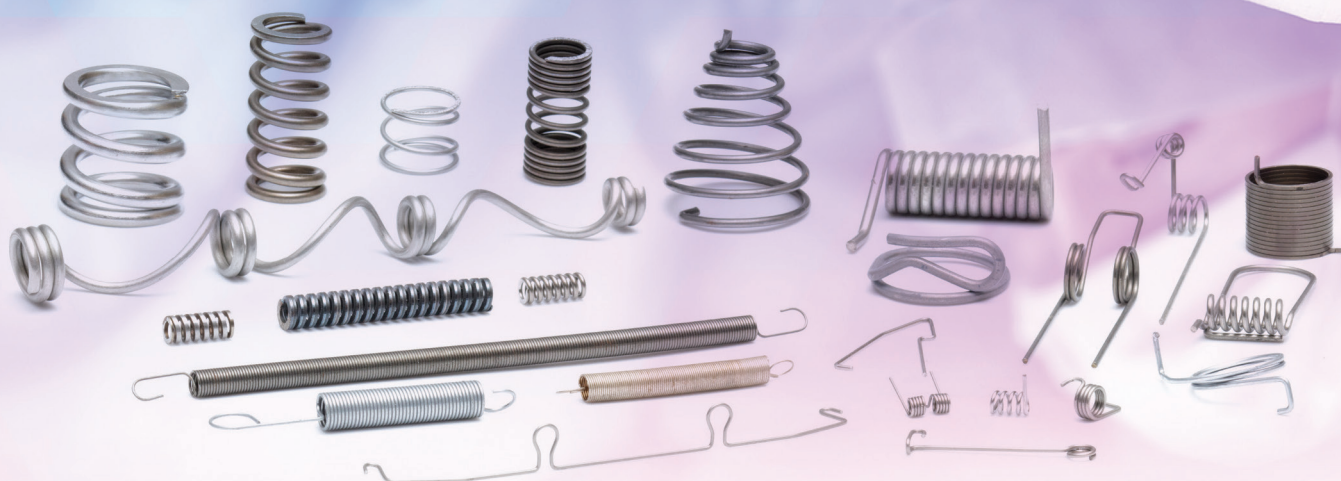
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# MONITORING NEBULISER USAGE & LUNG FUNCTION IN CLINICAL TRIALS

Adherence levels to inhalation treatments are known to be generally low. This issue is particularly important when testing nebulised drugs in clinical trials, since efficacy and safety cannot be properly evaluated otherwise. Carola Fuchs, PhD, Program Manager e-Health, and Yvonne Koehler, Study Manager e-Health, both of PARI Group, explain how PARI's special eTrack® Controller – part of the eFlow® nebuliser platform – can be used to monitor adherence during inhalation therapy which facilitates objective and remote monitoring.

In addition to efficacious drugs and efficient delivery systems, adherence to inhalation treatments is important to get the best result from respiratory therapies.<sup>1</sup>

It is known that adherence to everyday therapy for chronic conditions is generally low with an average of about 50%. This is also true for nebulisation therapy.<sup>2</sup>

It is therefore important to get accurate information about adherence. Electronic nebulisers are a good way of obtaining objective data about adherence – with an adherence average of 36%, they generally show lower adherence levels than those evaluated from diaries, medication consumption or estimation by study nurses.<sup>3</sup>

In clinical trials of new drug candidates for nebulisers, adherence is especially relevant to ensure that the efficacy and safety of a certain inhaled drug dose is evaluated

and maintained correctly. Adherence is an important control factor in clinical trials even though adherence rates are generally higher than in everyday therapy.

In one review, non-adherence to treatment protocol was reported in 98% of trials analysed for adherence issues. However, reporting on non-adherence is often vague or incomplete.<sup>4</sup>

In numerous studies, data have been analysed from clinical trials leading to the conclusion that adherence reporting is often inconsistent, resulting in biased data analyses.<sup>5</sup>

Osterberg reviewed 45 trials in 2005 and found that only 21 analysed adherence. The majority of those trials used unreliable methods to ascertain participant adherence, such as counting pills (11 trials) or questioning the participant in some manner (10 trials).<sup>6</sup>

“The impact of non-adherence on the cost of studies is immense. Higher rates of non-adherence compromise the significance of the outcome and, in turn necessitate higher numbers of participating patients. ”



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Figure 1: eFlow® Nebuliser System with eTrack® Controller can be used for adherence monitoring.

There is a need for more appropriate methods to adjust for any departures from treatment protocol. In addition, guidance is needed on how to choose the relevant patient group for analysis of outcomes in the presence of such non-adherence, as well as corresponding considerations in the study protocol.

The impact of non-adherence on the cost of studies is immense. Higher rates of non-adherence compromise the significance of the outcome and, in turn, necessitate higher numbers of participating patients. A non-adherence rate of 30% results in a 50% increase of the necessary sample size and a 50% non-adherence rate necessitates a sample size increase of 200%.<sup>7</sup>

PARI Pharma GmbH, an affiliate of PARI Medical Holding GmbH, has developed the special eTrack® Controller (eTrack®) as part of the eFlow® nebuliser platform to monitor adherence during inhalation therapy which facilitates objective and remote monitoring on the PARIttrack® web portal.

The eTrack® is already in use by more than 1,000 patients and has been proven to be beneficial in several multi-centre clinical trials performed by different pharma partners for different indications.

### eTRACK® & PARIttrack®

eFlow® technology nebulisers are based on PARI's proprietary vibrating membrane technology. These nebulisers offer short treatment times, are portable (battery operated) and virtually silent. They are used for the development and subsequent commercialisation of many drug products which need to be administered as a fine aerosol directly to the lungs of patients. PARI Pharma GmbH out-licenses its eFlow nebuliser platforms and has entered into close collaboration with pharmaceutical companies to develop drug/device combination products utilising customised eFlow® technology nebulisers.<sup>8</sup>

In order to objectively measure adherence to inhaled therapies that are administered via an eFlow® technology nebuliser, PARI has incorporated Bluetooth wireless technology and storage capacity on the circuit board of a special eFlow® control unit called eTrack® Controller (Figure 1). These features allow for data transfer from the device.

The eTrack® can operate all of the available eFlow® nebuliser handsets, including the eFlow® rapid nebuliser handset and a range of customised, drug-specific handsets.

Data on date, time and duration of nebulisation as well as end of nebulisation criteria are recorded for each nebulisation event. An option is included to select and transmit the name of the administered drug.

After each inhalation treatment, the locally stored nebulisation data are encrypted and automatically transferred via

Bluetooth to a 2net™ Hub (Qualcomm Life, San Diego, CA, US). The 2net™ Hub transmits the data via GSM to Qualcomm's cloud from where it is sent to PARI's central server (Figure 2).

The data can be accessed remotely via a web portal called PARIttrack® which has been specifically developed for use in clinical trials in compliance with the applicable data protection regulations. Study investigator and study personnel can access the relevant patient use data, depending on their access rights. Access to and evaluation of the data can be adjusted to suit the needs of each individual clinical trial.

PARIttrack® contains a dashboard that provides an overview of the adherence of all patients participating in the clinical trial. This dashboard enables the notifications for low adherence to be defined for each individual. It also summarises high level



Figure 2: Set-up of data transfer from eTrack® Controller to PARIttrack® web portal.



information on the number of patients and average overall adherence rates as well as average adherence rates for a recent period (e.g. the last few days). Notifications on the PARIttrack® dashboard allow easy data access and highlight individuals that might need to be contacted directly to provide assistance with any issues they may encounter or to remind them to adhere to their therapy.

The levels of notifications are study specific and can be set up and adjusted by the primary investigator.

Besides the dashboard, each patient inhalation dataset can be reviewed including details on time stamp, duration and switch-off criteria. Additionally, the adherence of each patient over a selected time period can be visualised graphically for easy evaluation.

If needed, the system can be adjusted to define the validity of a treatment session with respect to a minimum duration of nebulisation and the time interval between treatments, depending on the study protocol.

## RESULTS ON ADHERENCE MONITORING

The eTrack® and PARIttrack® have already been used in several clinical trials in Europe, the US and Canada.

Table 1 gives an overview of clinical trials of inhaled drug products that used eTrack® and PARIttrack® or former versions of the system to monitor adherence and shows the corresponding adherence rates within each study.

The results show that a very high level of adherence can be realised if the study protocol instructs that the system is used to

intervene directly in cases of non-adherence. Two studies (Studies 1 and 2 from Table 1) achieved average adherence rates of 98% and 96%, with adherence ranging from 82% to 100% and 64% to 100%, respectively for daily inhalations over periods of four and six weeks with daily remote monitoring and intervention as needed. Most patients were completely adherent and only very few patients had low adherence.

The very high adherence rates of Study 2 were sufficient for analysing the efficacy of the drug under investigation even in a small group of only ten patients. To increase the significance of the results, a sub-group analysis of all patients with an adherence rate of minimum 95% was possible.

Another study, which focussed on cystic fibrosis patients with a four-week treatment phase and a cross-over design with the control arm (Study 3), had the same high adherence rates even in the absence of direct intervention in case of non-adherence. Just the awareness by the patients that they were being monitored resulted in very high levels of adherence. Mean adherence was 99% (range 82–100%) for all patients and there was no significant difference between paediatric patients of 7–13 years of age with an adherence of 99% (range 87–100%) and the older patients (>13 years age) with an average adherence rate of 98% (range 82–100%). The adherence rate was comparable in all treatment cycles, independent of whether the patient was randomised to receive the investigational drug product within the first or the second treatment cycle.

The mean adherence rate in both studies with two prescribed daily inhalations over longer periods of six months and two years,

“The remote, automatic evaluation of therapy adherence and monitoring of lung function at home using the PARI devices is more convenient and more reliable than data collection from patient diaries.”

respectively, still averaged 76% (Studies 5 and 6). This level of adherence was achieved even though the therapy was for prophylaxis and did not result in any immediate relief of symptoms.

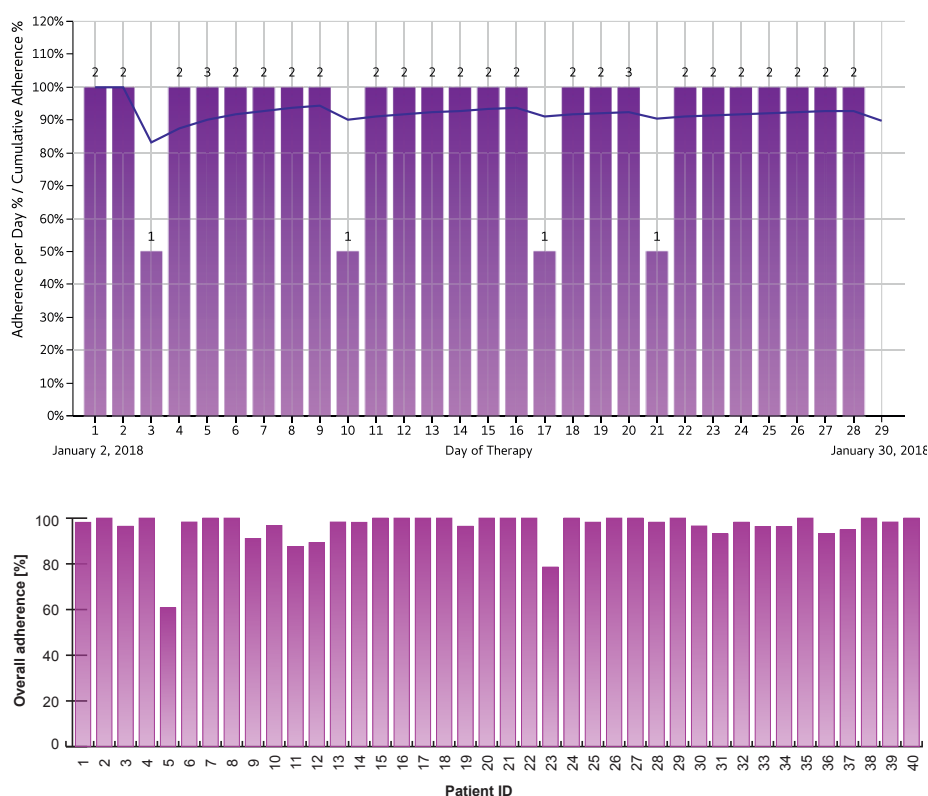
For clinical trials lasting from six months to two years, the adherence rate decreased over time as already observed by Griese.<sup>11</sup> In the first month of Study 6, average adherence was 78% and decreased to 71% for the last three months.

This study also enabled a comparison to be made between using an electronic nebuliser and counting drug vials to evaluate adherence. The average adherence for the electronic nebuliser was 76% measured objectively over the whole study period, whereas the adherence calculated from counting drug vials was 88%, which underscores the need for an objective method.

Figure 3 shows a graphical adherence report of one patient (upper graph) and an overview of adherence of all patients within Study 4 (lower graph). The first report shows daily adherence (purple bars) and cumulative adherence (blue line) over

Study	Indication (category of active component)	Intervention in case of non- adherence [yes/no]	Duration of study	Number of treatments per day	Number of patients*	Mean adherence (range) [%]
1	COPD (anti-inflammatory) <sup>9</sup>	yes	2 x 4 weeks	1	40	98 (82-100)
2	Undisclosed	yes	6 weeks	2	10	96 (64-100)
3	Cystic fibrosis (antibiotic) <sup>10</sup>	no	4 weeks	2	54	99 (82-100)
4	Undisclosed	yes**	4 weeks	2	40	96 (60-100)
5	Prevention of chronic transplant rejection by patients following lung transplantation (immunosuppressive drug)	yes**	2 years	2	120	76 (10-100)
6	Cystic fibrosis (anti-inflammatory) <sup>11</sup>	no	24 weeks	2	35	76 (20-100)

Table 1: Overview of clinical studies using eTrack® and PARIttrack® for adherence monitoring. \*Withdrawn patients were not considered for adherence calculation \*\*Intervention regarding adherence was only done at patients' visits in the clinic



**Figure 3:** Graphical display of adherence rates: adherence report of a single patient over a selected therapy period (top) and overview of adherence of all patients within Study 4 (bottom).

the selected period. Within this period the patient was fully adherent on most days. On four days the patient only administered one instead of two inhalations, resulting in an overall adherence in the displayed period of 90%. The second report shows that overall adherence of most patients in this study was above 95% and only very few had a considerably lower adherence rate. This may allow the investigator to select only the most adherent patients for the evaluation of drug efficacy and safety.

### ADDITIONAL MONITORING OF LUNG FUNCTION

PARItrack® was recently upgraded to also monitor lung function of patients

**Figure 4:** PARI's connected mobile home spirometer mySpirosense® Track.

with a Bluetooth-enabled mobile spirometer. This enables integration of the SpiroSense® spirometry solution from PARI GmbH into the digital platform by way of a new version called mySpirosense® Track (Figure 4).

The spirometer uses hot wire anemometry and does not require the patient to calibrate the device. It is developed for paediatric and adult patients and especially designed for use

in the home setting. Each home measurement provides lung function parameters and the entire flow-volume curve. All data is stored on the device and automatically transferred via Bluetooth to the 2net™ Hub and via cloud to the server corresponding to the setup in Figure 2. The remote availability of the flow-volume curve allows the physician to verify the validity of the breathing manoeuvre for each measurement, which is especially critical for home spirometry.

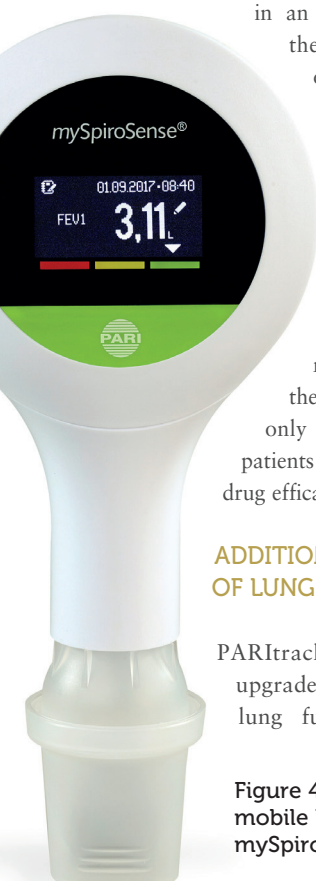
This new feature enables both therapy adherence and lung function to be monitored during any clinical studies based on the corresponding study protocol. eTrack® and mySpirosense® Track are both paired to the same hub and may be given to the patient at different time points depending on the individual treatment plan or individual study protocol. A graphical evaluation of adherence to therapy and lung function of a typical patient is shown in Figure 5.

The study personnel, investigators or physicians can interpret the combination of adherence and lung function easily on the basis of the displayed graphs.

For the spirometer data, study-specific notifications can also be implemented.

### SUMMARY

The remote, automatic evaluation of therapy adherence and monitoring of lung function at home using the PARI devices is more convenient and more reliable than data collection from patient diaries. In addition, remote monitoring allows for immediate intervention. The system can



**Figure 5:** PARItrack® enables remote monitoring of both lung function and adherence to therapy.

also be used in multi-centre studies; local site personnel can receive limited access to those patients just at their site, while investigators and personnel responsible for the overall study can analyse the overall patient group.

Site-specific adherence rates of all patients within one site in comparison to all sites can trigger site-specific training or customised notifications focused on non-adherent patients.

Monitoring both adherence and lung function are highly valuable for the interpretation of outcomes on clinical endpoints and may enhance the significance of efficacy and safety data, thus reducing the number of patients to be enrolled and the costs of the study. Linking potential side effects or adverse events to adherence may also help to identify potential correlations.

The monitoring feature offers the potential to trace the causes of observed treatment failure, which may, for example, be due to a lack of efficacy of a drug or non-adherence of a patient to the prescribed treatment regimen.

The high adherence rates achieved in the aforementioned trials demonstrate the utility and benefit of remote monitoring and immediate intervention to achieve good adherence and valuable results in a clinical trial.

## OUTLOOK

In future, the infrastructure of PARItack® may be extended with an app which will enable patients to access all their collected data and help them to improve adherence by using motivational reminders. The app could also be used to process questionnaires. For example, patient-reported outcome questionnaires are moving into the focus of clinical trials and could be controlled via an app linked to the web portal.<sup>12</sup>

Monitoring features of health status and adherence should be used in clinical trials and should then be transferred into patient-centred care management solutions for chronically ill patients. Improving adherence to long-term regimens requires:

- A combination of information about the disease and therapy
- Counselling about the importance of adherence and on how to organise the administration of medication
- Reminders about appointments and adherence
- Rewards and recognition for the patient's efforts to follow the regimen
- The enlisting of social support from family and friends.

Successful interventions for long-term regimens are all labour intensive, but can ultimately enhance outcomes and be cost-effective.<sup>13</sup>

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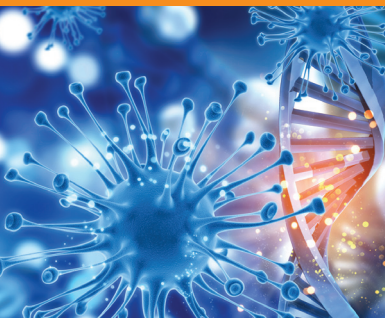
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## EXPANDING CONNECTIVITY: ADD-ONS FOR OPHTHALMIC AND NASAL DELIVERY

It's no secret that connectivity is the next big thing in drug delivery device design. In this article, Nemera introduces the company's latest offering in this space, the e-Novelia® and e-Advancia® add-ons for ophthalmic and nasal devices.

### INTRODUCTION

The drive towards connected healthcare has become a well-established facet of current drug delivery device development, the overwhelming potential benefits having led to an explosion of development projects aiming to create connected devices. The rationale behind this surging trend is by now equally well established, being based on the concurrent shift towards self-administration and advanced delivery systems, the booming biologics and specialty pharma sectors, and the enormous loss in revenue from patient non-adherence, estimated to have been US\$637 billion (£469 billion) in 2016 by Capgemini Consulting. These factors all feed into one another and, in turn, into connected devices.

Another factor is the excitement around connectivity is how readily the groundwork is laying itself. Smartphones are already widely used in Europe and the US, to the point of feeling ubiquitous in some

areas, and worldwide penetration is heading towards 50%. The wellbeing market, being far less stringently regulated than healthcare and thus having a head start experimenting with connectivity, shows that a significant portion of the population are more than willing to integrate apps and devices, Fitbit being a noteworthy example, into their daily lives. Harnessing this appetite for technology to serve the goals of healthcare would be an enormous boon to the industry.

The advantages that electronics and connectivity can provide at the device level, especially for self-administration, are well trod ground. In summary the major points are:

- Better communication with the user via electronic instructions for use (IFU), dedicated smartphone app, digital reminders, etc.
- Feedback on use technique/training.
- Data harvesting to enable analysis by patients, pharma and healthcare professionals.

Generally speaking, there are two methods of approach for developing connected devices: integration and add-ons. Both routes have their distinct advantages and disadvantages, with examples of both being widespread in development projects throughout the industry, primarily in the injection and pulmonary spaces. At present, Nemera has projects pursuing both approaches. This article will focus on Nemera's add-on

"Utilising an eyedropper successfully and accurately is somewhat difficult. There are common problems that an electronic smart device is uniquely positioned to tackle, including accurate targeting of the eyedropper. The standard Novelia goes some way to solving this with its signature blue dot, but with digital enhancement the e-Novelia can go the whole way."

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Figure 1: e-Novelia®, connected add-on for ophthalmic delivery.

technology for the Novelia® multidose eyedropper (see *ONdrugDelivery Magazine*, Issue 82 (Jan 2018), pp 16–20), and the Advancia® nasal spray (see *ONdrugDelivery Magazine*, Issue 85 (Apr 2018), pp 4–8).

## NEMERA'S CONNECTED OPTHALMIC & NASAL ADD-ONS

### e-Novelia®

Utilising a multi-skilled team across mechanical, electronic and software development, Nemera has developed e-Novelia® (Figure 1), a smart add-on device for the established Novelia eyedropper. The rechargeable and reusable e-Novelia boasts several advanced features:

- Sensors, including shaking, tilt, actuation, temperature and drop detection
- User interface, including a screen and buzzer/vibrator
- Mechanical improvements, including an ergonomic nozzle and bottle squeezing aid
- Drug identification using near-field communication (NFC)
- Connectivity via Bluetooth and smartphone.

e-Novelia was developed with issues and challenges specific to ophthalmic delivery in mind. Whilst seemingly simple, actually utilising an eyedropper successfully and accurately is somewhat difficult. There are common problems that an electronic smart device is uniquely positioned to tackle, including accurate targeting of the eyedropper. The standard Novelia goes some way to solving this with its signature blue dot, but with digital enhancement the e-Novelia can go the whole way, using sensors to detect when the inclination of the device is correct and signalling this to the user via a green light. The e-Novelia also provides a visual stimulus during

“e-Advancia features the full suite of features: reminders, shaking sensors, digital display, dose counter, posology indication, buzzer/vibrator, reminders and connected app.”

application to assist the user in keeping the eye open and digital readouts give feedback on the dose delivered and amount of medication remaining.

That being said, the greatest advantage of the e-Novelia, as expected of a connected device, is its ability to communicate with a smartphone app. This ability enables a slew of further features, including adherence monitoring, dosage history, digital tutorials, medication reminders and social network integration. The app also provides a more user-friendly interface for e-Novelia's readouts, such as dosage detection, battery life, eyedropper shelf-life/expiry and remaining volume. Finally, smartphone connectivity enables a “Find My Device” feature to help find e-Novelia when it has been misplaced.

### e-Advancia®

Using Nemera's wealth of development and innovation knowledge, Nemera's high performance nasal pump, Advancia, has also received an electronic add-on. As with e-Novelia, e-Advancia® (Figure 2) is a reusable, rechargeable add-on device for an already established product. e-Advancia also features the full suite of features: reminders, shaking sensors, digital display, dose counter, posology indication, buzzer/vibrator, reminders and connected app.

## CONCLUSION

Nemera has brought its extensive experience and know-how to bear in the field of connectivity, developing connected add-



Figure 2: e-Advancia®, connected add-on for nasal delivery.

ons for its Novelia and Advancia drug delivery platforms. The ophthalmic and nasal delivery routes rarely receive the same attention in the connectivity world as the pulmonary and subcutaneous, and these devices rise to meet that unmet need.

To make them the most attractive possible offering, e-Novelia and e-Advancia feature off-the-shelf technological bricks (sensors, motors, wireless, etc), patient integration during the development process, GMP for electronic manufacturing and regulatory support.

## ABOUT THE COMPANY

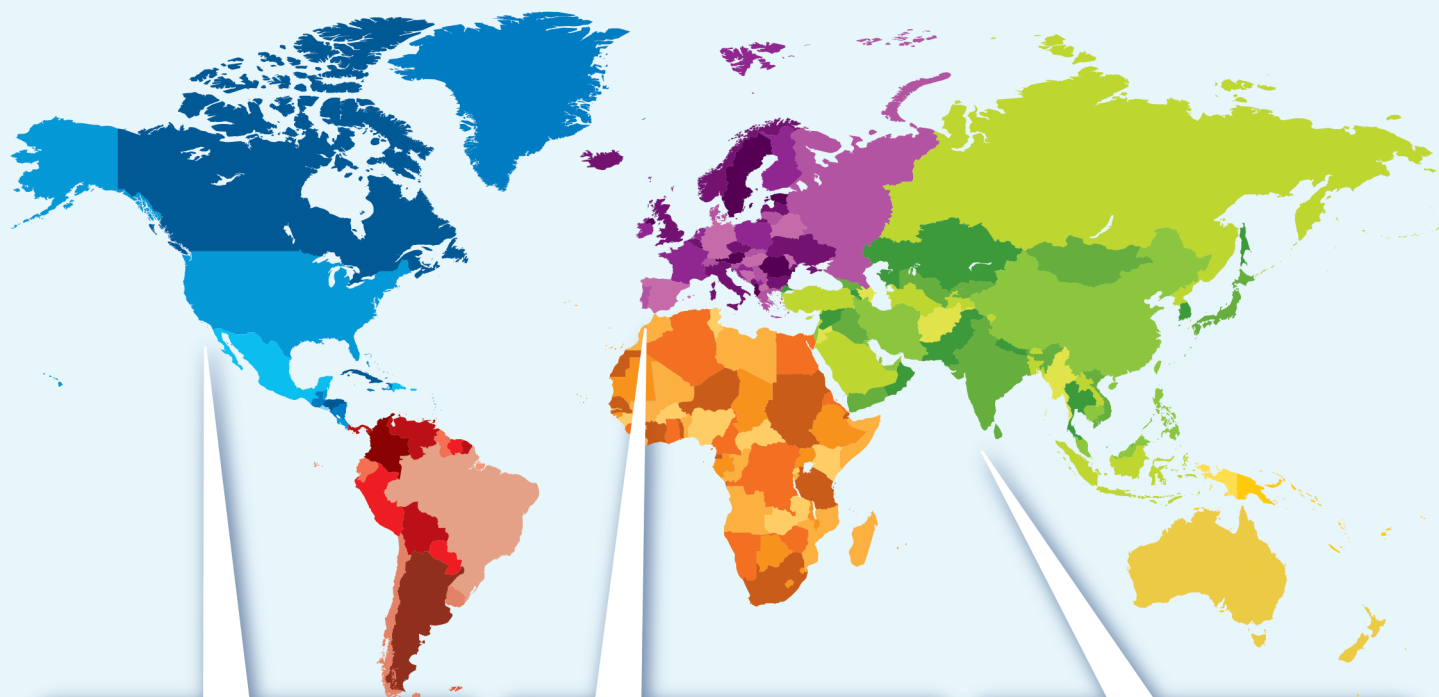
Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology & generics industries. Nemera's services and products cover several key delivery routes:

- Parenteral (autoinjectors, pens, safety devices & implanters)
- Ophthalmic (multi-dose, preservative-free eyedroppers)
- Nasal, buccal, auricular (pumps, valves and actuators for sprays)
- Inhalation (pMDIs, DPIs)
- Dermal and transdermal (airless & atmospheric dispensers).

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development, and contract manufacturing.



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# 5 THINGS TO CONSIDER WHEN MANUFACTURING CONNECTED DRUG DELIVERY DEVICES

The estimated number of connected drug delivery devices continues to increase and the impact of this trend could be significant, explains Phillips-Medisize



While digital connectivity or connected health can improve the coordination and delivery of patient care, original equipment managers need to keep these five things in mind when creating connected drug delivery devices:

- 1 Development strategy and design consideration**
- 2 Situation analysis and patient compliance**
- 3 Connectivity ecosystem**
- 4 Wireless subsystem**
- 5 Security of device and information**

As the Internet of Things continues to become an integral part of people's lives, the opportunity to use it within drug delivery device applications remains promising. The manufacturers and device designers must identify, investigate and overcome these challenges so that the implementation of wireless and other related smart technologies can be achieved. When done successfully, connected systems enable the patient and caregivers to have a 360° view of both the patient and the disease – not only to manage adherence, but to improve results by understanding the effect of the regimen.