

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 alone¹).
- **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 annually²).

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.

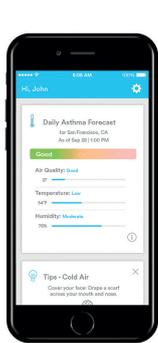
“Devices which have connectivity built into them from the beginning can make significant changes in user interaction. The design being built-in also allows for more substantial changes to the device, such as advanced features and sensing options.”



Tom Oakley
Director of Drug Delivery Device Development
E: tom.oakley@springboard.pro

Springboard
St. John's Innovation Centre
Cowley Road
Cambridge
United Kingdom

www.springboard.pro



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. (Copyright © Cohero Health, Inc. Used with permission.)

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,³ but is also upgrading the Breezhaler to the cloudhaler and adding built-in connectivity by working with Qualcomm Life (San Diego, CA, US).^{4,5}

H&T Presspart (Blackburn, UK) is working with Cohero to upgrade standard metered dose inhaler actuators with connectivity.⁶ 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 (Louveciennes, France) is partnering with Propeller to develop a new connected metered dose inhaler.⁷

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 $P < 0.05$).⁸

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.⁸

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

- 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 2012,¹⁰ and RebiSmart for multiple sclerosis, which was launched in 2007 and gained connectivity in 2011. They use the easypod Connect¹¹ and MSdialog¹² 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 use¹³ and reduced hospitalisations and emergency room visits.¹⁴ Adherium claims similar clinical evidence.¹⁵

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”.¹⁶

- An autoinjector patient preference survey found that 82% of BetaConnect patients were “highly satisfied” compared to 67% of RebiSmart and 60% of ExtaviPro patients.¹⁷ 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).¹⁸

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”¹⁹, Medicom 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 heterogenous 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.⁹
- 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.²⁰

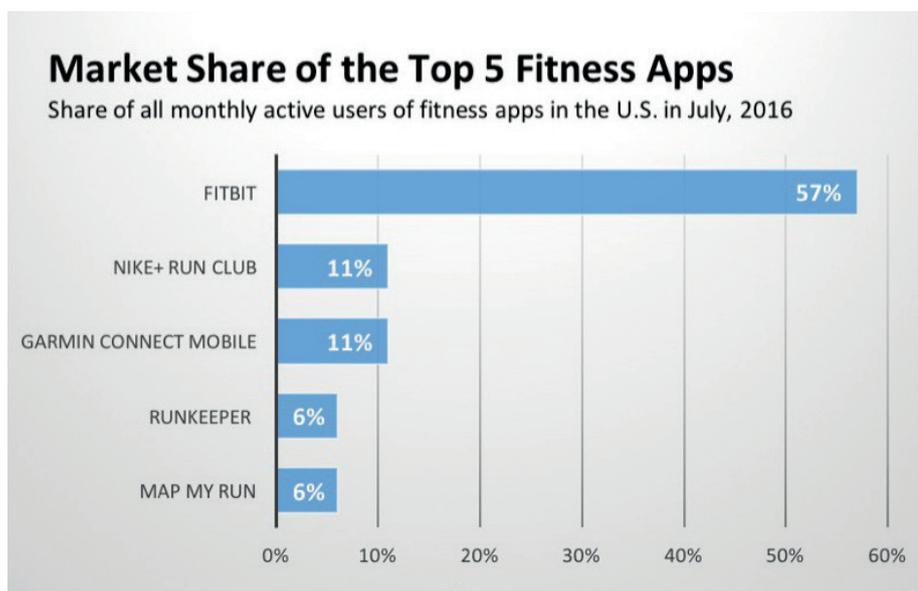


Figure 4: Week-to-week user retention for health-related apps. (SurveyMonkey)

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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ABOUT THE AUTHOR

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.