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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.

EDITORIAL CALENDAR

Jan 2020	Ophthalmic Drug Delivery
Feb	Prefilled Syringes & Injection Devices
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Nov	Pulmonary & Nasal Drug Delivery
Dec	Connecting Drug Delivery

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

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

MAILING ADDRESS:
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THE CURRENT STATE OF PLAY IN CONNECTED DEVICES

The discussion around connectivity in drug delivery devices has been ongoing for some time now. And still, despite all the compelling evidence, we have yet to see any large-scale commercial launches for connected devices. In this article, Marcus Bates, Director, External Partners Connected Devices; Joachim Koerner, Director, eDevice R&D; and Jerôme Praquin, Director, Connected Devices, all of Aptar Pharma, discuss the current state of play, what connected device advocates are doing to enable faster implementation, and how we can optimise connected technology while reducing the cost and improving human factors.

The initial focus for deploying connected devices was to improve adherence to prescribed drug dosing regimens. Some 60% of patients fail to take their medication properly – resulting in a significant impact on health outcomes and total healthcare spend. While this remains a focus and a growth area for connected devices in combination with digital platform solutions, adjacent benefit platforms have started to gain traction.

On-device training and diagnostic tools, remote patient monitoring, proximity alerts and emergency calls for rescue medications, electronic lock-out for scheduled drugs and heat mapping for public health initiatives, amongst others, are all gaining prominence. The bottom line is that a connected device can truly be a smart companion to improve outcomes for patients in terms of health, well-being and quality of life (Figure 1).

AN EVOLUTION IN CONNECTED DEVICES

When the concept of a digital health ecosystem was first introduced, along with the advent of connected devices, it was widely believed that implementation would be relatively rapid given the benefits to the entire supply chain – from patients to pharmaceutical companies, insurance companies, hospitals and care providers. It was envisioned that we would have a homogeneous, feature-rich, fully integrated connected device, capturing all the relevant data and transmitting it to the right stakeholders with all the associated data analytics and insights, creating a seamless patient experience.

While this continues to be the ultimate goal, there have been several challenges. Evolving regulation relating to connected devices and digital health, a perception of increased costs, sustainability, slower than expected physician and payer buy-in, a lack of sufficient real-world evidence and a not-quite-so-seamless patient experience have all slowed progress. This has resulted in a somewhat fragmented approach to

"When the concept of a digital health ecosystem was first introduced, along with the advent of connected devices, it was widely believed that implementation would be relatively rapid given the benefits to the entire supply chain."

Marcus Bates
Director, External Partners
Connected Devices
T: +44 7824 306 913
E: marcus.bates@aptar.com

Aptar Pharma
Cygna House, Opal Drive
Fox Milne
Milton Keynes, MK15 0DF
United Kingdom

Joachim Koerner
Director, eDevice R&D
Prescription Division

Aptar Pharma
Oeschlestrasse 54-56
78315 Radolfzell
Germany

Jerôme Praquin
Director, Connected Devices

Aptar Pharma
36-38 rue de la Princesse
78431 Louveciennes
France

pharma.aptar.com

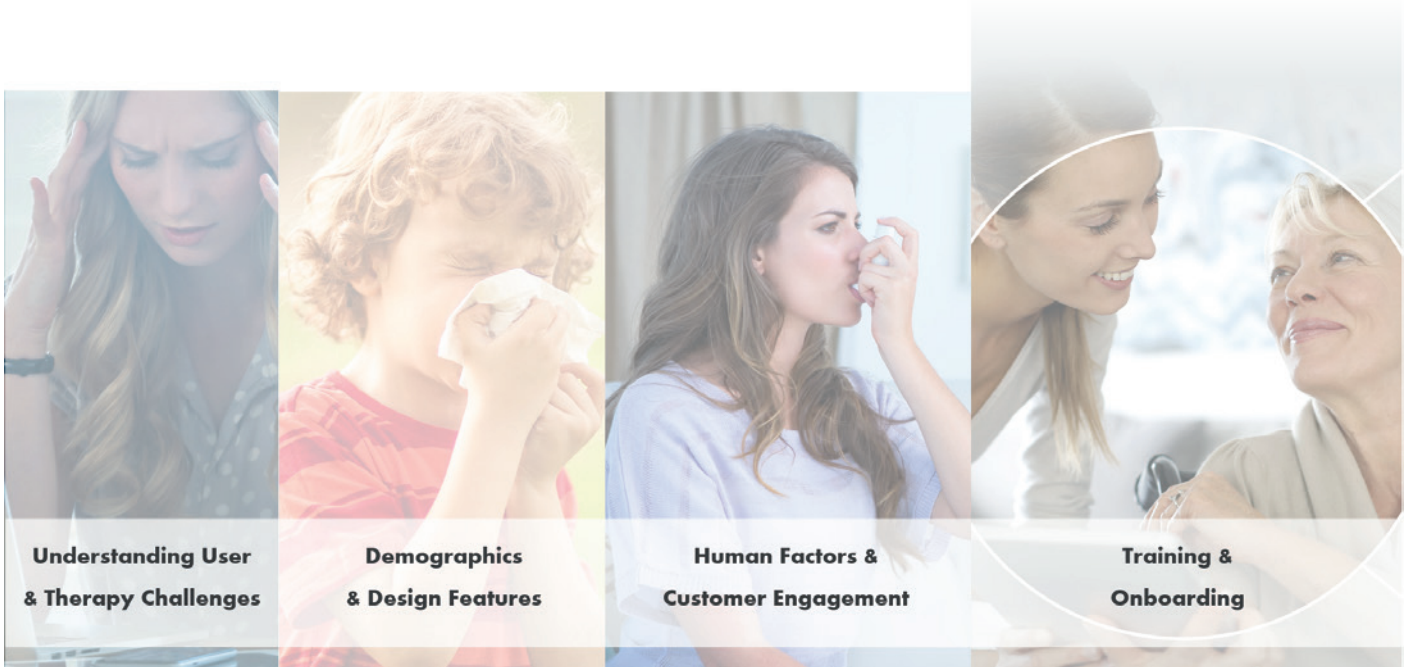

Figure 1: User-centric device design.

development and deployment of connected devices. But it isn't necessarily all bad news. It essentially means there is now choice beyond the single ubiquitous device, providing options that can be assessed in the context of the drug and the therapy.

CHOOSE THE LEVEL OF COMPLEXITY YOU NEED

For initial product introduction and collection of real-world data, add-on devices have been preferred for several clinical studies – and for commercial launch, in some cases. Add-on devices do bring with them some clear benefits for pharma partners. By using US 510(k) or EU CE clearance, add-on devices offer a faster pathway to regulatory approval compared with drug-device combination product approval. And as the cost of the device can be amortised over multiple uses, the total acquisition cost can be lowered. But although add-on devices can be designed to be feature rich and easy to use, they still require the patient to take a few additional steps before administering the drug, thus increasing the number of steps in the patient workflow. This change to the workflow needs appropriate training and onboarding to ensure it creates an engaging experience for the patient.

The challenge with patient workflow and the number of patient interaction steps for add-on devices can be addressed with an integrated connected device. From a pharma perspective, being integrated into an existing device would also offer some potential options to extend and/or protect intellectual property rights. However, these benefits must be viewed in the context that these devices are really only suitable in a single use/single product setting, thus increasing the total cost of ownership while lowering the burden for the patient and thus potentially increasing the acceptance level.

A potential compromise could be a reusable integrated device that offers the workflow and interaction benefits of a fully integrated device, while providing a sustainable solution that is reusable and therefore better value over life. The downside could be slightly more complex

development programmes, which would add upfront time and cost.

As connected devices evolve into smart companion tools, they are enabling additional diagnostic capabilities through a variety of sensors and algorithms (on-device and on the software platform). For example, flow sensor and microphone data during inhalation can be used as a surrogate measure to assess if there is a deterioration in lung function. While not immediately replacing existing standards for diagnosis, they provide another data point for patients and help them to better manage their health. Now, not only can devices capture patient data, they can also act as a training and diagnostic tool. This patient-centric training brings benefits to the patient – they feel more in control of their regimen – and it also delivers benefits to healthcare systems, for example, clinical staff can focus on priorities other than patient training.

As each of the device connectivity options (summarised in Figure 2) offers a different value proposition – based on the customer, stakeholder and region – Aptar Pharma has developed a portfolio of products that offers variations on these options. For example, integrated connected metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs), add-on devices for MDIs, add-on devices with flow sensors for MDIs, and integrated add-on breath-actuated inhalers (Figure 3). Each of these devices has a role to play, depending on factors such as where you are in the world. For example, in more price-sensitive markets in Asia, add-on devices have been a great way to create market engagement and gather real-world data to support broader adoption. In the US and EU, add-on devices have played a significant role in creating market awareness and now some are being transitioned to an integrated connected device.

REDUCING COST, INCREASING ACCEPTANCE AND ACCELERATING IMPLEMENTATION

Aptar Pharma employs a single platform for most of its devices, which means reduced time-to-market and lower development costs. Leveraging the power of our experience across three industry segments in which we

Figure 2: Aptar's portfolio of connected devices.

Figure 3: The changing landscape of connected device options.

"We need to focus on the key functional requirements and make the device as intuitive as possible."

operate – pharma, beauty and home, and food and beverage – we have established strong relationships with frontrunners in micro-electronics, giving us access to their R&D road maps for microprocessors and sensors, as well as competitive pricing. This exposure enables us to use the most optimum solutions, while ensuring security of supply. This commitment to partnership and shared learning between our business segments enables us to maximise cross-business developments such as our mobile application standard development kit (SDK) and device embedded software.

HUMAN FACTORS NEED TO BE AT THE CORE OF WHAT WE DO

Whatever the therapy or device, the value must be real, and this can only be realised by seeing an improvement in patient health outcomes that leads directly to a reduction in outpatient care or inpatient treatments. We need to focus on the key functional requirements and make the device as intuitive as possible. Knowing that the patient demographic is very different from one disease to another, and recognising that every patient will have different expectations and capabilities around technology, means that human factors are critical in connected device design. Patients do not want the time to take medication to be longer or more onerous than it already is.

An example of an early-stage patient-centric approach is the AdhereIT platform (Figure 4) from Noble, an Aptar Pharma company, which is created specifically for use during the training and onboarding phase to gather detailed information before patients begin self-injecting with the real drug delivery device. This creates increased value for both patients and pharma by going beyond data gathering – such as whether or not a patient injected – to also providing insights such as whether the self-injection was a "wet injection" or whether it was performed correctly. Using this more accurate data helps pharma partners implement solutions to improve patient adherence. Connected devices help bridge the gap between these critical upfront periods in the patient treatment process. Without accurate data collected by connected devices such as AdhereIT, pharma partners rely heavily on self-reported patient data, which is often less accurate.

Figure 4:
The AdhereIT platform from Noble, an Aptar Pharma company.

CONCLUSION

Today, patient adherence is at an unacceptably low level. With a greater proportion of the population suffering from chronic diseases such as asthma and chronic obstructive pulmonary disease (COPD) it therefore stands to reason that the number of people failing to follow their prescribed regimen will increase. Here technology really can support a significant shift in patient outcomes. As with all innovation, price is often the main barrier to early adoption. However, as with all innovation, technology is evolving, expertise is burgeoning, adoption is growing and costs are decreasing. Just look at the wearable market, where the number of connected wearable devices worldwide is expected to jump from 526 million in 2016 to more than 1.1 billion in 2022.

Aptar Pharma has developed a portfolio of connected devices that spans every delivery route from injectables to nasal to ophthalmics. With connectivity and digital health gaining further traction with all the key stakeholders – patients, pharma, payers and care providers – accelerated mass adoption of these solutions is set to happen soon.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across a wide range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma services provide early-stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, Aptar Pharma is developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 GMP sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc. (NYSE: ATR).

ABOUT THE AUTHORS

Marcus Bates is Director, External Partners Connected Devices at Aptar Pharma and has spent nearly 20 years working in the world of drug delivery devices and connected health. He has worked for two industry-leading organisations in a range of roles and is currently responsible for the implementation of the supply chain for the connected devices business at Aptar Pharma as well as leading business development activities in Europe.

Joachim Koerner is Director, eDevice R&D, Prescription Division at Aptar Pharma and has spent more than 25 years in highly regulated industries, including space technology. Working predominantly in the medical device industry across several R&D positions, he led the team that achieved the first EMA approval for an electronic lockout system. He is currently responsible for early-phase electronic device R&D worldwide.

Jerôme Praquin is Director, Connected Devices at Aptar Pharma, specialising in helping companies transition into the digital world by deploying process and building teams in cross-cultural and multi-functional environments. With more than 10 years' experience in innovation, electronics, materials and engineering, he has a proven track record of successful new product launches in connected consumer electronics. He handles programmes ranging from new product introduction to mass production.

Building a Connected Devices Eco-System for Digital Medicines

As Pharmaceutical companies around the world look to address the challenges of non-adherence to improve patient health outcomes, they turn to Aptar Pharma.

Today, we are leveraging decades of manufacturing excellence and proven device design to offer the widest portfolio of connected solutions and diagnostic tools across all our delivery routes. Complemented by our partnerships with leading digital healthcare platforms and key stakeholders in healthcare delivery models, we are building a connected device eco-system for digital medicines.

To see how you can move towards a connected future, contact with **Sai Shankar**, Vice President, Global Digital Healthcare Systems, at Aptar Pharma on **+1 847 800 6058** or email **sai.shankar@aptar.com**

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Aptar pharma

ON drugDELIVERY

2020 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January 2020	Ophthalmic Drug Delivery	Extended to Dec 31, 2019
February 2020	Prefilled Syringes & Injection Devices	Extended to Jan 13, 2020
April 2020	Pulmonary & Nasal Drug Delivery	Mar 5, 2020
May 2020	Injectable Drug Delivery: Formulations & Devices	Apr 2, 2020
June 2020	Connecting Drug Delivery	May 7, 2020
July 2020	Novel Oral Delivery Systems	Jun 4, 2020
August 2020	Industrialising Drug Delivery	Jul 2, 2020
September 2020	Wearable Injectors	Aug 6, 2020
October 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
November 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
December 2020	Connecting Drug Delivery	Nov 5, 2020

CHOOSING THE RIGHT CONNECTIVITY FOR DRUG DELIVERY AND MEDICAL PRODUCTS

In this article, Juan Nogueira, PhD, Senior Director, Wireless and Connectivity Center of Excellence; Tommaso Borghi, PhD, Senior Director, Design; and Marco Vergani, PhD, Senior Engineer, Hardware Development, all of Flex, discuss the factors that need to be taken into account in the selection of connectivity technology for a drug delivery device or other medical product.

In the world of drug delivery – and other monitoring and personal medical products – there are "before and after iPhone" eras. Such medical devices used to have limited capabilities to interact with the user – such as basic LCD displays and push buttons, small memory to store the collected data, unfriendly user interfaces and no link or communication between the device and the user. The user had to rely on paper-based log sheets to note the device readings (e.g. glucose levels) and decide what action to take on their own (e.g. insulin injections). Using these error-prone and punctuated data recording methods, it was difficult to find patterns, and doctors had to spend added time with patients to review sparse (e.g. lack of measurement time information) and incomplete data.

> "The number and feature sets of connectivity technologies have grown to such a level that the selection of the most appropriate one is a critical decision that will define the connectivity function and the product user experience."

The introduction of the iPhone and subsequent spread of smartphones as the personal data and communication device – in parallel with the maturity of new low-power and inexpensive short-range communication technologies – has changed that landscape completely. The smartphone was not only able to provide a new colourful and interactive user interface and a communication link between the device and the user, it could also store many device data measurements sets, with the corresponding time stamps (i.e. complete data sets), and share that data with the doctor. Furthermore, that data collection could be uploaded to a database to be analysed with computer-assisted algorithms to extract data patterns and sequence relationships.

In this sense, smartphones have been used as a communication gateway between the medical device and the data backend. Bluetooth has been the dominant technology to enable connection between the smartphone and the personal medical device, and cellular communication for the link to the database. Today, these databases have evolved to become the cloud, where data is not only stored but also processed and analysed using advanced and complex algorithms.

This allows us to move all or part of the data processing to the cloud but has a resultant impact on the required data link capacity. The more that processing is done in the cloud versus the device, the higher the requirements for that data communications link. This trade-off can today be well balanced as small microcontrollers that are part of every Internet of Things (IoT) device can run algorithms that would formerly have needed high computer processing power.

The number and feature sets of connectivity technologies have grown to such a level that the selection of the most appropriate one is a critical decision that will define the connectivity function and the product user experience. Some of these new technologies, including low-power wide-area networks (LPWANs), will enable the elimination of the smartphone interface. Further to that, the future availability of 5G and its advanced wireless technologies that provide low latency and ultra-high reliability will enable new levels of personal medical devices not viable today.

Dr Juan Nogueira
Senior Director, Wireless and Connectivity Center of Excellence
T: +49 171 720 0243
E: juan.nogueiranine@flex.com

Dr Tommaso Borghi
Senior Director, Design
T: +39 02 8732 9273
E: tommaso.borghi@flex.com

Dr Marco Vergani
Senior Engineer, Hardware Development
T: +39 02 8732 9207
E: marco.vergani@flex.com

Flex
6201 America Center Drive
San Jose
CA 95136
United States

www.flex.com/health

Technology	Use Case	Cost	Range	Bit Rate	Power	Comments
NFC/RFID	Medical adherence	Low (tag) High (receiver)	cm	100s of kbps	0 (tags) 100s mA (receiver)	Requires direct patient involvement to initiate the communication. Needs app/smartphone to connect with the cloud.
BLE	Medical adherence, wearables	Low	m	100s of kbps	5-10 mA	Needs app/smartphone to connect with the cloud
Wi-Fi	Home monitoring, telemedicine, hospital equipment	Low	10s of m	10s of Mbps	10s mA	Needs modem/router to connect with the cloud
Zigbee	Home monitoring, telemedicine, hospital equipment	Low	Up to 10s of m or more in meshed networks	100s of kbps	~10 mA	Needs hub to connect with the cloud. Requires direct patient involvement to setup the ZigBee network.
LPWAN - Unlicensed **LoRa SigFox**	Elderly care, monitoring open/close events with no real-time requirements	Low	10s of km	100 bps to 10s Kbps	10-30 mA	Direct access to cloud, no need for patient interaction to initiate the communication. Possible wide coverage by areas.
LPWAN - Licensed **NB IoT LTE-CatM**	Real-time applications, elderly care, emergency management, open/close events	Medium	10s of km	100 bps to 1 Mbps	~200 mA	Direct access to cloud, no need for patient interaction to initiate the communication. Future global coverage expected
5G	Real-time applications	High	10s of km	100 Mbs to 1 Gbps	100s mA	Can provide bidirectional communication with ultra-low latency and high data rate. Enables applications with real- time user feedback

Table 1: A summary of connectivity options with examples of medical use cases.

CONNECTIVITY TECHNOLOGIES LANDSCAPE

The various connectivity technologies can be classified using different performance parameters that can be inherent to the technology itself – like range, data rate or power consumption. Or they can be classified by implementation attributes like cost, size, etc. Table 1 summarises these connectivity options with some examples of typical medical use cases.

The value range of these parameters may also determine if one connectivity solution is suitable for a specific medical device. Figure 1 shows classification of various devices based on the range and latency parameters. But there are more parameters that need to be considered to make the most appropriate selection.

A very broad spectrum of devices, for instance, needs to be considered for the drug delivery market – ranging from drug monitoring devices (miniaturised devices often powered by primary coin cell batteries) to autoinjectors (bigger devices with motors and rechargeable batteries). Given that the requirements and constraints of different devices vary significantly, there is no one perfect solution. But understanding the trade-off relationship where the improvement of one parameter comes at the cost of another (i.e. range versus power consumption) allows confident and informed decision making.

In the following section we explore some questions that may help in selecting the most appropriate connectivity solution from several points of view – technical, user interface, cost, etc.

"Given that the requirements and constraints of different devices vary significantly, there is no one perfect solution."

HOW TO SELECT

The way the device is going to communicate and interact with the user (or patient) and caregiver, the device size, the available power, the amount of data to be transmitted, the market region in which the device is

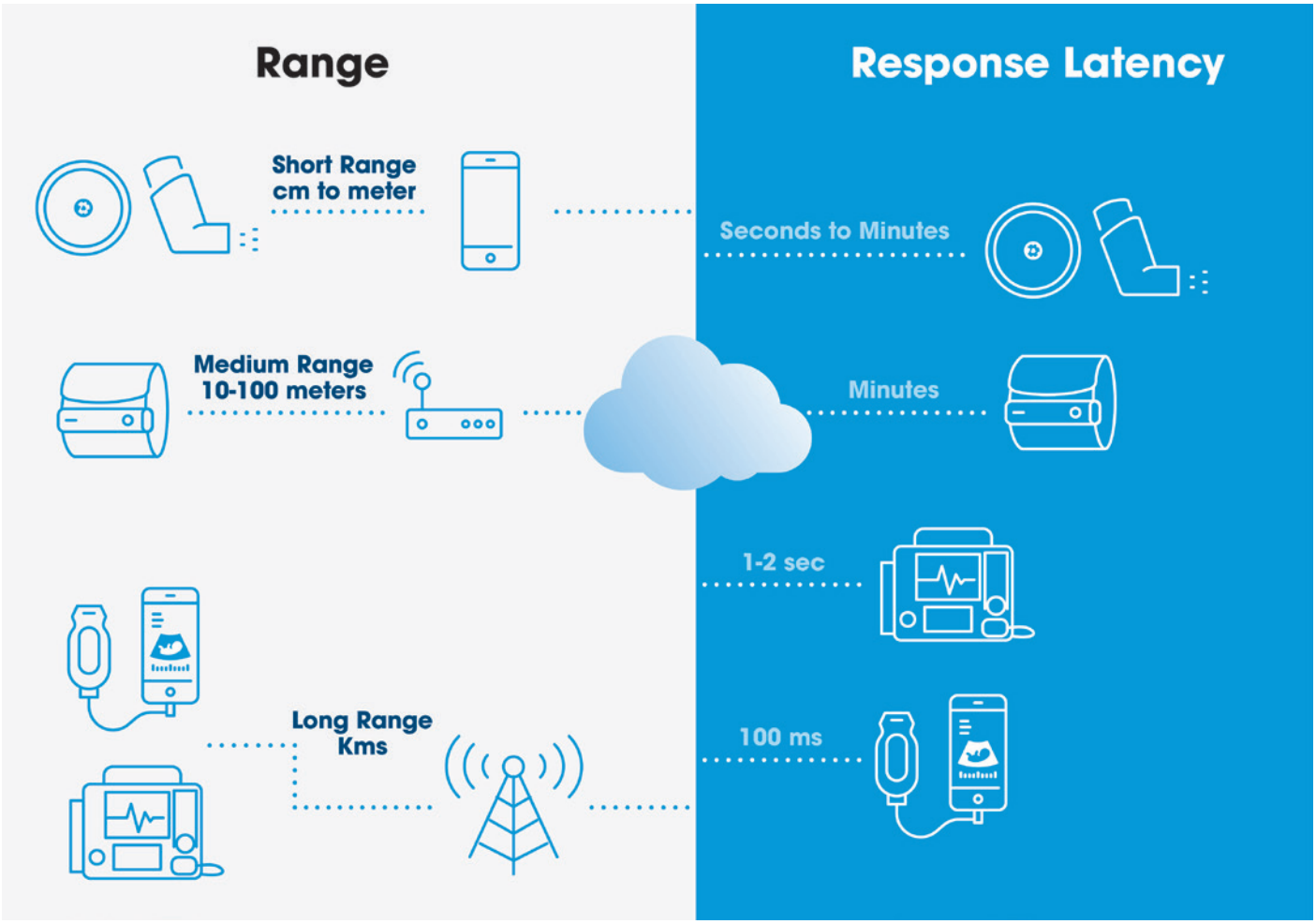

Figure 1: Example of device classifications based on range and latency.

> "The complexity of setting up and managing the communications can be a decision point."

going to be used and the need for real-time feedback will each have a direct impact on the selection of connectivity technology. Also, the complexity of setting up and managing the communications can be a decision point – older patients, for example, may have difficulties or lack of knowledge in how to pair a device with a smartphone, or how to access Wi-Fi networks in different locations.

The following are some of the questions a drug delivery device maker can ask to help guide decision making:

Data reader

What type of reader is needed? Is the end user's smartphone part of the ecosystem?

The early days of connected medical devices were dominated by custom protocols and readers. Part of the reason was the requirement for highly reliable channels that were not available on smartphones at that time – but also the complexity of the validation process of a non-medical device in the loop. But the market is adapting very quickly to the latest trends and, along with it, there is a more open attitude from regulators.

Several players have adopted this approach and created smartphone-based apps as the solution to interact with their devices. In this case, the smartphone will be used as a simple gateway that moves data from the device to the cloud by using a short-range communication technology like Bluetooth Low Energy (BLE) or near-field communication (NFC). But even this selection, which appears simple and straightforward, carries some caveats. For example, selecting NFC allows for a very low-power-consumption device profile and has very low cost but it would require user interaction to read the data, which will affect the user experience. Furthermore, NFC is not present in all smartphones.

Data

What type of data is generated and what type of data will be transmitted?

Every application has specific needs. For example, a wearable ECG monitor requires continuous and real-time streaming of data with a throughput of tens of kB/s, while an autoinjector only demands hundreds of bytes transmitted per day.

Power

What is the peak current that is required by the connectivity solution?

Small devices based on coin cells may not be properly driven at low temperature, where the battery cannot provide the peak pulses needed for some RF communication technologies. Cost and size of the device might increase due to extra storage or capacitors. Also, the required peak current may disqualify the use of long-range technologies with some coin cell operated devices. On the other hand, devices with rechargeable batteries and use cases where frequent recharge of the device is acceptable will enable the use of power-hungry technologies.

RF performance

How fast will the energy stored in the battery be consumed? Will the connectivity functionality demand peaks of high current to transmit data? Is the device intended to be connected while in use? Are there batteries or metal shields in the proximity of the RF block?

It is recommended that a detailed power and energy budget analysis is performed, based on an accurate definition of the device use cases, and evaluated over the device operating temperature range. Consider maximum transmission power, lack of network coverage if applicable (cellular network-reconnect takes time and is a power-hungry process) and retransmissions as worst-case scenarios. Special attention must be applied in devices that are handled, gripped by a hand or carried in a pocket, near the body or where metals are nearby. The antenna can be detuned and the RF link performance heavily reduced. RF simulations are suggested, evaluating different antenna positions.

User experience

How is the device going to be used? What is the patient's role in communicating? When will data be transmitted?

A very common dilemma in the industry is whether to involve patients in the communication process between the device and the reader or make the transmission transparent and seamless to their eyes. There are pros and cons for each solution.

Maintenance

Is a firmware update over the air required?

Connectivity technologies with low-data-rate solutions may not be supporting this function. Case-by-case evaluation is needed. For safety purposes, it is recommended to keep the previous firmware image of the code available until the new one is fully validated – at the cost of space because a bigger flash memory is required for storage.

"A very common dilemma in the industry is whether to involve patients in the communication process between the device and the reader or make the transmission transparent and seamless to their eyes."

Connectivity costs

Does the price to the user include the cost of ongoing connectivity?

Does the cost of connectivity fit into the target total cost of the device? Will recurrent connectivity costs associated with the device be accepted? Cellular connections may have a monthly fee, whereas connectivity via BLE or Wi-Fi are no-cost options adding no repeated cost to the user.

Security

What is the level of security and data protection required?

Does the connectivity standard being used provide methods to guarantee the level of security, authentication and data protection required? Is this true for all targeted geographies?

Mechanics

What are the mechanical constraints when it comes to fitting connectivity into the existing device?

Smart connected devices are often the result of retrofitting electronics into devices that were not designed to include extra components like PCBs, batteries and antennae. Much time is often spent in the design of custom solutions to cope with the tight mechanical constraints set by the legacy product.

Product cost

What is the budget available to add connectivity to a medical device? Is an application-specific integrated circuit (ASIC) the way to go?

While connectivity is a clear trend in this market, there is still little literature around the added value of these devices in specific use cases. Pharma companies must still prove the added value of connectivity to drive price and reimbursement increases. For this reason, pressure remains high to minimise extra costs associated with these types of devices and significant effort is spent on aggressive cost optimisation, especially where the unit volumes can be very high – e.g. disposables (Figure 2). A BLE chip might represent a major share of the costed bill of material.

Regulation

In what environment is the device meant to be used (hospital, home, indoor, outdoor)?

It is mandatory to consider all regulatory constraints and guidelines to design a properly connected device. The main driver is the quality of connection service that must be guaranteed in accordance with the risk profile of the application.

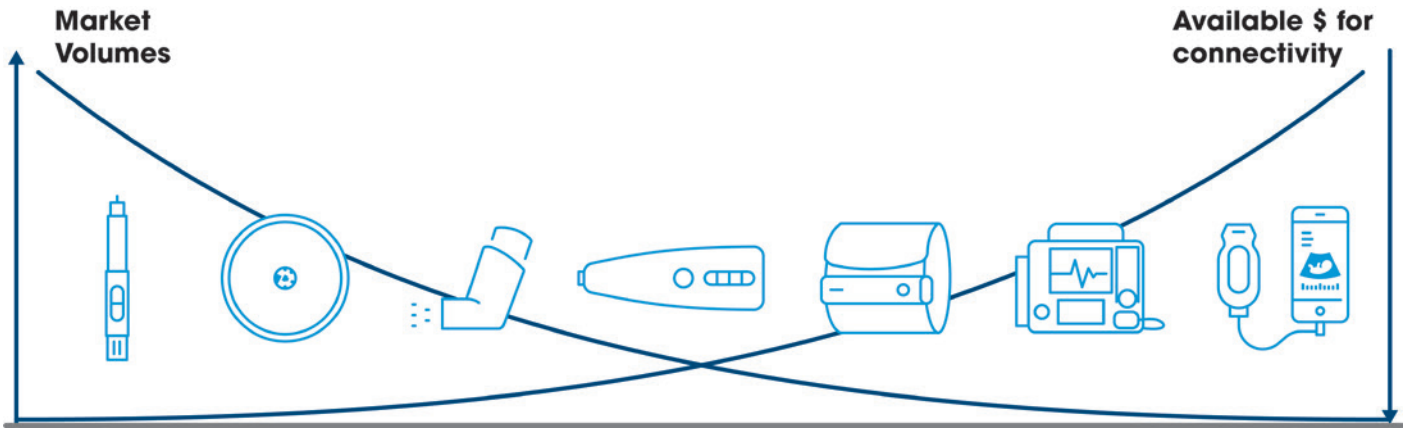

Figure 2: Budget available for connectivity versus the market volume.

Latency

Does the device require real-time and low-latency communication with the cloud while it is being used?

5G technology is going to enable new handheld medical devices which are today limited to trained professionals because of the usage complexity. Some assistance and usage feedback must be provided in real time so that the user is able to take the measurements in a proper way. A handheld ultrasound device is an example of this type of device (Figure 1).

A CONSEQUENTIAL DECISION

The selection of connectivity technology can have a dramatic impact on the performance and usability of a device. The range of options continues to grow as new technologies are developed and mature. A clear and deep understanding of the technology performance and characteristics is an essential element in the successful design of a device that fulfils all aspects of its intended performance.

First and foremost, drug delivery and medical devices are intended to deliver therapeutic and clinical benefit. That benefit can be supported and further enhanced by the addition of connectivity technology. The right connectivity technology will support adoption and adherence by meeting the requirements of all the various stakeholders. The wrong connectivity technology can have the opposite effect. Selection is a consequential decision. Understanding the details of connectivity technology, the limitations and the trade offs is the best approach to de-risk the design, development and market adoption of a device.

> "The selection of connectivity technology can have a dramatic impact on the performance and usability of a device."

ABOUT THE COMPANY

Flex is a global provider of design, engineering, manufacturing and real-time supply chain insight and logistics services to companies worldwide. Flex Health Solutions focuses on medical device and drug delivery design, development and manufacturing solutions for pharmaceutical and medtech companies, including extensive work in injection pens, autoinjectors, wearable pumps and smart inhalers. Its approach is supported by US FDA-registered and ISO 13485 compliant and ISO 11608-1 accredited facilities, with a world-class quality system.

ABOUT THE AUTHORS

Juan Nogueira is Senior Director of the Center of Excellence for Wireless and Connectivity at Flex. With a long history in this field, Dr Nogueira defines the company's technology roadmaps, evaluates innovative solutions, establishes strategic collaborations with partner companies and leads internal research programmes in wireless communication. He holds a PhD in Telecommunications Engineering from the University of Vigo (Spain) where he was also an Associate Professor in the Electronic Technology Department.

Tommaso Borghi is Senior Director of Design at Flex. In the past 10 years, he has led R&D teams through the development of connected devices for top medical device and pharmaceutical companies, working in close collaboration with marketing departments, top design firms and production sites around the world. Dr Borghi holds a PhD in Electrical Engineering from Politecnico di Milano (Italy) and has worked as Visiting Scientist at the Massachusetts Institute of Technology on the development of brain machine interfaces.

Marco Vergani is a Senior Hardware Development Engineer at Flex. During the past seven years he has been developing drug delivery devices with wireless connectivity for top pharma companies. He is responsible for electronic design following full device development, from feasibility studies to regulatory certification and mass production. Dr Vergani holds a PhD in Information Engineering from Politecnico di Milano (Italy).

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THE TRUSTED TABLET: A NEW LEVEL OF SUPPLY CHAIN SECURITY FROM MASS DIGITALISATION OF MEDICINES

Here, Kelly Boyer, General Manager Film Coating, Colorcon; Trent Lund, Partner, Head of New Ventures Australia, PricewaterhouseCoopers (PwC); and Barry McDough, Senior Vice-President Sales & Business Development, TruTag Technologies, describe a means of mass digitalising medicines to addresses the problem of illegal and unauthorised production of pharmaceutical products in a meaningful way.

THE CHALLENGE OF ILLEGITIMATE MEDICINES

Unauthorised and illegitimate production of medicines continues to jeopardise patient safety across the world. While regulators and manufacturers have made progress to secure global pharmaceutical supply chains, many of the predominantly packaging-based security approaches are ineffective.

The operational challenges of the modern pharmaceutical supply chain are well established. Globalisation, outsourcing and online retailing have significantly complicated the operating environment. As supply chains become more complex, a loss of control and visibility has occurred. Each node in the supply chain represents a potential point of failure where there is an opportunity for illegitimate products to enter. The incidence of counterfeit medicines, unauthorised generics, expired lots and diverted products have all become significant challenges.

The risk posed to public health and safety of illegitimate medicines is extremely worrying – particularly in the case of counterfeit products, which are often manufactured in squalid conditions. At best, they will be a placebo with no active pharmaceutical ingredients and can lead to therapeutic failure. At worst, they might contain heavy metals and even poisons, causing sickness and even death.

The WHO estimates that counterfeit medicines account for 10-30% of the market in developing economies and up to 1% in some developed economies.

In addition to the threat to patient safety, the cumulative commercial costs of unauthorised products is staggering. While the insidious nature of counterfeiting makes it difficult to determine the size of the problem, the pharmaceutical industry consensus is that 2% or more of top-line sales are impacted.

Barry McDough
Senior Vice-President Sales & Business Development
T: +1 510 879 6408
E: bmcdonogh@trutags.com

TruTag Technologies, Inc
2200 Powell Street, Suite 1035
Emeryville
CA 94608
United States

www.trutags.com

Trent Lund
Partner Head of New Ventures
Australia
T: +61 2 8266 0686
E: trent.lund@pwc.com

PricewaterhouseCoopers
Level 1, 121 Harrington Street
Circular Quay
Sydney NSW 2000
Australia

www.pwc.com

Kelly Boyer
General Manager Film Coating
T: +1 215 616 6260
E: kboyer@colorcon.com

Colorcon, Inc
275 Ruth Road
Harleysville
PA 19438
United States

www.colorcon.com

Beyond this direct commercial impact, illegitimate medicines have a wider impact on the economy – damaging patient trust, brand reputation, tax revenue, investment and even innovation.

INDUSTRY RESPONSE TO ILLEGITIMATE MEDICINES

In response to external supply-chain threats, the pharmaceutical industry has sought to protect products through serialisation and other secure packaging solutions. While every effort helps, there are a number of shortfalls in relying on serialisation and other packaging features as a means of product authentication:

- **Serialisation is not secure.** Serialisation in itself is not a secure solution. Serialised data carriers can be reproduced with ease and en mass, especially where serialisation is sequential.
- **Re-use of original packaging.** Original packaging is retrieved, reused and resold having been filled with counterfeit, expired or unauthorised generic products.
- **Packaging is being copied.** The availability of high-tech, low-cost scanning and production technologies enable sophisticated replication of packaging by counterfeiters that is often indistinguishable from authentic packages.
- **Repackaging.** Pharmaceutical products are often removed from their original packaging and repackaged, rendering the original packaging security features obsolete.

> "Serialisation and authentication of packaging on its own cannot be considered a dependable means of product verification. Relying exclusively on this approach provides healthcare professionals and patients with a false sense of security that the product within is genuine."

For these reasons, serialisation and authentication of packaging on its own cannot be considered a dependable means of product verification. Relying exclusively on this approach provides healthcare professionals and patients with a false sense of security that the product within is genuine. In addition, the information systems that store serialisation data and information on provenance are typically not accessible by the general public.

A STEP TOWARDS THE DIGITALISATION OF MEDICINES

With the limitations of serialisation and packaging authentication in mind, a coalition of supply-chain partners – Colorcon, TruTags and PwC – came together to offer a new digitalisation approach to solving the challenges of illegitimate medicines. Whilst the benefits of digitalisation of medicines have been well documented, progress towards this goal has been inhibited by the economic and regulatory barriers created by the available technology solutions. The mass application of sensor technology directly on medicine doses is cost prohibitive for the majority of therapies, while the need for regulatory approval means that implementation can take several years.

This case study presents the findings of a supply-chain simulation in which innovative technologies are utilised to overcome the hurdles for on-dose security solutions mentioned above and illustrate a clear path towards the mass digitisation of medicines.

This simulation demonstrates how supply-chain actors and even patients can be empowered in the verification process, and how medicines can become trusted once more.

Three major technology elements were utilised in the simulation:

1. Application of Edible Barcodes

The first component of the system is on-product identifiers called TruTags®. TruTags are microtags — effectively, edible barcodes — that can be easily and economically incorporated onto tablets and capsules via existing coatings or inks (Figure 1).

TruTags are made from microparticles of silicon dioxide, a material designated as Generally Recognised as Safe (GRAS) for ingestion and already commonly found in medicines. Because this material is readily present within tablets and capsules, the adoption of TruTags is relatively straightforward even for products that have already been launched on the markets.

During their manufacture, TruTags are encoded spectrally so they reflect light at a known spectral index. This spectral code can be directly associated with a product, a designated market, a production facility or even a batch.

In this supply-chain simulation, TruTags were mixed with a formulated Opadry® complete film coating system, from Colorcon, to create an intelligent coating. This coating was then simply applied to a batch of tablets using a standard coating process.

Figure 1: TruTags are microtags — effectively, edible barcodes — that can be easily and economically incorporated onto tablets.

Figure 2: TruTags can be authenticated using either proprietary imagers or by using an application for commonly used cell phones.

2. Authentication of Edible Barcodes

The second component of the system is the authentication technology. The authentication technology provides a link between the physical tablet and the digital backend. TruTags can be authenticated using either proprietary imagers or by using an application for commonly used cell phones (Figure 2).

"Pharmaceutical brands can communicate directly with their patient populations and personalise the treatment experience – monitoring patient compliance and treatment efficacy, all the while assuring the quality and safety of the medicines being consumed."

The authentication option used depends on the problem the brand is facing and who the company would like to be able to authenticate their products. Various stakeholders can be given the ability to authenticate, from quality assurance and security teams to law enforcement, to healthcare professionals and patients.

In addition to facilitating immediate authentication of medicines, anytime and anywhere, the application of cell phone technology affords an incredible opportunity for patient communication.

Pharmaceutical brands can communicate directly with their patient populations and personalise the treatment experience – monitoring patient compliance and treatment efficacy, all the while assuring the quality and safety of the medicines being consumed (Figure 3).

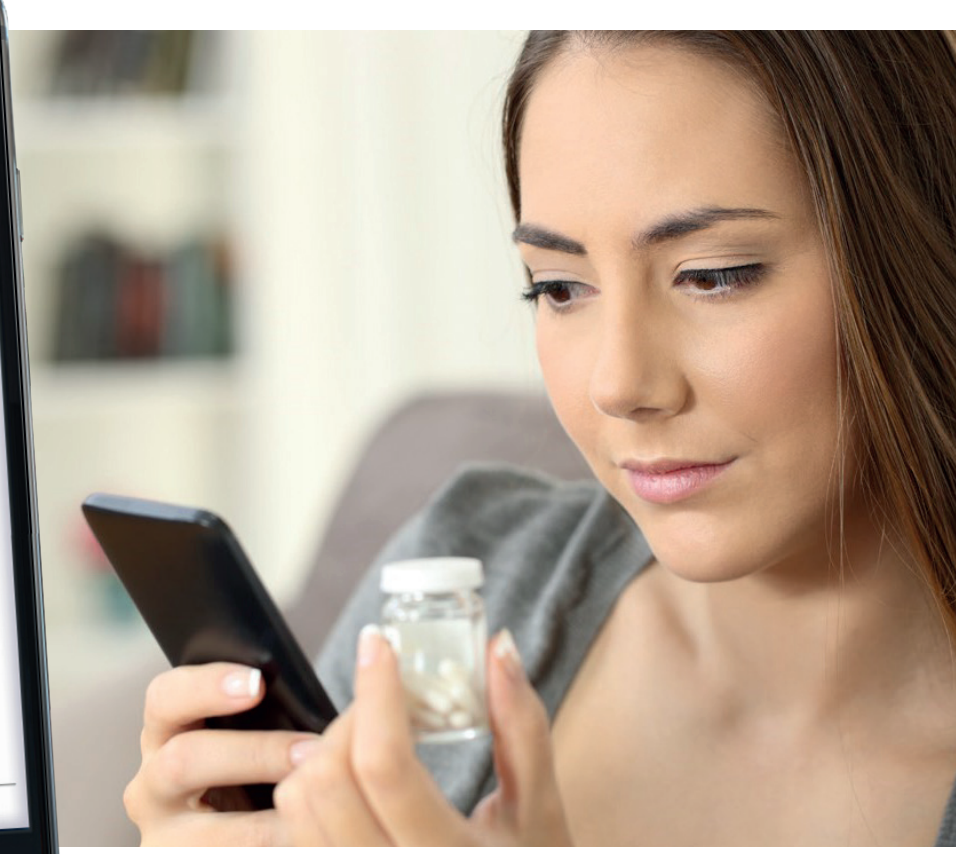

Figure 3: Pharmaceutical brands can monitor patient compliance and treatment efficacy.

3. The Digital Backend

The third component of the solution is a fully integrated, distributed ledger operated by PwC. The platform uses a Google technology called Trillian, a verifiable data structure that provides a transparent, immutable, and cryptographically verifiable transaction log (Figure 4). The platform integrates directly with the authentication application facilitating a secure link between the physical and digital world and delivering absolute supply-chain security and transparency.

"Untagged tablets were successfully identified, as were tablets being authenticated outside of their designated sales markets. No false positives were recorded during the trial."

As tablets are scanned with the application, the platform is instantly updated providing details on time, location and authentication result.

By setting up exception-reporting, brands can be automatically informed of instances of counterfeit, expired or diverted product.

THE SIMULATION

The supply-chain simulation of this technology was conducted over a six-month

Figure 4: Google Trillian integrates directly with the authentication application facilitating a secure link between the physical and digital world.

period between March and August 2019. A batch of 1,000 tablets were coated in a cGMP facility in Kapolei, HI, US, using three variants of an intelligent Opadry coating system, with TruTags included, to represent two different sales regions. Non-tagged coated tablets were also included amongst the tagged tablets to represent counterfeits.

The tablets were then sent to six known parties in the US, Australia and Europe who simulated regional wholesalers and patients. Each party was provided access to the cell phone application and requested to authenticate the tablets distributed to them.

Over 5,000 authentication events were recorded on the PwC platform over this period. Information on user, scan time, location and authentication outcome were all recorded.

Untagged tablets were successfully identified, as were tablets being authenticated outside of their designated sales markets. No false positives were recorded during the trial.

CONCLUSION

In this case study, the coalition of partners successfully demonstrated how individual tablets can be digitalised, linked to a distributed ledger platform and authenticated by supply-chain patients, providing absolute supply- chain security and transparency. By enabling instant authentication, anytime, anywhere, the pharmaceutical industry can secure the supply chain and, in doing so, safeguard their patients and their brands.

Beyond improved supply-chain integrity, this innovation has the potential to connect brands directly with their patient populations. This can help drive engagement between healthcare providers and patients, with the potential to improve patient outcomes.

ABOUT THE COMPANIES

Colorcon is a world leader in the development, supply and technical support of formulated film-coating systems, modified release technologies, and functional excipients for the pharmaceutical and nutritional industries. Its products and technologies are complemented by value-added services, supporting all phases of solid dose design, development, and manufacture.

PwC, a multinational professional services provider, is a network of firms in 158 countries with more than 236,000 people who are committed to delivering quality in assurance, advisory and tax services.

TruTag Technologies is a leading provider of product identity solutions. TruTag offers a range of on-product (e.g on-dose) and on-package security solutions that provide manufacturers and government regulators with an effective means of securing their supply chains and safeguarding consumers.

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ABOUT THE AUTHORS

Kelly Boyer is General Manager for Film Coatings at Colorocn, where she heads the Global Business Development team responsible for the design, supply and technical support of formulated film coating systems for the pharmaceutical and nutritional markets. Ms Boyer has a degree in Chemical Engineering and over 30 years of experience in delivering innovative technology solutions around the world.

Trent Lund is the Lead Partner for Innovation & Ventures at PwC Australia, where he helps organisations leverage emerging technologies to innovate new business models. With PwC Ventures, Mr Lund sits at the intersection of corporates and start-ups, enmeshing the agility and speed of a start-up with corporate rigour and scale. He leads a team of innovators and software developers that build Cloud SaaS platforms and products to address global trust and market confidence such as interpreting regulation, protecting against fraud and counterfeit products. Mr Lund is the sponsor of PwC's Food Trust platform, that is built in collaboration with Google's Trillian security and TruTag's patented tagging and mobile scanning technologies.

Barry McDonogh is responsible for the identification and development of key commercial opportunities and strategic initiatives that expand TruTag Technologies' products and services into new markets. Prior to his current role, he served as Vice President, Business Development and Corporate Strategy at Systech International. Before Systech, he was Director of Corporate Development at UDG Healthcare, an international provider of clinical, commercial, communication and packaging services to the healthcare industry where he drove the commercial development of United Drug subsidiaries in North America. Mr McDonogh has a BS from University College Dublin, Ireland, and a MBS from University College Dublin's Smurfit Graduate School of Business.

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HOW TO DEVELOP A CUSTOMISED DRUG DELIVERY IOT PLATFORM WITH A RUNNING START

Do you need a drug delivery Internet of Things (IoT) platform across your entire portfolio of drugs that is agnostic to the type of source container, drug viscosity and the volume to be dispensed? Rachel An, Medical Device Manager, and Gillian Harding-Moore, Director of Global Marketing, both of Quantex Arc, discuss how to develop such a platform with a running start.

The market for connected drug delivery devices is predicted to grow at an exponential rate over the next 5-6 years.[1] The obstacles to adoption are centred around data security, patient safety and regulation – but the potential benefits for pharma companies, patients, payers, doctors and hospitals are unquestionable, and therefore the industry is beginning to make this technological leap forward. Drug companies are recognising that it will be essential to provide connectivity in order to remain competitive, so we predict that, by 2030, connected drug delivery devices will be regarded as the norm.

One of the main benefits of using connected devices will be improvement of – and insight into – patient adherence. The effectiveness of any medicine is impossible to measure without knowing whether a patient is, in fact, taking the medicine. The consequences of poor adherence to long-term therapies are poor health outcomes and increased healthcare costs. But current methods for measuring adherence are usually subjective and remain only an estimate of patients' actual behaviour.[2]

Smart drug delivery devices not only provide immediate feedback to the user on how and when to take their medication but also track what treatments the patient has taken. Big data insights are invaluable for companies to gather patient feedback, habits, indications and side effects, providing significant opportunities for product improvement.

There is a rise in demand for home treatment, driven by a growing ageing patient population, an increase in the prevalence of chronic conditions and patient preference. The ability to monitor patients' home infusions remotely will also free-up general practices and hospitals – saving healthcare costs. Finding ways for patients to use one device that can be used throughout treatment in hospital, then taken home with them to continue treatment is far more cost effective and easier for the patient to learn how to use. It also provides reassurance that the device used in the hospital is the very same as the device taken home.

> "Pharma companies are now faced with the daunting task of creating connected devices that are customised to their specific drugs or specific range of drugs."

It is difficult and costly to track and retrieve expensive equipment once it leaves

Rachel An
Medical Device Manager
T: +44 20 8735 5880
E: rachel.an@quantex-arc.com

Gillian Harding-Moore
Director of Global Marketing
T: +44 20 8735 5880
E: gillian.harding.moore@quantex-arc.com

Quantex Arc
85, Richford Street
London
W6 7HJ
United Kingdom

www.quantex-arc.com

> "Building a custom pump solution from scratch is a huge financial and resource-time risk."

the hospital, so less expensive solutions are in demand. Spending less time in hospitals and more time self-administering at home is far more comfortable for patients, who will also largely be assured by the knowledge that their progress is being monitored by a healthcare professional in real time.

So pharma companies are now faced with the daunting task of creating connected devices that are customised to their specific drugs or specific range of drugs. Fortunately, innovation is happening in this space, and more and more connected devices are launching into the market for pharma companies to adopt for their purposes.

THE PROBLEM WITH OFF-THE-SHELF CONNECTED DEVICES

Connected devices available today can provide neat solutions that have been tested and regulated. Using an off-the-shelf device means a product can be launched to market relatively quickly. However, these devices tend to be designed for a wide range of applications, with multiple features that cover the requirements of their range of compatible conditions. This means they often contain too many options – which can be confusing to the patient because they are not all required by their specific treatment, which can lead to misuse or user errors.

Building a custom pump solution from scratch is, however, a huge financial and resource-time risk, as it will require a large focused team and colossal financial investment. So, is there a way to mitigate that risk and ensure you can create a perfectly bespoke solution, based on your requirements, that you can still take to market relatively quickly and will lead to an early win?

The answer today is YES... you develop and customise an existing drug-delivery IoT reference platform that is driven by a flexible and unique precision pump technology.

CONNECTED DRUG DELIVERY REFERENCE PLATFORM

Before we talk about the platform, we need to introduce its most important and unique element – the Quantex precision pumps, which we like refer to as the "Intel Inside". These patented pumps use a positive displacement rotary action to carry a fixed volume of fluid from inlet to outlet. This unique pumping mechanism allows for accurate dosing without any software calibration, even when pumping viscous fluids against high back pressures. The pump generates enough vacuum pressure to pump from bags, syringes and vials and is not sensitive to head height.

All of this is achieved with one moving part, which means it is reliable, low-cost and easy to control. Because they are so inexpensive to manufacture, the pumps are single use and can be integrated in-line with the disposable drug pack and infusion set, which means no maintenance or calibration is required. The CS-3 and CS-6 micropumps (Figure 1) are standard medical pumps within the Quantex portfolio. These two pumps will infuse anything from doses of 1 uL up to flow rates of 2.4 L/hr.

Due to these properties, Quantex pumps allow for flexibility in the design of an integrated system. Fittings on the inlet and outlet of the pump can either be standard (luer, hose barb) or custom fittings, allowing for easy integration of the pump in-line. The simple rotary action of the Quantex pumps means flow is easily controlled with a motor: the speed of the motor controls the flow rate, and the number of revolutions determines the volume pumped. Furthermore, the pumps have a low torque requirement which means the device can readily be battery powered. Since the information required to control the pump is simple, different wireless communication methods can be used to transfer information to and from the device.

QUANTEX 4C

To showcase the possibilities of integrating the Quantex pumps into a drug delivery system, Quantex has developed an IoT reference platform that takes advantage of the pumps' unique features. The Quantex 4C system consists of a Quantex single-use pump and re-usable pump driver device. A smartphone application is used to program the device and report information

> "Information on any logged infusion events, adherence and patient experience can be gathered to personalise treatments for greater effectiveness."

Figure 1: Quantex CS-3 and CS-6 micropumps.

Figure 2: The Quantex 4C range of devices – all compact enough to fit in the palm of your hand.

back from the device. Real-time infusion data is relayed to a web portal, where a doctor or other healthcare professional can remotely monitor their patients' infusions.

Information on any logged infusion events, adherence and patient experience can be gathered to personalise treatments for greater effectiveness. Appropriately depersonalised data can be used by companies for valuable business insight and post-market surveillance, as well as by insurance companies for value-based contracting.

There are currently three devices in the Quantex 4C family (Figure 2), all with different capabilities and features to show a range of what is possible:

1. Quantex 4C: This device has been designed for the single-use CS-3 pump and can dose at a rate up to 110 mL/hr. The device uses wireless charging which allows for a fully sealed, waterproof design and can pump up to 100 mL on a single charge
2. Quantex 4C Lite: This device is so inexpensive to manufacture that both the CS-3 pump and driver device can be considered single use and would typically be used in emergency situations. It can pump up to 10 mL at flow rates up to 0.5 mL/hr
3. Quantex 4C Hi-Flo: This device has been developed for the larger CS-6 pump and can reach flow rates of 2.4 L/hr.

MODES OF COMMUNICATION

Three different modes of wireless connectivity have been incorporated into the Quantex 4C system. Near-field communication (NFC), as the name suggests, is a short-range wireless connectivity standard. This technology is used in contactless card payments, where magnetic field induction enables communication between devices placed in close proximity (a few centimetres). NFC is intuitive and does not require a search-and-pair procedure like other methods to establish connectivity.

The Quantex 4C system uses NFC communication both to program an infusion profile (drug information, flow rate, volume, etc) and also report information from the device, with just the tap of a smartphone. Its high level of encryption, as well as the need for the phone to be physically held near the device, offers security benefits.

Bluetooth Low Energy (BLE) is a longer-range wireless connectivity standard with minimal power consumption. BLE allows for real-time feedback from the device to the smartphone, as well as the integration of other peripheral devices or sensors into the system. The Quantex 4C smartphone application uses BLE to display current status of infusion from the device, as well as send commands from the phone to pause or resume the infusion.

The Quantex 4C platform has integrated a flow sensor by Sensirion (Stafa, Switzerland) that monitors the flow of the infusion near the injection site. This information is sent via BLE to the smartphone, allowing for detection of occlusion and air-in-line. This means there is an independent method of confirming the flow rate and total dose into the body, with the added benefit of allowing self-priming without needing calibrated lines.

Internet connectivity (4G, Wi-Fi, NB-IoT, etc) is used to transfer infusion data gathered from the devices to a web portal. This opens the range of connectivity of the system to anywhere that has internet access. Doctors can monitor their patients' infusions, as well as send prescriptions and infusion profiles remotely.

Determining which mode of communication is most appropriate for each type of data transfer (doctor to device, device to doctor, device to patient, etc.) will largely be based on the application or use case. The Quantex 4C system has flexibility on which method(s) of connectivity are used, allowing flexibility in developing the best workflow and system architecture for all stakeholders.

FLEXIBILITY AND CUSTOMISABILITY OF A REFERENCE PLATFORM

The potential benefits of connected medical devices for patients, pharma companies,

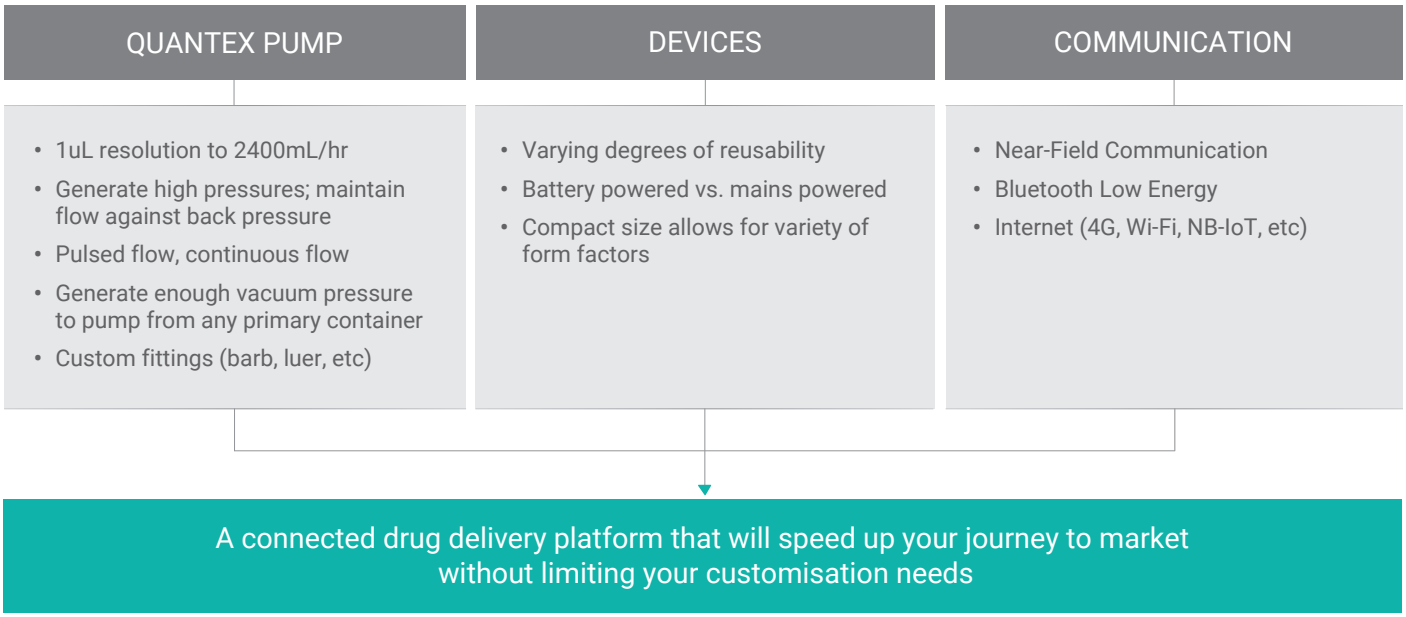

Figure 3: A summary of the flexibility and customisability of the Quantex 4C drug delivery IoT platform.

payers and healthcare professionals are undeniable – improving adherence to treatments, freeing up hospitals and big data insight will bring great returns to those who adopt connected device systems, as long as they "do it right". There is already increased adoption of IoT, patient connectivity and engagement – the trend is rising but it needs careful execution.

Adding connectivity and dedicated apps to support specific therapies has never been easier and, with the rapid onset of new wireless technologies, it's important to also have a pump technology that is able to take full advantage of all this potential. Quantex aims to make it easier for companies to enter this exciting new world of connected devices by providing a foundation on which to build their custom connected systems with Quantex pump technology at their core (Figure 3).

ABOUT THE COMPANY

Quantex is an innovative leader in single-use disposable pump technology. The pump technology has been adapted globally by blue-chip organisations in medical, pharma, food and beverage, consumer and industrial markets. The Quantex range of off-the-shelf pumps holds 74 global patents – and, for bespoke requirements, it can build on the technology to provide customised-catalogue pumps, bespoke-designed pumps or even entire system designs. Its engineers and designers provide design expertise throughout the development programme and assistance into volume production.

ABOUT THE AUTHORS

Rachel An is the Medical Device Manager at Quantex Arc, where she leads the development and medical applications of the CS-series micropumps. Ms An holds a BSE in Bioengineering from the University of Pennsylvania (USA) and a MSE in Bioengineering Innovation and Design from Johns Hopkins University (MD, USA). During her time at Hopkins, she managed a surgical device project from needs finding in the operating room, and technical design in collaboration with surgeons to developing a regulatory strategy and business plan. She also led a neonatal monitoring global health project that won many grants including the Gates Foundation Grand Challenges Exploration Award.

Gillian Harding-Moore is Director of Global Marketing at Quantex Arc and has more than 20 years' experience in marketing, graphic design, advertising and branding. She ran her own agency successfully for more than a decade, working closely with a large global pharma company to deliver multiple high-profile digital projects. Ms Harding-Moore also headed up the European arm of a fashion industry SAAS company. Now she uses her marketing communications knowledge at Quantex Arc to build its brand profile and reach a wider audience, through video making, social media, web and app design, copywriting and advertising.

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AN INJECTION OF CONNECTED NEEDLE-FREE INNOVATION

In this article, Barb Taylor, Senior Director of Marketing at Portal Instruments, discusses the next generation of needle-free injection devices.

It's that time of year again – turkey feasts, holiday songs, festive parties... and the flu! While I am a strong believer in all vaccinations, I will secretly admit that sometimes the kids (due to their anxiety, fear and complaining) win and we skip the flu jab. But this year, with my parents' health not 100%, the flu shot was non-negotiable.

As we sat in the waiting room at the paediatric clinic, my kids naturally brought up my work and asked when they could get a needle-free shot from Portal. The nurse, who was fast and efficient but looking rather harried, overheard us and asked if it worked. The quick answer is yes, it works. But you can't get the shot (or the injector) for your own use from Portal – it will be distributed through our pharma partners as part of a combination device with an approved drug.

Figure 1: Flu vaccine time.

The nurse continued to recount a tale I have heard many a time. The anticipation of the injection is usually worse than the actual shot (Figure 1). But that fear can often be debilitating and the difference between a successful vaccination and an unsuccessful one. She guessed that 5-10% of patients don't come in for the influenza vaccine because of the struggle and anxiety of having to get a shot. A 2012 paper by Taddio *et al*[1] shows her guess is not far off – a survey of parents (n = 883) and children (n = 1024) found that "altogether, 24% of parents and 63% of children reported a fear of needles. Needle fear was the primary reason for immunisation non-compliance for 7% and 8% of parents and children, respectively." I am not alone.

> "Portal is reinventing needle-free drug delivery with technology that is substantially different from any other needle-free injector that has been on the market."

Barbara Taylor
Senior Director of Marketing
T: +1 617 500 4348
E: barb.taylor@portalinstruments.com

Portal Instruments, Inc
190 5th Street
Cambridge
MA 02141
United States

www.portalinstruments.com

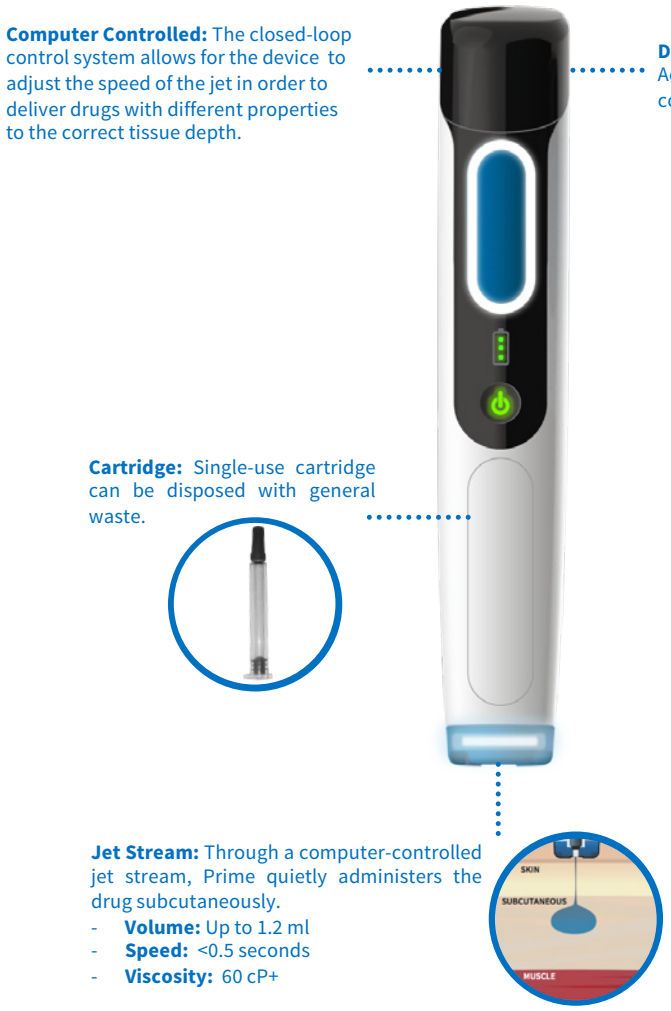

Figure 2: The Prime device offers next-generation, connected needle-free drug delivery.

"With data and analysis, teams will be able to identify challenges related to adherence, predict trends in patient populations, and use that data to create a better patient experience."

"The Prime needle-free device logs all injections and can be automatically connected to patient apps or physician records."

PORTAL PRIME DEVICE – NEXT-GENERATION NEEDLE-FREE

Our nurse continued to tell another story of nasal spray flu vaccines and other needle-free injectors she had seen over her career – and her ambivalence towards them. My quick answer was that Portal Instruments is reinventing needle-free drug delivery with technology that is substantially different from any other needle-free injector that has been on the market.

Here's the long answer as to what that means and how Portal is different – Portal Instruments is modernising drug delivery by using novel, electromechanical technology to deliver and track injections, needle-free and automatically. Portal's injector, called Prime (Figure 2), administers the drug through a highly pressurised, computer-controlled jet stream. The narrow jet pierces through the epidermis and delivers the drug into the subcutaneous space (Figure 3).

This is different from mechanical needle-free injectors as Prime's computer-controlled motor and internal feedback control system work together to sense the pressure and adjust the velocity of the jet stream accordingly. This results in a very quick injection (<0.5 seconds) even at high volumes (1 mL) and high viscosities (tested up to 60 cP).

CONNECTIVITY & ANALYSIS TO DRIVE OUTCOMES

As with most next-generation technologies, the Prime needle-free device logs all injections

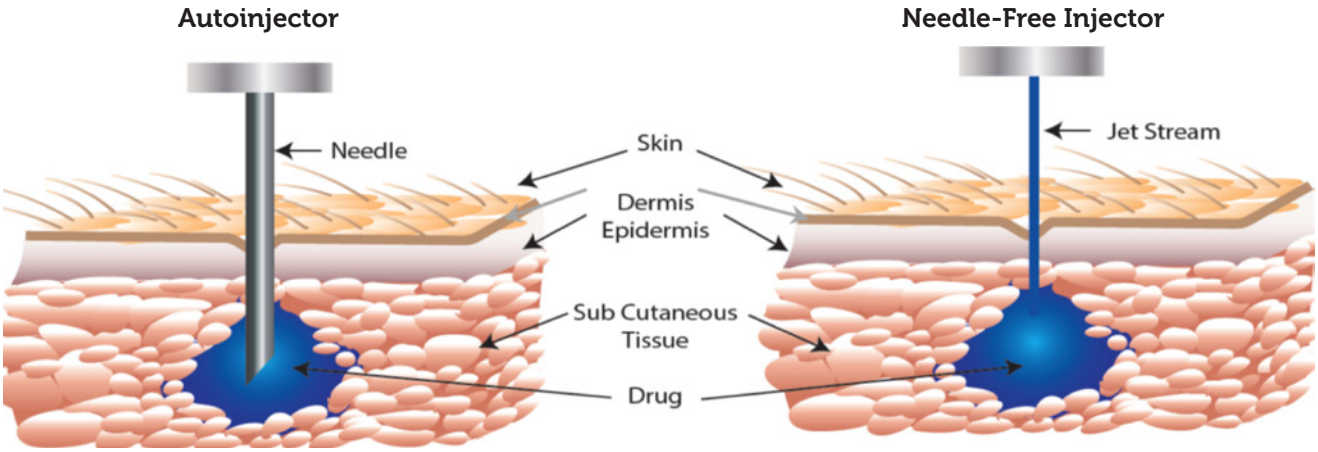

Figure 3: Conventional needle-based injection from an autoinjector (left), compared with needle-free injection (right) where a high-pressure, narrow jet pierces through the epidermis, delivering drug into the subcutaneous space.

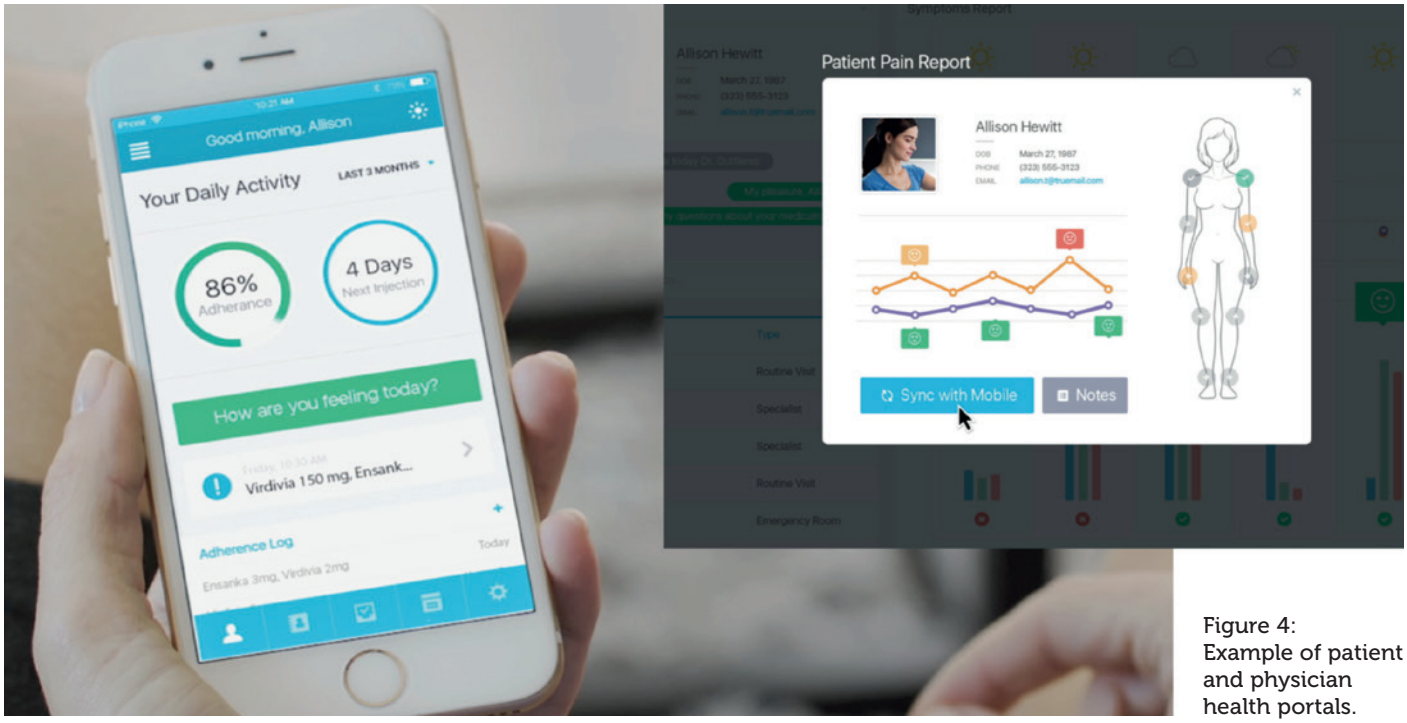

Figure 4: Example of patient and physician health portals.

> "Our vision is that connectivity within the injector will empower patients to have better control over their treatments."

and can be automatically connected to patient apps or physician records (Figure 4).

Portal's vision is for this data to provide real-time adherence insights which can ultimately be used by the healthcare team to drive improved adherence and better outcomes. For example:

- Pharmaceutical partners can analyse aggregated and de-identified data to enhance pharma lifecycle management and use the quantitative insights to launch specific, targeted campaigns to drive population penetration and adherence programmes.
- Patient service providers can quickly identify "late doses" before they become "missed doses" and be proactive in reaching out to patients who may need support.
- Payers could use this adherence data to inform value-based contracts that are dependent on adherence.

With data and analysis, teams will be able to identify challenges related to adherence, predict trends in patient populations, and use that data to create a better patient experience. Trends that were previously undetected may become noticeable.

Likewise, our vision is that connectivity within the injector will empower patients to have better control over their treatments. Patients can track their injections and other variables to improve their ability to self-manage their disease. If patients share their data feeds with caregivers or family members, those family members can remotely and non-intrusively check to make sure the medication was taken on time and offer support if needed. Patients may choose to share injection and self-reported data with their physicians in order to have a more well-rounded picture of their disease progression. This insight may create more efficient physician visits and more tailored treatment plans.

A VISION FOR THE FUTURE

While I reflect on how a needle-free vaccine would be great for my family, I cannot help but think of patients who need to have injections monthly, weekly or daily. In this season of thanks and reflections, I am indeed grateful for the many advances in pharma therapies and drug delivery devices that can improve, empower and ease the journey for patients.

ABOUT THE COMPANY

Portal Instruments is a clinical-stage connected drug delivery firm, commercialising a next-generation needle-free drug delivery platform to transform the drug delivery experience for patients suffering from chronic diseases such as ulcerative colitis, multiple sclerosis, rheumatoid arthritis and psoriasis.

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ABOUT THE AUTHOR

Barbara Taylor leads the marketing team at Portal Instruments. With more than 20 years' experience in health tech strategy and marketing, she brings to Portal expertise in healthcare software development, new product introduction, lifecycle and service strategy, and business model innovation. Prior to Portal Instruments, Ms Taylor was at a number of large and small firms including Philips Healthcare and Mercer Management Consulting. She holds an MBA from the Kellogg Graduate School in Evanston (IL, USA) and a BS in biology from the University of Michigan in Ann Arbor (MI, USA).

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NEXT-GENERATION CONNECTED DRUG DELIVERY SUPPORTS DATA LIQUIDITY & COST SAVINGS

Here, Neil Williams, Director of Front-End Innovation and Head of Connected Health at Phillips-Medisize, discusses the global challenge of medication non-adherence, the toll it takes on the healthcare system and how integration, analytics and more affordable connectivity in drug delivery devices as part of a connected health ecosystem can help improve patient care and lower costs.

The issue of medication non-adherence has long been raised as a global challenge that not only has a deleterious impact on patient outcomes but also creates a large burden of cost to the healthcare system. With accountable care organisations (ACOs) and payment-by-results agreements springing up rapidly, value-based care is no longer a vision but a reality. The pay-for-performance model has created an incentive-based environment where payers no longer just reimburse providers to manage a patient's condition during a finite snapshot in time. When providers can show progress over the long term and demonstrate a reduced burden of unnecessary costs and deliver demonstrable benefits to all stakeholders, they're eligible to receive a stipend for the savings created. In this sense, the outcome now becomes the income.

> "The pay-for-performance model has created an incentive-based environment where payers no longer just reimburse providers to manage a patient's condition during a finite snapshot in time."

More than ever, providers need to be able to monitor medication usage and, more importantly, measure changes in a patient's health status. Statistics show that up to 50% of medications are not taken as prescribed and that 33% of US hospital admissions are due to poor medication adherence.[1]

Drug adherence, while important, is only part of this equation. What's needed today is a much broader, more holistic view of the patient. Metadata and big data can show not only whether a patient was taking a medication on time as prescribed but also multiple factors that contribute to that individual's overall health and well-being.

DIGITAL HEALTH IS THE NEW NORM

This is where connected health comes in. Sensor-embedded devices that are part of a connected health ecosystem and can digitally transmit data back to the patient's electronic health record through an app on their smartphone – and automatically alert providers of any issues or inconsistencies – have come a long way. Currently, there are more than 165,000 health-related apps available on iOS and Android, and that number is increasing. The growing popularity of wearables, home-use scales, blood pressure monitors, glucose meters and drug delivery devices that measure vital signs and adherence rates can offer a remote

Neil Williams
Director of Front-End Innovation and Head of Connected Health
T: +44 7775 027 207
E: neil.williams@phillipsmedisize.com

Phillips-Medisize
Milton Hall, Ely Road
Milton, Cambridge
CB24 6WZ
United Kingdom

www.phillipsmedisize.com

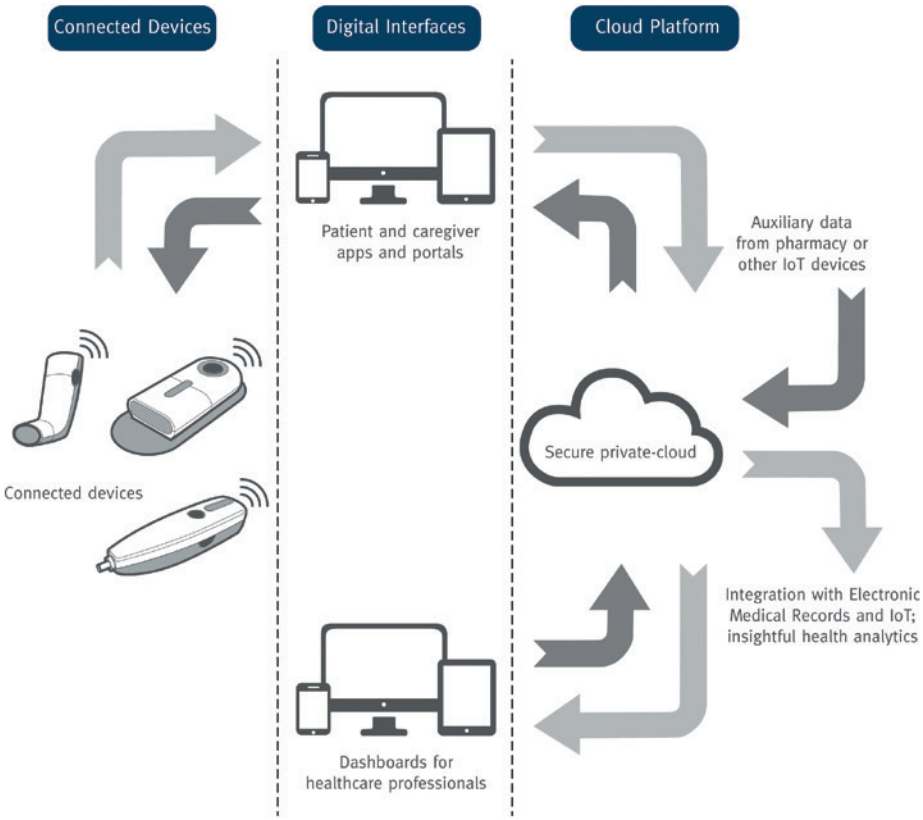

Figure 1: The Connected Health Platform by Phillips-Medisize encompasses extensive information-sharing, analytics capabilities, robust cybersecurity and streamlined regulatory documentation to support pharmaceutical, medical device and diagnostics companies worldwide.

glimpse into a patient's health status.

The potential for capturing a more all-inclusive perspective of the patient through digitally connected drug and monitoring devices looks promising but it's still maturing as the "Internet of Medical Things" (IoMT) evolves. As more patient data is collected, moved into the health system and shared back out to patients from providers, it becomes that much more valuable. Essentially, this "data liquidity" allows patients to commission their data to their providers and receive professional guidance to tailor individual treatment more finely.

While the world has come to expect digital health as the norm, strides are under

"The potential for capturing a more all-inclusive perspective of the patient through digitally connected drug and monitoring devices looks promising but it's still maturing."

way by global leaders like Apple, Google and many others to make data liquidity that much more accessible. Just recently, Google announced its acquisition of Fitbit, a pioneer in wearables, to continue advancing this category by delivering innovative, affordable and engaging devices. Being "on Fitbit" is not just about the device – it represents an immersive experience from the wrist to the app, designed to help people understand and change their behaviour.

In a similar fashion, embedding connectivity in drug delivery solutions like inhalers, injectors, patch pumps and infusion devices enables patients and healthcare professionals to track device status, as well as when patients are taking their medication and the dosage amount. Advantages of shared data through device connectivity include increased patient feedback, improved targeting of clinician support and the delivery of actionable insights. Furthermore, connectivity provides valuable opportunities to engage and support patients through reminders, incentives and peer communities

to improve adherence. For example, Phillips-Medisize's cloud-based connected health platform (Figure 1), which builds on the success of the first US FDA-approved connected autoinjector device, facilitates this secure data sharing between provider and patient.

INTEGRATION & ANALYTICS: KEY TO HOLISTIC PATIENT VIEW

As progress is being made toward greater data liquidity through connected wearables, monitors, drug delivery devices and more, there are many more touchpoints involved in capturing and transmitting patient information. Ideally, the goal is to ensure this flow of data is integrated directly into a patient's electronic health record – not just in isolation but consolidated with all the other multiple data points in the full digital ecosystem to create a 360° view of the patient. A connected health platform should combine a reliable analytics tool with a powerful integration engine that integrates patient data with electronic medical records and other data from pharmacy, mHealth and IoMT devices.

Analysing this cumulative data can ultimately provide valuable insights that may help drive better patient outcomes on an individual level as well as across patient populations, such as those with chronic diseases. By leveraging analytics, providers can begin to identify outliers, intervene earlier, steer patients toward behavioural changes and deliver more personalised care tailored to the individual. Everyone benefits – the patient, the provider and the payor – as a result of improved medication and disease management, which reduces the burden of cost, which can improve outcomes, reduce co-morbidities and the overall cost of care.

The global cost of not enabling data sharing through digital health is significant. On the flipside, connected healthcare has the potential to create up to US$450 billion (£350 billion) in savings in the US alone. In a McKinsey consumer health insights survey, 68% of 14,500 respondents reported behavioural change as a result of using devices and services to manage chronic conditions.[2] Greater patient engagement and increased data liquidity, empowered by connected health solutions, therefore helps solve a widespread human problem and drives inefficiency out of the healthcare system.

Figure 2: The smart, reusable autoinjector can handle multiple drugs through a syringe RFID reader and has an intuitive user interface with illuminated user graphics and audible feedback.

Even though connectivity is a relatively recent innovation in drug delivery devices, the benefits are clear and important to the entire healthcare industry. Greater adherence has the potential to increase drug sales and provide a return on investment to pharma companies who typically bear the additional device and service costs.

As today's drug delivery devices continue to evolve from purely mechanical in design and function to more sophisticated solutions that embed electronics (Figure 2), there is a trend toward adding connectivity to support data sharing. Adding connectivity to next-generation devices, however, has been met with some resistance by medical device companies, who are under increasing pressure to keep manufacturing cost down.

COST-EFFECTIVE CONNECTIVITY IS A REALITY

The initial manufacturing cost of integrating connectivity into a drug delivery device can be high. Adding even $3 to the manufacturing cost of an insulin injection pen translates into roughly a sevenfold increase in cost per unit and, for a low margin medication, it is prohibitive. This additional cost can't realistically be recouped through price increases.

One way to make connected medical devices more economically viable is to rethink the initial approach to product design in order to reduce manufacturing expenditures for a lower cost per unit. Simply put, how can companies lower the cost of integrating connectivity into drug delivery devices as a viable alternative to a bulky add-on connectivity device to achieve an affordable price point, especially for those with higher production volumes?

Phillips-Medisize is an example of an outsourced manufacturing partner that benefits from Molex's electronics capability and ownership. The combined businesses benefit from a dedicated low-cost connectivity project team including mechanical, electronics and embedded software engineers, as well as app designers and human-factor specialists, all focused on market- and customer-specific needs. By leveraging their collective industry expertise and specific skill set in device development, the team is focused on one goal – to successfully integrate connectivity features into drug delivery devices at a lower cost than previously considered possible. Given the new level of affordability, incorporating connectivity even in disposable devices is now possible.

"Greater adherence has the potential to increase drug sales and provide a return on investment to pharma companies who typically bear the additional device and service costs."

CONCLUSION

Pharma companies are under growing scrutiny from regulators and health insurers to do more to demonstrate the value of their medications, which puts increased pressure on drug delivery device manufacturers to rise to the challenge – all while saving costs.

In the end, connected health solutions should be useable and affordable to meet industry, provider and patient needs – no matter if it is for a common disease or a complex rare disease. Successful products are built on three essential foundations: robust technology, solid business planning and empathetic patient engagement. Connectivity technology promotes data liquidity by providing an effective and efficient way to collect patient information and capture insights that inform better, two-way decision making.

If we are to raise patients' medication adherence, it is essential that we succeed in creating a 360° focus on patients, caregivers and healthcare providers and their interactions, as well as catering to the full ecosystem. To accomplish this, we need a well-functioning, reliable connected health system that embraces all aspects of digital health.

ABOUT THE COMPANY

Phillips-Medisize is a provider of outsource design, development and technology-driven manufacturing, with a primary focus in the medical device and diagnostics, drug delivery, primary pharmaceutical packaging and commercial markets. Phillips-Medisize operates on a partnering business model, and works with pharmaceutical, biopharmaceutical, consumable diagnostic and medical device companies with the purpose of increasing speed to market. It was the first company to deliver a US FDA-approved connected health system to the market.

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ABOUT THE AUTHOR

Neil Williams is Director of Front-End Innovation and Head of Connected Health at Phillips-Medisize. Previously he was with Medicom Innovation Partner, which he joined in 2015 and which was acquired by Phillips-Medisize in 2016. One of his key roles is to evolve the company's third-generation connected health software platform. Having started his career in the clinical setting, working in the critical care faculty with a leading University Hospital. Williams moved into industry where he has focused for many years on connected health including medical devices, clinical decision support, health analytics and care pathway design.

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PRODUCT SHOWCASE: Injay – Connected Prefilled Syringe

BIOCORP

The need for connected solutions is growing and all healthcare players are committed to providing solutions that make patients' lives easier and improve compliance. However, until now, there has been no solution to answer the need to connect a prefilled syringe (PFS).

More than five billion PFSs are used each year, and the self-injection market is constantly growing. PFSs are widely used to administer vaccines, anticoagulants, anti-arthritic, anti-anaemic and many other drugs. And the biologics approval rate is intensifying, with a wide variety of new products being cleared by the US FDA and the EU EMA. Most biologics are delivered through injections, making them attractive to use with a PFS, and there is a growing demand for home therapies and easy adoption of devices.

There are four fundamental principles that a connected PFS must respect: treatment adherence of commercialised drugs, quality of reporting, secure treatment protocol and traceability. With Injay (Figure 1), the first prefilled syringe with built-in connectivity, Biocorp provides a simple, cost-effective and easy-to-implement solution. The use of Injay is totally transparent and does not interfere in any way with the user's traditional injection process.

Injay is a built-in solution for PFSs, based on a custom finger flange (with backstop function) and a custom syringe piston rod with a near-field communication (NFC) label. The device is adaptable to any standard size of PFS (0.5, 1, 2.25 mL etc) or material (glass, plastic/cyclo olefin polymer etc).

Injay is able to track any state of injection completion and collects key information such as time and date, drug type, batch number and expiry date. Moreover, the data can be customised up to 150 characters so that any appropriate information can be encoded. The shape and colour of the backstop can also be customised, to meet patients' needs better, and to maintain ergonomic and intuitive handling of the device.

The information is sent via NFC technology to an app on a smartphone or tablet. Recent updates on commercially available smartphone terminals now enable coverage and reading of NFC technology on iOS and Android platforms. However, the choice of the reader can be adapted according to the drug and healthcare setting – special NFC readers could be provided if the injection is delivered in hospital,

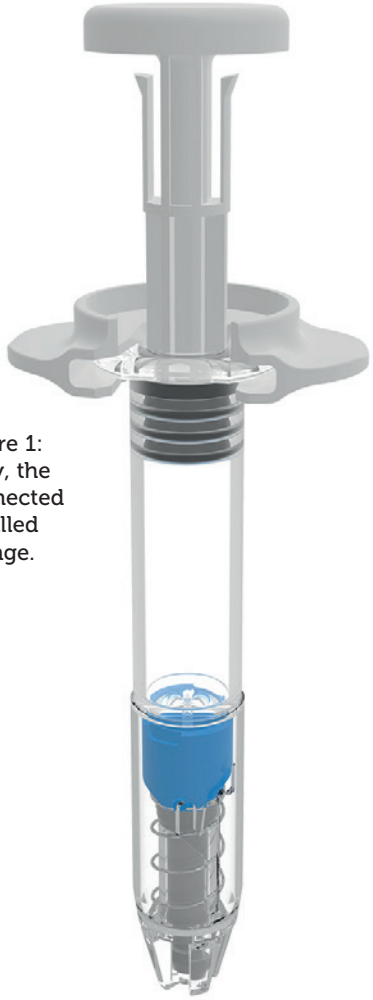

Figure 1: Injay, the connected prefilled syringe.

Figure 2: Overview of potential applications of Injay, in clinical trials, in the hospital setting and at home.

Figure 3: Injay presents a clear path towards better reimbursement or market protection.

for example, or could even be integrated in a sharps container so as not to require any additional effort from the patient or healthcare practitioner.

Injay is a cost-effective solution since it is easy to integrate into the conventional industrialisation process. The finger flange and custom piston rod with NFC chip are assembled after the conventional filling process of the PFS. Injay has many fields of application (Figure 2), as the device is adaptable to different contexts and environments.

It could be a suitable solution for connecting autoinjectors, for example, where a case-by-case integration assessment will have to be made. It can optimise clinical trial performance – key information is automatically collected and transferred to a mobile application, allowing data to be archived and subsequently accessed and analysed. It can also help to check the degree of adherence and compliance – answering the question of whether a patient has correctly followed the prescriber's recommendations. The device also guards against reporting errors.

Injay can be used by patients at home – offering compliance monitoring as it reports that the injection is made in its entirety, and also reporting the time and date.

At a time of cost constraints in major markets, Injay enables pharma companies to provide a simple and reliable solution to payers for tracking the correct use of a drug and could facilitate negotiations on price-to-performance tracking strategies (Figure 3). Injay is due to be available on the market for clinical testing early in 2020.

ABOUT THE COMPANY

Biocorp specialises in the development and manufacturing of medical devices and innovative drug delivery systems. With 25 years of experience, more than 35 million units produced each year and 25 patent families, Biocorp is a key player in the industry, providing drug delivery solutions that meet the evolving needs of patients. Biocorp is constantly innovating on medical plastics, its core business and to market traditional devices (alternative to aluminum capsules, syringe and vial administration systems). Our strong expertise and innovative capacity have also allowed us to develop a range of connected products, including Mallya™, a smart cap for pen injectors that captures injection data and automatically transmits data to a mobile app.

Biocorp
Parc Technologique
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TRANSFORMING HEALTHCARE – HOW CURATIVE THERAPIES WILL DISRUPT THE MARKET

The shift to curative treatments promises to transform the entire healthcare ecosystem. Patients whose conditions were previously managed through ongoing, long-term medication can now be cured through specific courses of treatment. This transforms their lives. But it also has a disruptive effect on the wider market – as explained in this article by Ulrica Sehlstedt, PhD, Managing Partner; Craig Wylie, Managing Partner; Thomas Unger, PhD, Associate Director; Rebecka Axelsson Wadman, Principal; Vikas Kharbanda, Partner; and Satoshi Ohara, Partner, all members of Arthur D. Little's Healthcare and Life Sciences Practice.

The combination of scientific advances, increasing patient expectations, the emergence of new technologies and growing concerns around cost are driving an unprecedented level of change encompassing whole healthcare systems across the globe.

One key part of this is the shift towards curative treatment for conditions that were previously considered chronic or untreatable. Essentially, patients who previously had to rely on ongoing medication can now be cured through a specific, time-limited course of treatment which transforms their lives.

But this will disrupt the entire healthcare ecosystem. With curative treatments, payers' expenditure drastically shifts from ongoing, long-term and relatively low-cost drugs to large, front-loaded therapy costs. Revenues for therapy providers will also shift, focusing on when they are introduced to the market. This transformation will lead to a number of consequences for patients, policy makers, payers, providers and pharma companies alike.

WHAT ARE CURATIVE THERAPIES?

Our definition of a curative therapy is a time-limited treatment that removes the symptoms of a disease through permanent (or semi-permanent) correction of the underlying condition. In contrast, a pill that a patient needs to take for the rest of their life to manage symptoms or disease progression is not curative.

From our analysis, we have defined three archetypes of curative treatments:

- **Biology-modifying drugs** – a good example of this is the hepatitis C virus (HCV) treatment Sovaldi (sofosbuvir) (Box 1), created by Gilead Sciences

> "The first mover can effectively eliminate any market opportunities for competitors by curing the backlog of patients either waiting for treatment or receiving chronic care. The only remaining need will then be from newly diagnosed patients.."

- **Gene therapy** – this addresses underlying causes of a disease by correcting the missing or mutated genes. It can be divided into somatic and germ-line therapy, with the latter treatment curing not only the current patient but also their future offspring. Examples include Luxturna (Box 2) from Spark Therapeutic for patients with inherited retinal diseases (IRDs)
- **Cell therapies** – genetically re-engineering cells, such as CAR-T and stem-cell treatments.

The number of curative treatments is increasing. Analysis of the clinical trials pipeline undertaken by Arthur D. Little shows that approximately 5% of all drugs currently registered as active at *ClinicalTrials.gov* are potentially curative. The highest share of potentially curative treatments can be observed in Phase I (Figure 1) which indicates that we will see a significant increase in the number of curative treatments reaching the market over the next 10 years.

Author for correspondence:

Dr Ulrica Sehlstedt
Managing Partner
T: +46 8 50 30 65 00
E: sehlstedt.ulrica@adlittle.com

Arthur D. Little AB
Kungsgatan 12-14
107 25 Stockholm
Sweden

www.adlittle.com

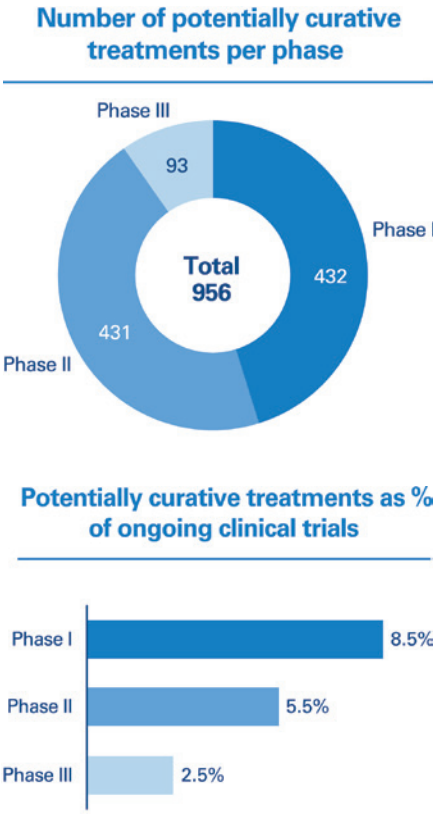

Figure 1: Analysis of clinical trials pipeline of potentially curative therapeutics.

IMPLICATIONS FOR CARE PROVISION

Curative treatments have the potential to lower the overall impact and cost that particular diseases have on healthcare systems, as they eliminate the need for long-term chronic care. This will change the way we treat patients and impact how healthcare providers organise care and its delivery. The sales and upfront cost profiles of these new treatments will have an immense impact on payers and providers. It will demand the development of new models for payment and reimbursement in order for their introduction to be affordable.

This impact is already being seen. Many one-payer health systems have observed significant increases in drug spending directly attributable to the introduction of Sovaldi, which costs US$84,000 (£65,000) for a three-month course of treatment. For budgetary reasons, the UK NHS tried to delay its availability (along with next-generation therapy Havoni) to patients – and looked to cap the annual number receiving the treatment.

In the US, some state Medicaid programmes and private health insurers restricted access to curative therapies, which has led to warnings from federal officials and lawsuits from patients. Medicaid programmes in 29 states said Sovaldi was the first or second most costly pharma outlay they had to make. While payers recognise that drugs such as Sovaldi lead to bigger medical savings later on – for example, if hepatitis C is left untreated, it can lead to cirrhosis, liver failure or liver cancer – its immediate financial impact has a profound impact on the current budgets of insurers and payers. And this is for a drug that is relatively low cost compared with some curative treatments.

In contrast, imagine the cost and operational impact for a cancer centre if multiple expensive curative treatments were introduced in the same year. This higher

BOX 1: CASE STUDY – SOVALDI

A recent example of the shift in sales patterns is Sovaldi, which was launched in 2013. This is the first curative treatment that effectively cures 99% of HCV cases.

When competitors entered the market in 2014, a large share of patients had already been treated. Based on its successful record, Sovaldi was the natural first choice for prescribing to new patients. To demonstrate the importance of first-mover advantage, when AbbVie launched its first hepatitis C drug about 12 months later, sales were disappointing. However, in 2018, it launched a significantly improved follow-up drug, Mavyret, which is currently the leading treatment for new patients. While this has managed to gain AbbVie a strong long-term market position, the company clearly missed out on the lion's share of treatment revenues.

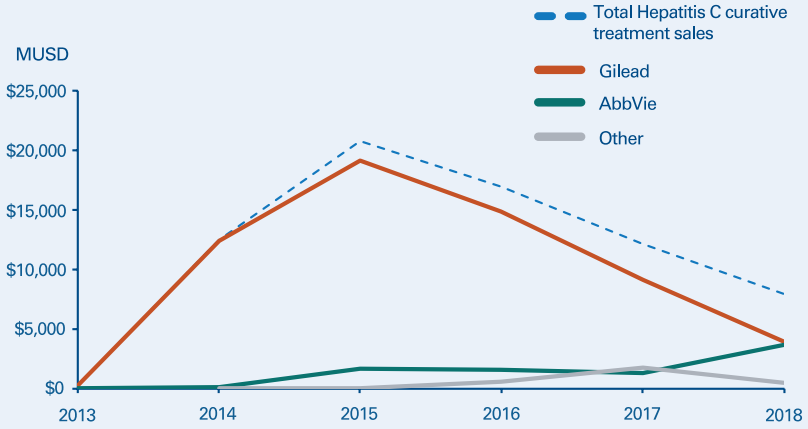

Figure 2: Sales for hepatitis C curative treatments (2013–2018).

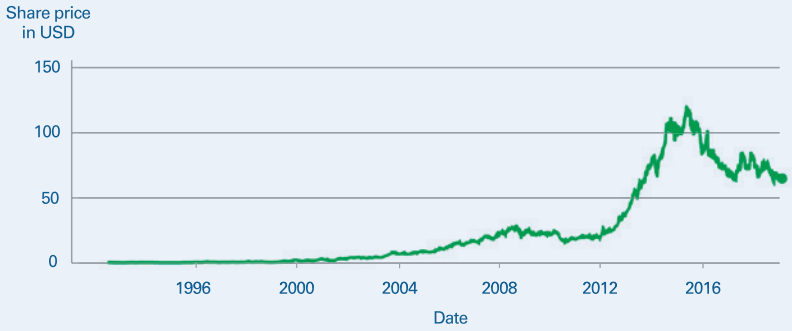

Figure 3: Gilead share price movement.

The unusual sales profile shown in Figure 2 had a clear and unexpected effect on Gilead's share price (Figure 3). Even though investors understood that Sovaldi was a curative treatment, shareholders weren't expecting the peak and consequent drop in sales, which led to the share price slumping as sales naturally slowed down. This demonstrates that pharma companies will need to anticipate this issue and either educate the market or, more likely, try to balance product portfolios to counteract potential large swings in sales.

variability in costs makes it increasingly difficult to plan and budget – aspects that are key to healthcare systems, given that they are under continuous cost pressure.

IMPLICATIONS FOR PHARMA COMPANIES

The revenue models for curative treatments are radically different from those for existing drugs. Traditionally, new therapies tend to show a modest bump in sales when introduced, which then stabilises and remains steady until patent expiration. This delivers predictable revenues and requires stable, ongoing drug production.

Curative therapies, however, are one-off treatments. Once a patient has been treated, they will not require any further treatment. That means peak sales will appear earlier and be higher than for traditional therapies, as the populations of eligible patients will all be treated in a short space of time. However, sales will then drop off much faster once this pent-up demand has been met. Figure 4 compares revenues for a traditional therapy versus a curative one.

This new model represents a clear break from typical pharma sales profiles – which will, in turn, impact the way pharma organisations need to be set up and function. Manufacturing needs to be able to deliver large-scale production in the short term but – once the peak has passed – it needs to be scaled down to more modest, "steady-state" production volumes. The same is true for marketing and sales.

This also affects competitive products. When there is already unmet demand, the first mover really does have a significant advantage. It can effectively eliminate any market opportunities for competitors by curing the backlog of patients either waiting for treatment or receiving chronic care. The only remaining need will then be from newly diagnosed patients.

KEY FACTORS TO CONSIDER IN ANTICIPATION OF CURATIVE THERAPIES

Curative therapies have the potential to disrupt the healthcare market and, most importantly, to dramatically improve the lives of patients struggling with significant, long-term conditions. In order to control this disruption and maximise their positive impact, a number of questions need to be addressed by treatment providers, care providers, payers and policy makers.

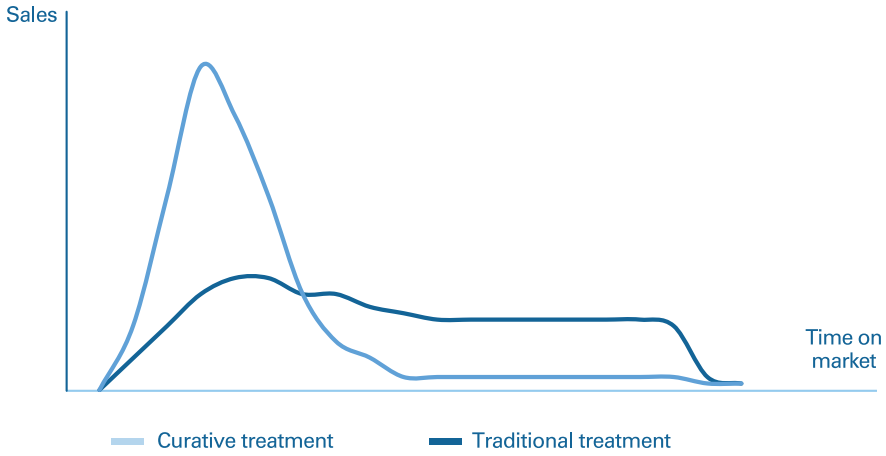

Figure 4: Revenue curves for traditional versus curative treatments (illustrative).

Payers and Policy Makers

In a world of limited resources, tough decisions need to be made. While curative treatments have the potential to reduce costs down the line, they are increasingly expensive, which adds to the accelerating overall cost pressure on healthcare systems. What diseases should be treated over others, what curative treatments should be funded, and for whom? These are ethical questions that need to be answered, and the answers will have significant impact on patients and their health.

The timing of costs also needs to be controlled, with the financial impact of new treatments evened out to reduce cost volatility. There are a number of potential payment model options that could be used, either alone or in combination, to address this:

- Survival/outcomes-based payment – the treatment is only paid for when successful. This shifts part of the risk of unsuccessful treatment to pharma companies, effectively lowering the risk that payers will have to fund both an expensive treatment and continued treatment for a chronic condition
- Interim payments – payments are spread out over longer periods. This aligns the cost profile much more closely to that of a chronic/long-term treatment and reduces the immediate cost for payers
- Companion diagnostic-based payment – treatments are only approved when a companion diagnostic has shown that the patient is highly likely to respond to the treatment. This also serves to limit the number of patients subjected to ineffective treatments, which, by extension, also reduces costs for payers.

If the payer is a private insurance company, its models for calculating risks and costs, as well as for pricing, will need to be changed, as past actuarial data will no longer be accurate. In addition, payers and policy makers will need prior warning when new curative treatments are about to hit the market, so that they have time to accurately plan, budget and adapt policies.

Care Providers

Care providers are facing a multitude of changes due to the increase in curative treatments. They will need to shift their organisations and infrastructure from chronic care and surgery to curative treatments.

Care providers will need to shift their financial models, as well as their operating models, to better account for swift changes in standards of care. A key component here is training of staff – as new treatments are introduced more often and for shorter time spans, training models will need to be adapted to focus on faster learning and higher degrees of staff specialisation.

Pharma Companies

Ensuring first-mover advantage is key for any pharma companies that operate in fields in which curative treatments can potentially be introduced. They need to focus on market intelligence and build portfolio decision-making models that take into account the unique properties of curative treatments.

They will need to understand if the new treatments they are developing are curative, if products being developed by competitors are curative, what their own time to market is, and whether they can gain first regulatory approval and be first on market. If first approval is possible, but they face competition, they should assess how they can accelerate time to market to beat rivals. If first approval is not a possibility, they need to be prepared to significantly revalue potential market

BOX 2: CASE STUDY – LUXTURNA

Luxturna (voretigene neparvovec) from Spark Therapeutic is the first US FDA-approved gene therapy for patients with IRD caused by mutations in both copies of the RPE65 gene.

- Patients suffering from IRD risk partial or complete blindness and, while current treatments can help slow down the advancement of IRD, they cannot stop disease progression
- Luxturna carries a list price of $850,000 (£660,000) or $425,000 per eye – a high cost for payers to bear despite there being a limited number of patients
- In order to address this, Spark set up a payment agreement with Harvard Pilgrim Health Care – the first health plan to cover the treatment. Under its terms, Harvard Pilgrim Health Care will only need to pay for patients who are successfully treated
- The outcomes-based contract pays Spark in full only if the drug works after 30 months, with an interim payment based on preliminary effects at 30–90 days
- Before being treated, patients need to undergo genetic testing to confirm the gene mutation, and it must be confirmed that the patient has enough viable retinal cells to restore or preserve vision.

revenues, move away from the project, or know for sure that the product is superior to the competition.

Pharma companies also need to rethink their reimbursement models. The greater the certainty that a treatment will be curative, the greater its worth, and this enables it to command higher prices. If a specific patient type is responsive, the company needs to ensure there are diagnostics in place to demonstrate this. It will need to charge more if it knows the treatment is going to work and reduce long-term costs – or leverage the use of contingent payments to allow care providers to pay over time or when results have been achieved. This makes it hard for anyone else to break into the market.

Companies will also require a proactive approach to portfolio management. They must understand the timing of revenues and plan for dealing with revenue cycles that are radically different from the pharma industry standard. Finding a way to balance revenue – either through portfolio management, business/price model changes or financial planning – could help avoid large share-price fluctuations. Factoring companies could become important players in the industry by financing peak manufacturing costs and then taking upfront revenue and paying it out to the pharma company over time, thus helping to manage peaks in costs and revenue.

> "High initial sales caused by the treatment of large backlogs will lead to distinct first-mover advantages and large fluctuations in production volumes."

INSIGHT FOR THE EXECUTIVE

An increase in curative treatments will lead to tremendous clinical progress and drastically improved quality of life for affected patients. It will also, however, put significant pressure on healthcare systems, as well as change revenue models for pharma companies providing such treatments. High initial sales caused by the treatment of large backlogs will lead to distinct first-mover advantages and large fluctuations in production volumes.

To prepare for this major change, there are a number of concrete items that policy makers and executives in the healthcare industry must focus on:

- New payment and reimbursement models need to be put in place. Pharma companies developing curative treatments need to engage with care providers, policy makers and payers to develop financial models that are sustainable for all parties. Engaging with payers and providers early on will also help them plan and prepare for implementation of new treatments. In order for patients to fully benefit from the new developments, healthcare provider operations need to be able to accommodate rapid changes in care practices. Training, education, facilities management and executive decision-making processes will all be impacted.
- Policy makers, payers and care providers should start to build up better analytical capabilities tailored to assessment of new curative treatments and their implications. These must focus on quantifying the value of the new therapies, in terms of both the value to patients (improved quality of life, increased lifespan) and the financial side (the upfront cost of treatment versus the long-term costs of managing the disease, as well as the cost of treating medical issues caused by the disease). Models for quantifying and analysing treatment impact should then be used to make qualified decisions around treatment funding and prioritisation of healthcare spend in order to balance expectations around treatment access with overall cost and value.
- Pharma companies need to review their drug pipelines, portfolio management practices and launch plans (marketing, sales, manufacturing) to accommodate the different properties of curative treatments so that they can proactively push for first-mover position or adapt their strategies if that isn't possible.

Developing these new capabilities across the healthcare system will be essential to ensure new therapies can be brought to market and implemented in clinical practice in an efficient and sustainable manner – prioritising high-value treatments for the benefit of patients.

ABOUT THE COMPANY

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A FLEXIBLE, MODULAR PLATFORM TO DISRUPT THE BLOCKBUSTER MANUFACTURING MODEL

In this article, Nick Rollings, Co-founder, Colin Barker, Co-founder, and Richard Vellacott, Non-executive Chairman, all of BiologIC Technologies, discuss the drug delivery scenario in the advanced therapy (AT) era. They look at how the current slow-moving blockbuster treatment model will make way for a fast-moving, patient-focused era of personalised medicine – creating new opportunities for flexible, decentralised AT manufacture closer to the patient.

Drug delivery is currently predominantly based on the "blockbuster" model, with a single therapy developed to treat a large patient population. Blockbuster therapies are manufactured in centralised biomanufacturing plants configured to produce large quantities of a single therapy in each batch. But although the blockbuster model has worked for decades, it is now facing disruption from multiple developments occurring in the pharma and broader life sciences sector. The life sciences sector is in the early stages of a "digital" revolution, with potential to significantly disrupt pharma.

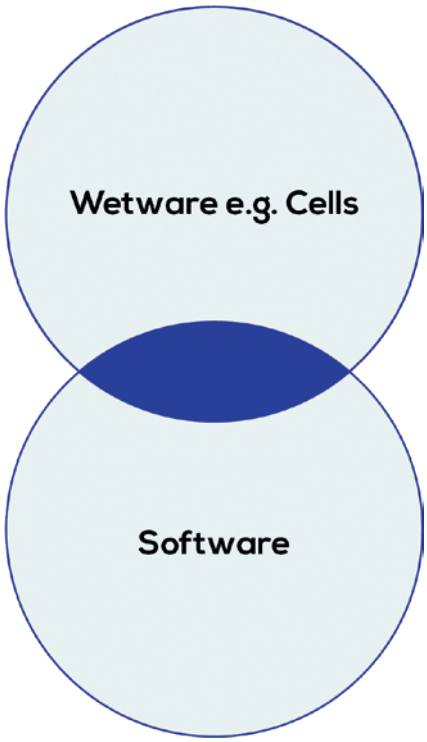

Figure 1: Emerging digital model for life sciences.

> "Digitisation is enabling the emergence of an exciting, dynamic new model underpinned by extensive use of data science and the application of digital software."

Digitisation is enabling the emergence of an exciting, dynamic new model underpinned by extensive use of data science and the application of digital software. Increasingly, artificial intelligence (AI) and machine learning (ML) are also being applied to the life sciences tool chain – influencing all aspects from experimental design through to experimental data capture and analysis (Figure 1).

Despite these developments, pharma and the life sciences sectors still lag behind other industries – and large tech companies see opportunities to enter the life sciences sector, as evidenced by the ambitious recent announcement of the Novartis and Microsoft collaboration to transform medicine with AI.[1]

NEW THERAPIES

The use of digital tools and large data sets has enabled a transition towards more complex science which, in turn, has allowed a focus on areas of unmet medical need, such as treatments for smaller patient populations. New ATs such as two Novartis gene therapies, Kymriah (tisagenlecleucel) for the treatment of B-cell acute lymphoblastic leukemia, and Zolgensma (onasemnogene abeparvovec) for the treatment of spinal muscular atrophy in children under two years old, are early examples of the increasingly powerful ability to target very specific conditions

Nick Rollings
Co-Founder
E: nick@biologic-tech.com

Dr Colin Barker
Co-Founder
E: colin@biologic-tech.com

Richard Vellacott
Non-Executive Chairman

BiologIC Technologies Ltd
Cambridge
United Kingdom

www.biologic-tech.com

and smaller patient populations. Currently, however, these therapies have very high cost of goods (CoGs) which has limited the ability of patients to access them.

As the ability to develop therapies for smaller and more targeted patient populations grows, the next decade will see greater stratification of patient populations and increasing personalisation, with a greater variety of cell therapies and gene therapies being developed.

AWAY FROM THE BLOCKBUSTER MODEL

These exciting developments will significantly disrupt the blockbuster model, with current industry tools and approaches being wholly incompatible with cost-effective development and production of bespoke products.

The next decade will require a transition of the "10-year, US$1 billion (£800 million)" development cycle to much leaner development, whilst simultaneously managing high-complexity science and associated high-complexity biological workflows.

It is, however, the manufacture of personalised medicines that will undergo the most significant disruption. Manufacture of high-value therapies will need to be in closer proximity to patients, with a requirement for on-demand manufacturing to suit different patients in varying states of health. There will be a need to accommodate high-complexity biological workflows that can differ considerably between each therapy, in addition to requiring real-time, in-process quality control (QC) analytics, as each therapy becomes a manufacturing batch in its own right.

This departure from the existing reliance upon economies of scale is a significant challenge for slow-moving incumbents in the pharma sector – and a significant opportunity for new entrants that can grasp opportunities in the fast-moving, patient-focused era of personalised medicine.

FUTURE DRUG DELIVERY SCENARIO

The future drug delivery scenario requires a targeted therapy to be manufactured specifically for each patient. This will result in fewer therapy administration occurrences. Following administration, there is then a reliance on frequent diagnostic monitoring and collection of a larger underlying data set to establish the patient's response to that therapy. Patient response may then trigger the manufacture of a second one-off therapy, modified to suit the patient response. Data and the use of digital tools will be the underpinning enablers of this new personalised medicine era.

This drug delivery scenario places considerable emphasis on the manufacturing of the AT, driving an urgent need to consider alternatives to the current model of central manufacturing reliant on economies of scale. There is a considerable need for new, disruptive manufacturing solutions to deliver the future of personalised medicine.

ALTERNATIVE THERAPY MANUFACTURING MODELS AND CHALLENGES

Decentralised manufacturing is an exciting new opportunity that requires brand new tools and technologies, and which has significant implications for existing pharma models.

The decentralised manufacturing model is seen as a solution to enhance the availability of cell and gene therapies whilst reducing CoGs of the manufactured therapy[2] and simultaneously addressing product stability challenges. Autologous therapies often have shelf-lives of only a few hours, necessitating production close to the clinical setting.[3]

The primary requirements of a decentralised manufacturing capability are enclosed, automated, controlled processes delivering a consistent quality target product profile, at a cost that is affordable to health providers.[4]

However, by its very nature, decentralised manufacturing closer to the clinic creates secondary challenges, such as integration of the decentralised manufacturing process into existing treatment pathways and minimising the need for extensive retraining of clinical staff. These primary and secondary challenges will need to be addressed by hardware solutions capable of satisfying the following requirements:

- Execution of controlled therapy manufacturing processes, delivering a consistent quality target product profile
- Adherence to good manufacturing practice (GMP) conditions whilst maintaining sterility of bioprocessing equipment
- Processing varying ranges of patient raw material whilst still producing the final therapy to a fixed specification
- Reduce the need for specialist manufacturing staff and for clinical staff to become AT manufacturing experts
- Capable of manufacturing several therapies for different patients simultaneously.

There is also a need for digital solutions capable of collecting and aggregating therapy manufacturing data as a critical input to the determination of patient response to a therapy.

Addressing these requirements will require a new capability – essentially a "flexible, sterile, factory-in-a-box" with digital capabilities closer to the patient. This represents an exciting new paradigm for therapy manufacturing.

COMPLICATION

Evaluation of existing lab automation finds there is still a fundamental gap in the availability of appropriate solutions and technologies to satisfy requirements for decentralised manufacturing of ATs.[2]

Current lab automation solutions are large, capital-intensive and inflexible, requiring skilled users to operate them. Solutions are orientated towards high-volume production (few tasks, high repetition) rather than low-volume production (multiple tasks, low repetition). Biological workflows are forced to adapt to the fixed functionality of a hardware platform, rather than flexible platforms adapting to the biology.

In addition, the emerging digitisation of biology and fast-paced development of digital tools have resulted in a disconnect between the biology, the software and the actual hardware used to execute experiments. An existing AT manufacturing protocol can require multiple hardware systems from multiple vendors with multiple standards, lacking a common approach – resulting in data silos and an inability to leverage the true potential of emerging AI/ML approaches (Figure 2).

The separation between existing hardware and emerging digital approaches is now constraining personalised medicine manufacturing, where there is a need significantly to reduce CoGs to enable democratisation of personalised therapies.

LESSONS FROM PREVIOUS REVOLUTIONS

Given the fundamental shortcomings of existing lab automation, it is useful to consider previous technology revolutions where a revolution in hardware has previously occurred.

The current generation of lab automation – whilst smaller and less expensive than centralised manufacturing plants – is still expensive, with varying architectures and operating systems, and little standardisation. These systems are comparable to mini computers of the late 1960s that still required dedicated facilities and trained staff.

It was the development of the desktop PC in the 1980s that created an accessible, affordable, standard yet flexible platform that made computing accessible for the masses (Figure 3). The decentralised manufacture of ATs will require hardware analogous to the desktop PC – a physically small, closed, standard yet flexible automation solution capable of customisation to specific therapy manufacturing workflows.

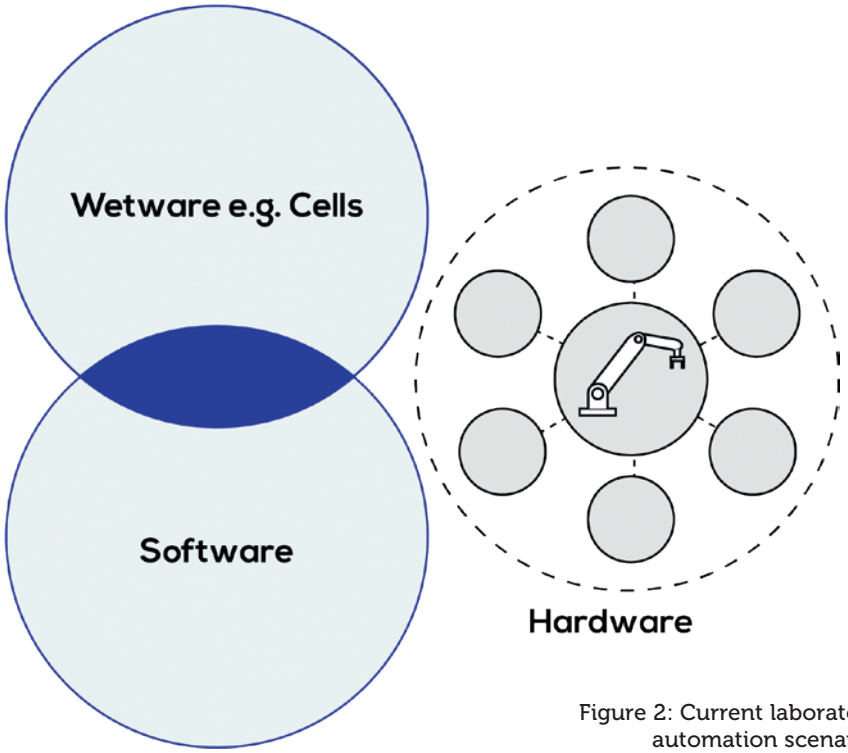

Figure 2: Current laboratory automation scenario.

NEXT-GENERATION MANUFACTURING PLATFORM

BiologIC Technologies is developing a new, disruptive therapy manufacturing platform. It is a standard, yet flexible, platform capable of customisation to suit differing therapies and address the needs of decentralised AT manufacture.

The platform represents a disruptive approach to life sciences automation as an affordable and accessible platform. The ability to develop and execute high-value biological workflows rapidly in affordable, application-specific consumables enables life sciences innovation in the same way that the PC made computing accessible for the masses (Figure 4).

HARDWARE ENABLERS

The BiologIC platform exploits knowhow from the semiconductor sector to create

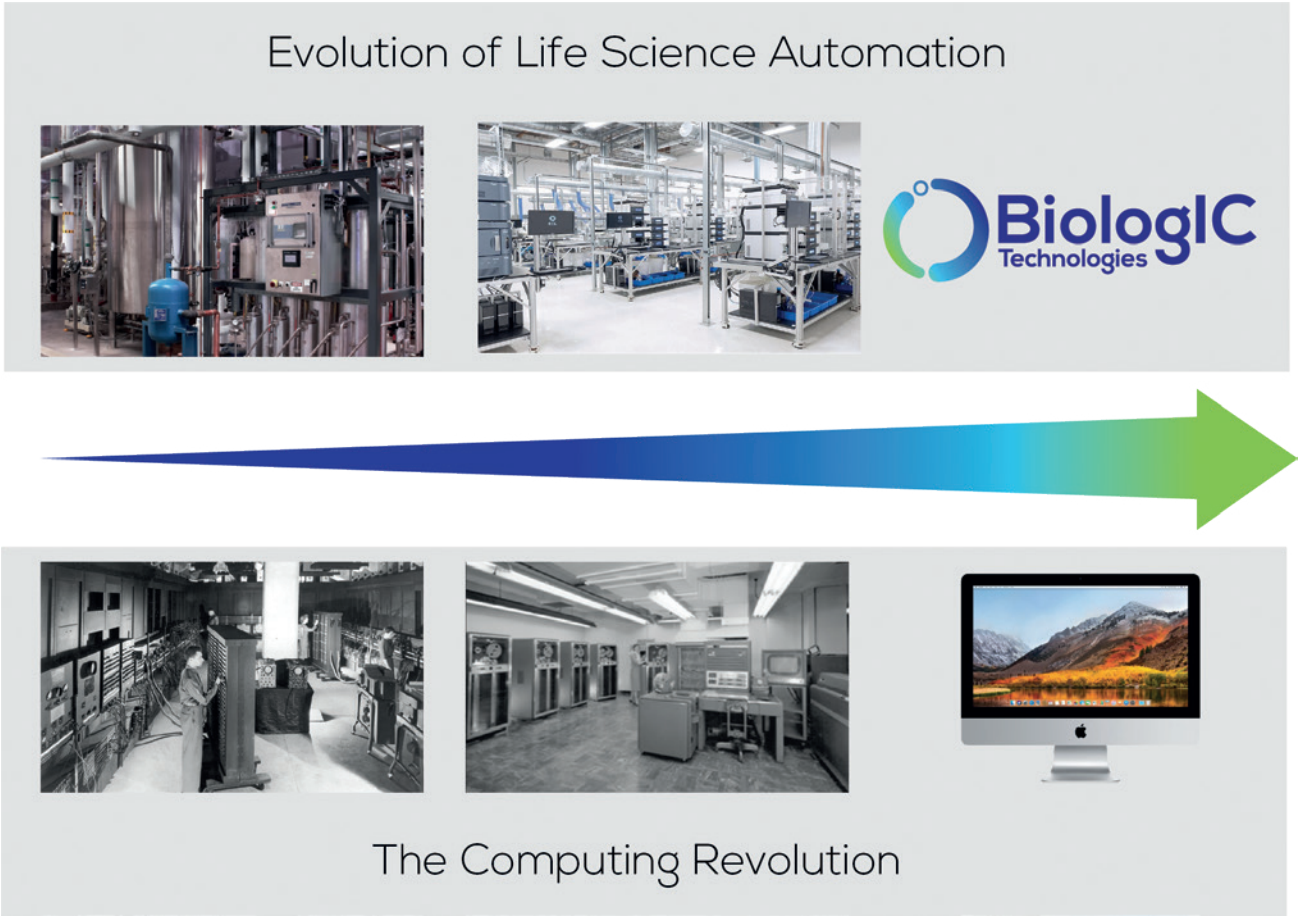

Figure 3: Evolution of life sciences automation and the computing revolution.

integrated systems that are not only physically small but also highly powerful. The small yet powerful approach enables miniaturisation of a large factory into a flexible, sterile, factory-in-a-box.

The integrated and miniaturised hardware architecture is particularly advantageous. Integration of several solutions provides an economic approach to the creation of larger systems within a closed automation platform that has a high density of function per volume and low unit cost.

The BiologIC platform enables modular solutions within a standardised hardware architecture. The standard, yet flexible, modular architecture presents an opportunity for risk-sharing schemes across the cell and gene therapy sector.[3]

Proven, verified modules available to multiple users reduce technical risk and enable the pooling of learning across the AT sector. Rapid reconfiguration of modules to suit specific needs and create custom solutions reduces development cost and risk.

In addition to risk mitigation, there are also benefits from the use of custom, modular solutions – such as enhanced protection of manufacturing-related intellectual property. In addition, pooled solutions reduce barriers to entry for smaller therapy developers otherwise unable to afford the creation of automated manufacturing solutions.

This modular approach to complex systems has been extremely successful in the semiconductor sector with the likes of ARM (Cambridge, UK) providing a wide range of microprocessors, modules and supporting tools, enabling customers to create a custom solution for their own needs.

COMPLEMENTARY DIGITAL SOLUTIONS

In addition to standardised hardware, the BiologIC platform enables the collection of in-process AT manufacturing data in a standard format. The close integration of hardware and related digital tools allows the adaption of the hardware around the biological workflow and required data – streamlining traditional bioproduct and biotherapy development processes (Figure 5).

BiologIC's combination of digital biology and digital hardware will enable the rapid creation of lab automation capable of customisation on a project-specific and ultimately experiment-specific basis.

Figure 4: BiologIC's advanced therapy manufacturing hardware.

The underlying digital tools used to create the hardware will also enable creation of an ecosystem where workflows/modules/consumables can be shared or created as required in a manner analogous to an Apple or Android app store.

The application of ML and AI also represent opportunities to drive value from data collected by the BiologIC hardware during therapy manufacturing.

LONGER-TERM OUTLOOK

Over time, BiologIC sees the opportunity to standardise the hardware used for life sciences and the opportunity to become the supplier of the underlying core technology powering the future of life sciences in a manner analogous to Intel and ARM in the smart devices sector.

CONCLUSION

The AT era will be a fast-moving, patient-focused era of personalised medicine – creating a requirement for new flexible, modular tools and technologies. It is only through the development of these new disruptive solutions that the benefits of AI will be realised.

ABOUT THE COMPANY

The pioneering vision of Cambridge, UK-based BiologIC Technologies is to become the enabling architecture for a disruptive generation of integrated and miniaturised life sciences automation. BiologIC's unique and powerful combination of digital biology and digital hardware is set to enable the next wave of laboratory automation – including applications in cost-effective advanced cell therapy manufacturing – and drive the democratisation of personalised medicine.

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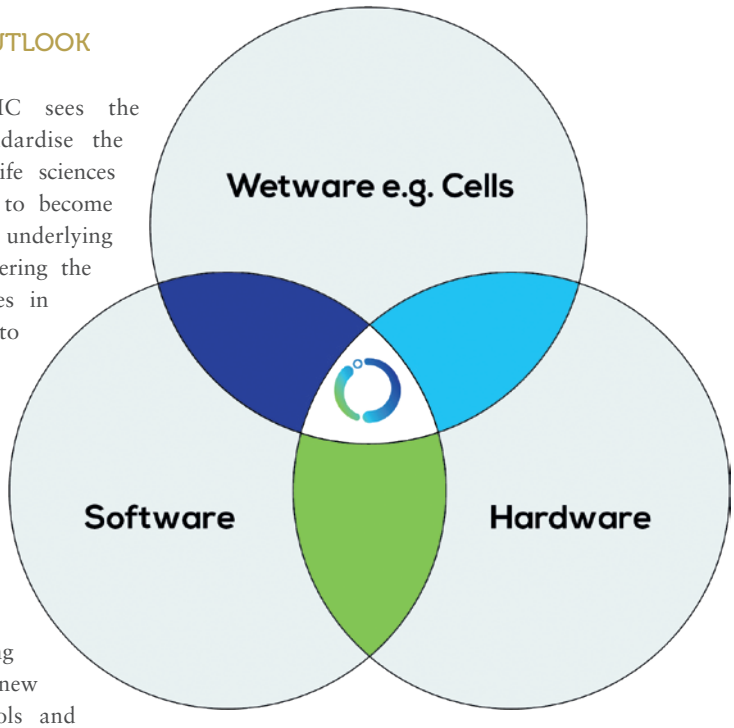

Figure 5: BiologIC Technologies' platform.

ABOUT THE AUTHORS

Co-founder **Nick Rollings** is a Chartered Engineer and technologist who has spent the last 10 years working in technology consultancies in the Cambridge cluster, including nearly five years at Cambridge Consultants. Prior to this, Mr Rollings worked in industry in manufacturing engineering and mechanical design roles and was a founder member of a spin-off company from FTSE 100 technology firm Smiths Group – developing a novel medical diagnostic platform for veterinary and clinical diagnostics. Mr Rollings has experience of developing devices in the broader medical technology area and has a particular focus on the development and commercialisation of platform technologies for biology and life sciences. His experience includes development of point of care diagnostics, instrumentation for synthetic biology and decentralised biomanufacturing solutions, including manufacturing of ATs.

Co-founder **Colin Barker** is a biologist with an engineering habit. With a degree in Genetics and a PhD in Toxicogenomics, he has a solid scientific background but over the years has broadened his skill set to include software programming, management and leadership, and automation design and fabrication. Dr Barker has over a decade of experience in the development of commercial products and services – from innovation and proof of concept through to commercialisation and ISO accreditation. In addition to product development, he has worked at a strategic level, building new value propositions and refining business processes and workflows. With an emphasis on production methodologies and design for manufacture, this has enabled rapid scale-up, increased efficiency and reductions in cost of goods. Through his commitment to best practice in leadership and management, Dr Barker holds a Fellowship of the Chartered Management Institute.

Non-executive Chairman **Richard Vellacott** was previously Chief Financial Officer of Horizon Discovery Group for seven years, leading one of the most successful ever life sciences IPOs on AIM – raising £68.6 million in a heavily oversubscribed IPO at the top of its valuation range – followed by two major US acquisitions within six months. He has a first-class degree in Biological Sciences from Durham University (UK) and is a qualified chartered accountant, advising numerous companies from lab bench to global pharma. Mr Vellacott has also been Vice-President, Finance at FTSE 250 company CSR. Before that, he was a director in Deloitte's life sciences practice, working with leading life science companies such as AstraZeneca, Vectura, Cambridge Antibody Technology and Abcam. He specialised in capital market transactions including numerous IPOs, mergers and acquisitions, and fundraisings.

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