Review Article: Jean-Claude Muller

The advance of digital medicine

We live in an age which is increasingly dominated by digital technology. In its simplest terms, digital technology is a process by which information, whether it be in the form of images, sound or documents, is converted into a format that can be read by a computer and more recently, displayed through an application on a tablet or a cellphone. Digital technology has already transformed telecommunications, printing and computing. Now, it is on the verge of reshaping medicine.

The first applications of the new technology are devices that can be worn on the body to monitor physical well-being. For example, activity trackers record a person's daily routine in order to capture calorie consumption, circulating glucose levels, heart beat and sleeping patterns. The devices contain micro-controllers that collect, store and analyse information and give the wearer a health update or an early warning if something has gone wrong.

The new digital technologies are also being used to treat disease. The convergence of four distinct disciplines - nanotechnology, biotechnology, information technology and cognitive science – is making this possible. Together with artificial intelligence, they are yielding new approaches for the treatment of heart disease, eye disease, diabetes, neurological disorders and cancer. Moreover, the new disciplines, plus robotics, are making it possible for operating theatres around the world to offer patients minimally invasive surgical procedures which are more effective than conventional methods.

"At an industrial level, the new digital technologies are already shaking up the executive suites at large pharma companies."

All the while, data collected from patients is being fed back into the healthcare system to inform future treatments. According to the market research firm Berg Insights AB, an estimated 36 million patients will be using home monitoring devices connected to the internet by 2020 to engage with doctors and insurers. These will go further than the activity trackers of today because they will provide the basis for future digital medical solutions.

At an industrial level, the new digital technologies are already shaking up the executive suites at large pharma companies and changing the competitive dynamic within the marketplace. In mid-2017, both Novartis and GlaxoSmithKline Plc appointed executives from the retail sector who will be responsible for digital strategy. Bertrand Bodson joined Novartis from Sainsbury's Argos where he was chief digital and marketing officer and Karenann Terrell joined GSK from Walmart where she was chief information officer. Despite this, the pharma industry faces increasing competition from information technology specialists and data providers which have invested heavily in platforms to help patients capture data on their health. These companies include IBM Watson Health, Google Inc, Apple Inc, Microsoft Corp, Samsung Group, Dassault Systèmes SE and Qualcomm Inc.

Eight projects currently underway in digital medicine illustrate the trend.

The first is a wireless implant developed by **Pixium Vision SA** of **France** which is intended to restore visual perception in elderly people with atrophic age-related macular degeneration (AMD). This is a condition in which small yellow deposits, known as drusen, form under the macula, causing a loss of central vision. To correct for this vision loss, a micro photovoltaic chip has been designed for implantation under the retina of patients. The implant is intended to act like a solar panel, receiving light from a tiny projector and creating images that can be interpreted by the patient. The projector sits on a pair of eye glasses which in turn is connected to a pocket-size computer powered by a battery. On 25 January, Pixium reported results from the first patient to be tested with the device. One month after implantation, the patient reported a first perception of light – where light had not been seen previously. Pixium is trialling the product in Europe in preparation for approval as a Class 3 active implantable medical device. It also plans further trials for a regulatory submission to the US Food and Drug Administration.

Digital drug-device product

Meanwhile, the FDA gave its first approval on 14 November 2017 for a digital drug-device combination product. This is a treatment for schizophrenia developed by **Otsuka Pharmaceutical Co Ltd** of **Japan** and **Proteus Digital Health Inc** of the **US**. It consists of the antipsychotic drug Abilify in pill form which has been embedded with a sensor. When the pill is swallowed, the sensor is activated by fluids in the stomach and this generates a signal which is detected by a patch on the patient's left rib cage. This patch records the date and time of the ingestion of the tablet via Bluetooth to a dedicated cellphone application. The main purpose of the digital pill is to encourage patients with schizophrenia to comply with their treatments. Importantly, it gives the physician the ability to monitor the patient's drug use over time.

A similar technology is being developed by **etectRX Inc** of the **US** to help physicians monitor patient compliance with their treatment programmes, such as those taking HIV medications. The technology consists of a capsule imbedded with an ingestible wireless sensor. Made from magnesium and silver chloride, the sensor generates a low-power radio signal from within the patient's stomach. The signal is

picked up by a small external antenna that can be fitted onto a watch band or a cellphone case. The company says the goal of its technology is to get "real time, per dose, medication adherence confirmation."

VitalConnect Inc, also of the **US**, recently launched an FDA-approved disposable patch that is intended to monitor in real time several vital signs of a patient's health including heart rate, heart rate variability, respiratory rate, skin temperature and posture. The patch sends the data via Bluetooth on a mobile device to healthcare providers. The patients can be in a clinical setting or remote from a doctor's office, in which case the device is expected to speed up the response of the healthcare system to an emergency. The patch is based on the company's expertise in bioengineering, data analysis, integrated circuit design and the manufacturing of wearable patches.

Interface between biology and electronics

The **UK's GlaxoSmithKline Plc** is one of the earliest big pharma investors in digital technology for health. In 2012 it set up a dedicated unit to research new products on the interface between biology and electronics. At the time, these were defined as silicon chips that could identify specific biological molecules which could predict disease, or electrical devices that could modulate neural impulses to treat disease. Since then, the company has been developing a 'nerve atlas' with information about each nerve in the human body and its links to specific organs and diseases. In 2016, GSK launched a joint venture company, Galvani Bioelectronics Ltd, to advance its work in this area. Its partner is Verily Life Sciences LLC, a subsidiary of Alphabet Inc, which is the holding company of Google Inc. The two companies have committed up to £540 million over seven years to bring several preclinical projects into clinical development and registration. Galvani has been working on prototype devices that can stimulate or block nerve transmission with the objective of treating chronic diseases such as Type 2 diabetes and asthma. The goal is to have a device ready for proof-of-concept trials sometime this year. Meanwhile, on 17 January, GSK obtained exclusive rights outside of the US to wearable technology for treating chronic pain. This device, called Quell, was developed by NeuroMetrix Inc and has been cleared by the FDA for sale without a prescription. Quell electrically stimulates sensory nerves in the upper calf which upregulate the central pain inhibition system leading to analgesia in the feet, legs and lower back Scientists believe that high-frequency nerve stimulation induces the release of enkephalins, a natural pain reducing agent produced by the central nervous system. The Quell device is a novel digital medicine product that combines neurostimulation with a dedicated application. The application controls the device, visualises and optimises the pain episodes and collects valuable clinical data for the healthcare professional.

Switzerland-based **G-Therapeutics SA**, a spin-out of the Swiss Federal Institute in Lausanne, is developing a therapy that combines an epidural spinal cord implant with gravity-assisted exercise. The technology for 'reversing paralysis' was given top ranking in the March 2017 edition of the *MIT Technology Review*. The electrical stimulation of the lumbar spinal cord reawakens the injured neuronal circuits that coordinate leg movements. The progressive rehabilitation triggered by the stimulation with well-programmed gravity assistance enables and guides the remodelling of neural circuits, thus triggering the brain to help itself. The technology has already been tested in man.

Akili Interactive Labs Inc of the **US** recently made headlines with the results of a trial of its therapeutic video game for children with attention deficit hyperactivity disorder (ADHD). The digital medicine, called AKL-T01, is a game that children can play on a tablet device. They are rewarded for a good performance with art, music and storytelling as is customary in video games. However in addition, the device uses adaptive algorithms to deliver the presentation of stimuli that engage neural systems in the prefrontal cortex. This is the part of the brain that is responsible for cognitive control and which is deficient in children with ADHD. The Phase 3 trial enrolled 348 children diagnosed with ADHD. Patients were randomized to AKL-T01 or to an active control. Those in the treatment arm showed a statistically significant improvement in their ability to sustain attention, as measured by an attention performance index. On the basis of this data, Akili plans to make an application with the FDA to have the digital medicine approved as a medical device. Separately, the company recently partnered with Noah Falstein, the former chief game designer at Google. The company has also worked with Pfizer Inc on a fast-paced video game that can differentiate between subjects with and without brain amyloidosis. In theory, this would be a way of identifying people with early, or prodromal, Alzheimer's disease. Akili is reportedly also investigating the possible application of its technology in autism, major depressive disorders, Parkinson's disease, multiple sclerosis and traumatic brain injury.

Other technologies

If approved, the Akili product would not be the first prescription digital medicine to reach the US market. This distinction was won by **Pear Therapeutics Inc** in September 2017 when the FDA authorised its digital therapeutic to treat patients with substance use disorder. Called Reset, the device is a medical application intended to be used on an outpatient basis to help people recover from alcohol, cocaine, marijuana and stimulant abuse. Another product being developed by the company targets opioid addiction. The Reset device delivers a cognitive behavioural therapy programme with the goal of helping patients abstain from addictive substances and remain in their outpatient programmes.

On the laboratory front, **Switzerland's Roche** and **GE Healthcare** of the **US** announced a partnership on 8 January to jointly develop and co-market digital clinical decision support systems to help healthcare practitioners improve the treatment options for patients with cancer and other critical conditions. The concept is to create a seamless display of *in-vivo* and *in-vitro* data, patient records, medical best practice and the latest medical research to guide physicians in providing individualised treatments to patients. The partnership combines GE Healthcare's expertise in medical imaging with Roche's capabilities in in-vitro diagnostics (for further information, please see the article on page 12 of this issue).

Finally, **France's Sanofi SA** and **TriNetX Inc** announced a collaboration on 16 January to use digital technology to help improve the design of clinical trials, including the writing of trial protocols. TriNetX operates a cloud-based research platform. Drawing information from this platform, which includes anonymised patient records, researchers can quickly draw up model protocols and visualise how they would be expected to operate in an actual clinical trial. As new information emerges, the protocols could be modified. The technology also has the capacity to predict certain outcomes so that researchers can forecast the number of patients required to meet specific study criteria. Sanofi has two other collaborations using digital technology to manage clinical trials. One is with Science 37 Inc on real-time data collection, and the other with Evidation Health Inc to monitor digital biomarkers in trials.

The regulatory issues

Right now, it can take up to 24 months to get an application for a digital medicine reviewed and approved by the FDA using the 510(k) regulatory pathway. According to a strategic review published on 9 January, the agency considers digital health one of its key priorities. Therefore to encourage innovation and improve efficiency, the FDA has taken steps to simplify some regulation (for further information, please see article on page 13 of this issue). For example, not all clinical decision software would be defined as medical devices and therefore would not be regulated by the agency. Another initiative involves establishing common principles for regulators to use in evaluating the safety, effectiveness and performance of software as a medical device (SaMD). Several companies including Apple Inc, Fitbit Inc, Verily Life Sciences LLC, Johnson & Johnson Inc, Pear Therapeutics Inc, Phosphorus Inc, Roche and Tidepool Inc have been selected by the agency to participate in a discussion about novel regulatory approaches to digital health. Assuming this leads to pilot projects to test some of the concepts, these projects would likely take place where sophisticated and integrated platforms are already in place and where it will be easy to monitor data quality.

Many of the new entrants to the healthcare field will want to engage directly with patients, collect their data and deposit it in large harmonised data platforms. Using artificial intelligence, they could then theoretically analyse the data and offer advice to individuals about healthy lifestyles, the prevention of disease and if necessary, treatments. But it remains to be seen whether the regulatory rules will allow access to individual patient data to any entities other than healthcare professionals.

The broader challenges

There are many issues still to be resolved including how to ensure the protection of patient data, secure the digital networks against cyber attacks and demonstrate to payers that the new digital medicines are cost effective.

Physicians will only accept digital medicine if they are confident the products will deliver clear-cut benefits and improve patient compliance with existing treatments. They will need to be confident they will not be overwhelmed with data without having the tools to cope with it. The issue of the monitoring adverse events from digital devices and software, with appropriate reporting systems, also has to be addressed.

Many patients will be keen to test the new digital medicines in so far as they might be seen as extensions of digital devices, such as the mobile phone, which are already part of everyday life. Nonetheless, there is also the risk that the new medicines could be seen as invasive, a kind of 'biomedical big brother.'

Health insurers will need to know whether the new digital medicines, which are starting out as adjunct therapies, will increase the overall cost of treatment, or make existing procedures more efficient. It will take a while for many of these products to become first-line treatments for major medical conditions.

Patient outcomes

As with other medical interventions, the new digital technologies will be valued according to their ability to improve patient outcomes and empower people to play a bigger role in their own care. The new technologies are developing at a faster pace than most biopharmaceutical companies are accustomed to; their adoption is likely to lead to massive disruption. Biopharma companies will need to prepare for this new paradigm. Although digital medicine will bring new companies into the healthcare arena, it is likely that established biopharma companies will still dominate the field. This is because, thus far, they are the only ones to master the entire value chain from the concept of a new medicine, to validation, through clinical development, to health authority clearance, customer distribution and patient compliance.

The industry is slowly realising that drugs and pills may no longer be the dominant component of healthcare. Value will increasingly be generated by the total package offered to a patient, rather than isolated components. This new approach, which is described as systemic, will require biopharma companies as well as information technology and digital device companies to build partnerships and alliances – different from the ones they currently are used to.

This article was written by Jean-Claude Muller, an international industry consultant and former senior vice president for research and development at Sanofi SA. He is a member of the *MedNous* editorial board.