

Drugs go wireless

Electronic drugs and delivery systems are reaching the market, giving drug developers and healthcare providers a way to improve patient compliance and more. Emily Waltz reports.

In September, the FDA accepted for the first time a new drug application that joins a prescription medication with a monitoring device. Tokyo-based Otsuka Pharmaceutical combined its blockbuster antipsychotic Abilify (aripiprazole) with an ingestible sensor made by Proteus Digital Health in Redwood City, California, that tracks when pills are taken. Last year, Petach Tikva, Israel-based generics giant Teva Pharmaceuticals revealed its interest in this area with a partnership with Microchips Biotech of Lexington, Massachusetts, which makes an implantable drug dispenser, and its acquisition of Gecko Health Innovations, a Cambridge, Massachusetts-based maker of smart inhalers that digitally track their use.

These new technologies wirelessly monitor administration of drugs and can even deliver drugs through wireless prompts. The goal in most cases is to improve the consistency and accuracy of medication taking—a practice called patient adherence or compliance. Some device makers have been able to demonstrate clinically that their technologies do that. They've also been able to convince drug developers that the devices may offer a way to extend a drug's market exclusivity and thwart generic competition. But the success of digital drugs hinges largely upon whether improved adherence will translate to better health and outcomes—something insurers and payers will reimburse. That evidence has yet to be demonstrated, and digital drug makers are sorting out how to address the challenge, along with concerns about data privacy and consent.

Beyond the app

Countless health-tracking devices worn on the outside of the body have emerged on the market, enabling continuous monitoring of metrics, such as sleep, heart rate, body temperature and exercise. The trend is naturally extending to drugs with the advent of digital pill bottles and dispensers that help people stay on top of their medications. The devices track when the medication is dispensed, and the data are sent to an app and can be shared with a third party, such as, doctors and family members who want to help, or perhaps snoop on, their patients or loved ones. New York-based AdhereTech has one such smart pill bottle that notifies a healthcare provider

when it has been used or when a dose has been missed, and is marketing it to pharma companies and research institutions. Smart inhalers follow the same vein, tracking when the inhaler has been used. Propeller Health in Madison, Wisconsin, received clearances from the US Food and Drug Administration (FDA) for sensors designed to work with inhalers made by GlaxoSmithKline of London and Boehringer Ingelheim of Ingelheim am Rhein, Germany (Table 1).



E-detecting. This wireless tracking device, which is embedded into a standard gelatin capsule, communicates with an external hub. Source: Glen Flores, eTect Inc.

But, for assurance that a drug is delivered, not just dispensed, the sensors must go inside the body. To that end, device makers, such as Proteus, have developed ingestible sensors that are embedded in pills and communicate with external software when they are ingested. Taking it one step further, Microchips Biotech's device is implanted in the body, preloaded with drugs, and can be programmed to dispense them without the user doing anything.

The devices have been called a lot of names: smart drugs, digital drugs, electronic drugs, and for those of a certain perspective, snitch pills. The applications are easy to imagine. The elderly, the mentally ill, the chronically ill, teenagers, addicts—anyone who has trouble remembering to take their medication, or needs another set of eyes on them, might benefit from some digital medication tracking.

The statistics for medication adherence are compelling. Cambridge, Massachusetts-based Network for Excellence in Health Innovation in 2009 reported that medication nonadherence is a \$290-billion problem. The percentage of people who fail to take their drugs varies by disease, but many estimates put it as high as 50%.

So it's easy to see the attraction of the idea of putting a sensor on every pill. "Yes, there are many people who don't take their pills, but there is a large body of people who do take their medicine on time, and adding technology isn't necessarily going to make them better," says Eric Buffkin, president and COO at eTect Bio, a Newberry, Florida-based startup that is developing a digital pill. "And there's also a smaller segment for whom it doesn't matter what you do, they're not going to take their medicine as prescribed. So the people we're going to provide the most help to are the ones

who can be influenced—the folks who will respond to some sort of intervention to change their behavior. That dynamic will have a say in which therapeutic areas these technologies will be successful," he says.

The sweet spot for this technology, adds Eric Topol, professor of genomics at the Scripps Research Institute in La Jolla, California, "is in select clinical indications where adherence is absolutely vital," such as infectious diseases. Besides, adherence has been magnified to the hilt, Topol says. "One thing about adherence that gets to me is that everybody talks about how 50% of people are nonadherent, but they forget to mention that most drugs don't work in most people. In those cases, so what if they don't take the drug?" he says.

And focusing on improved adherence stops short of the goal. "To get reimbursement you're going to have to prove your sensor does more

Table 1 Wireless devices in commercial development or on the market

Company/Institute	Product	Technology	Status
Proteus Digital Health	Abilify/Proteus	Ingestible sensor, activated by stomach fluid, sends signal to an external patch, which tracks medication taking, steps, activity, sleep and heart rate, and is delivered to “discover app,” which can be shared with a third party.	FDA accepted in September NDA for first drug/device tablet
Covidien (formerly Given Imaging), Yoqneam, Israel	SmartPill	Ingestible capsule that measures pressure, pH and temperature as it travels through the GI tract to assess GI motility disorders.	FDA clearance, July 2006
Covidien	Bravo pH	Capsule-based monitoring for presence of acid reflux. Capsule is attached to esophagus, and after a few days, proceeds through the GI tract. Capsule transmits pH data from the esophagus wirelessly to external recorder. The company recalled the device in 2012 for failing to attach to the esophagus, and terminated the recall later that year.	Approvals by FDA, 2010
HQ Inc., Palmetto, Florida	CorTemp & AgriTemp	Human and animal versions. Capsule wirelessly transmits core body temperature to an external recorder. A crystal sensor vibrates, producing a magnetic flux and transmits a low-frequency signal harmlessly through the body. The sensor passes through the body. Single-use device. Human applications: sports, military, research, firefighters.	FDA cleared, 2012
Medimetrics	IntelliCap	Capsule with drug reservoir, pH and temperature sensors; releases drugs to defined region of the GI tract. Microprocessor and transmitter provides two-way real-time wireless communication.	CE Mark 2011; expanded use, July 20, 2015
Propeller Health	Propeller	Device attaches to the top of an existing inhaler, which syncs with a Bluetooth technology. App provides data and feedback and collects time, date and location when inhaler is used.	FDA clearance for use with GlaxoSmithKline's Diskus and Boehringer Ingelheim's Respimat inhalers
eTect	ID-Cap	Wireless sensor embedded in capsule with prescription drug, which communicates with a wearable device.	Used in IRB-approved clinical research
Microchips Biotech	Microchip	Implantable silicon chip with multiple microreservoirs that hold drugs; activated by wireless signals on preprogrammed schedule or prompt.	Used in a clinical trial in Denmark with approval by Danish Medicines Agency for delivering parathyroid hormone to postmenopausal women

than improve compliance. You have to show it improves outcomes,” says Riccardo Panicucci, vice president of pharmaceutical development services at Cambridge, Massachusetts-based WuXi AppTec. “And to prove that can be incredibly expensive—years of clinical studies. And until somebody does that, I don’t see payers being held accountable to pay,” he says. Panicucci was previously global head of chemical and pharmaceutical profiling at Novartis, where he helped oversee an early collaboration with Proteus.

For market or for research?

Despite the unknowns, Proteus has pressed forward through the regulatory processes in both the US and the European Union (EU; Brussels). The regulatory road in the US has been bumpy, because it was unclear, at least at first, whether wireless drug tracking and delivery technologies would be considered a device or a drug or a combination of the two. It helped that the FDA in January 2015 put out guidance for industry for combination products—a category under which many of these products will likely fall. But companies will probably need to approach the FDA on a case-by-case basis to determine whether these wireless products will be regulated as more of a drug or a device.

Proteus’s sensor pill works much like a grade school kid’s potato battery. The sensor is about the size of a grain of sand and includes two dissimilar metals that act as electrodes. After

being swallowed, it comes into contact with stomach acid, which acts as an electrolyte and closes the circuit, generating an electrical signal. The signal travels through the body and, like an electrocardiogram, is picked up by electrodes in an external patch that sticks to the skin. The signal is translated into a series of 1s and 0s that indicate the pill’s identity and dose, the time it was ingested, and potentially other pertinent information, such as when and where it was manufactured. The data are relayed to an app, and can be shared with a third party, such as a family member or doctor.

Proteus combines its sensor with pills in two ways: by co-manufacturing and by overencapsulating. In the overencapsulation route, the sensor is placed in a capsule that is otherwise empty, and can be filled with a drug of choice at specialty pharmacies through a semi-automated process. The FDA approved this form of the device in 2012 and in July 2015 expanded the indication for the device to allow Proteus to claim that it could be used to measure adherence. The device received Europe’s CE Mark in 2010.

The overencapsulation route was a way to get to market quickly and generate data, says Erika Karplus, head of strategy and corporate development at Proteus. The company is selling the capsule to integrated health systems in the US and to the UK’s National Health Service in the hope that their using it will build evidence on the benefits of such systems.

The company’s long-term play, however, is to combine the sensor with drugs by embedding it in tablets at the point of manufacture, a process called co-manufacturing. The regulatory pathway for this approach is longer, but the manufacturing process is scalable because it would be fully automated. To get regulatory approval for this version of the device, the FDA has said that Proteus must show that its embedded sensor does not change the stability or shelf life of the drug or sensor—data that will take about 12 months to gather for every drug that Proteus wants to digitize. Proteus has completed its stability testing for one drug: Otsuka’s Abilify, whose new drug application (NDA) the FDA has said it would make a decision on by April 2016.

Adding a sensor to a drug may be attractive to pharma companies, particularly as a last-minute fix to thwart competition or create market exclusivity. In the case of Abilify, the key patents for it in the US and EU expired in 2014 and 2015, opening the drug to generic competition. A digital version of Abilify would give Otsuka a way to extend the drug’s life on the market—one of several approaches the company is taking. “Smart Abilify will be a new product with a unique drug code for reimbursement—one that cannot be substituted for a ‘dumb’ version,” says Karplus. Twelve months of data collection is short compared with the work required for most NDAs, she says. “We don’t have to do

efficacy studies, and we don't have to do clinical studies," she says.

Of course, outcomes studies are one way to generate evidence for payers, who want to see cost savings from healthier people. "Someone is going to have to take the risk of doing outcomes studies and I don't think it's going to be pharma. So there's a gap there," says Panicucci.

Karplus says Proteus is building outcomes data through clinical studies and by targeting integrated health systems that play a role as both the payer and the care provider. Through those partnerships, Proteus can build evidence showing how digitizing can improve clinical and economic outcomes, says Karplus. "We and others in the space are taking that approach as a stepping stone to payers such as insurance companies and self-insured employers," she says.

Karplus adds that she has found that health insurance companies have in the past year been more receptive to evaluating and piloting new technologies. "A traditional payer used to say, 'Don't come to me until you have complete and total evidence that's pretty incontrovertible that you can save me money.' But now some of them are saying they want to get an early look."

One way to avoid the payer problem is to market digital pills to pharma companies as tools for clinical trials rather than as add-ons to commercial drugs. Newberry, Florida, startup eTect is targeting that market with its digital pill 'ID-Cap'. The device is similar to Proteus's in that it is an ingestible sensor that is placed in a capsule that can be filled with a drug of choice. The sensor is attached to a piece of film that has a microelectronics circuit, metallic pads that act as electrodes and an antennae. Once the device is activated with stomach acid, a radio signal is created and communicates with a business card-sized reader device that is kept near the user, such as in a pocket. The data are then delivered to a phone app and can be relayed to eTect's portal.

Medication adherence is critical in clinical trials—particularly those with small patient populations. "When you spend a billion dollars developing a new drug and 20–30% of that is in the clinical testing of that drug, having a high level of precision in the clinical study is valuable," says eTect's Buffkin. Confirmation that study subjects are taking the medication or placebo removes ambiguity and improves the power of the data, allowing pharma companies to get to their decision points faster, he says. The digital pill is also useful for blinding studies. Drugs and placebos must be placed in opaque capsules so that they look the same to study participants and researchers. ID-Cap can serve that purpose while adding the digital monitoring capability.

Panicucci says targeting clinical trials as an initial market was a smart move on eTect's part. "That lowers the risk for pharma to take up these technologies," he says, whereas Proteus's attempts to leap directly into the commercial market may have been a bit bullish, and in the process may have left some opportunities on the table, he says.

Buffkin says eTect is currently marketing ID-Cap for use in institutional review board (IRB)-approved clinical trials, but not for the purpose of avoiding the challenge of convincing payers. "We are targeting clinical trials because they have an immediate need and there is a substantial market," he says. So far, they have not needed additional FDA clearance for those uses. To market ID-Cap more broadly, eTect will need to file with the FDA a 510(k) device application—a regulatory trail Proteus already blazed. Buffkin says he hopes for FDA approval some time in 2016.

Combining targeting and sensing

Several groups are taking the idea of digital drug delivery a step beyond an ingestible sensor. Eindhoven, the Netherlands-based Medimetrics, a spin-out of Philips Innovation Services, the Dutch electronic service provider, has developed an electronic capsule that delivers drugs to specific parts of the gastrointestinal (GI) tract. As the capsule travels through the GI tract, it measures pH and temperature, indicating the location of the capsule, and reports it wirelessly to an external device. Entry into the small intestine, for example, is indicated by a steep rise in pH. A drug dispenser in the capsule is programmed or commanded in real time to release the drug at a particular location.

The system can be used to extend the release of a compound and gain *in vivo* data to guide the development of a compound. "Drugs are absorbed differently in different places in the GI tract, and knowing exactly where a drug is released is very useful in creating a strategy for delivering the compound in the body," says Jeff Shimizu, chief technology officer at Medimetrics.

Drug developers often put an enteric coating on a capsule that protects drugs from the acidity of the stomach. The coating breaks down further along in the intestinal tract releasing the drug inside. "But that is highly variable," says Shimizu. "The rate at which the coating degrades and releases the drug [is] different in different people." In the early stages of drug development, it's hard to know whether unsatisfactory clinical results are artifacts of the efficacy of the drug or the delivery process. "That's where a tool like this is very helpful," Shimizu says.

Medimetrics collaborated with Basel-based Novartis to test its capsule, called the IntelliCap,

with the blood pressure medication Onzem (diltiazem) as a model drug to quantify its absorption (*AAPS PharmSciTech.* 15, 1490–1497, 2014). The company has also worked with AstraZeneca of London in a study of the release of Toprol (metoprolol) (*J. Control. Release* 217, 300–307, 2015).

The inside game

If there's a way to remove nearly all uncertainty of nonadherence, it's through an implantable electronic drug delivery chip. That's the focus of Microchips Biotech. The company's device stores drugs in tiny reservoirs and releases them on cue through a wireless remote. The reservoirs are hermetically sealed with a thin layer of metal. When it's time to release a drug, a low electrical current is sent to the appropriate reservoir, melting the metal cover plate. Body fluid goes into the reservoir, allowing the drug to diffuse out to the body. The device can be programmed to release a drug at a scheduled time, such as in the middle of the night, so that the user can sleep through the side effects.

The silicon chip is housed in a titanium casing about the size of postage stamp and a few millimeters thick. A battery and other electronic components are also enclosed in the titanium housing, and the device is implanted under the skin just below the waistline. In a 2012 proof-of-concept study in humans, the company demonstrated that the device delivered precise doses, and that the drugs diffused into the body despite the layer of fibrous tissue that forms around the device after implantation (*Sci. Transl. Med.* doi:10.1126/scitranslmed.3003276, 16 February 2012).

The company is targeting disease areas that require frequent, long-term dosing, such as diabetes, osteoporosis and contraceptives. "For people who suffer from chronic illnesses, not having to be a slave to those medications is a big deal for them," says Cheryl Blanchard, president and CEO of the company. The multiple sclerosis (MS) treatment interferon beta 1a, for example, must be given by injection every 48 hours. "I have a sister-in-law and a brother-in-law who both have MS, and I think once-a-week my sister-in-law looks at me and says: 'When can you put my drugs in this thing so I don't have to think about it? I don't want to be reminded every day that I'm sick.'"

In June 2015, Microchips Biotech received a \$35-million upfront payment from Teva Pharmaceuticals in a partnership to explore ways to pair the device with Teva's portfolio of chronic disease therapies. The Seattle-based Bill & Melinda Gates Foundation has given Microchips grants of undisclosed amounts to support development of a contraceptive chip that can be turned off and on. It is

aimed at women in developing countries who have limited access to long-acting, reversible contraceptives.

Blanchard says the company is in discussions with the US military for rescue applications as well. “You can imagine soldiers in the battlefield, and they are exposed to things for which you want to provide solutions instantaneously” from a remote location, she says. “These are all possibilities but not things that we’re starting out with.”

One limitation of the device is the small size of the drug reservoirs. Drugs that would be good candidates for the chip would have to be potent at microgram to milligram quantities. “Things like insulin are not good candidates,” says Blanchard.

Microchips’ device grew out of the work of its co-founder, Massachusetts Institute of Technology (MIT) professor Robert Langer, who described a prototype of the drug delivery chip in 1999 (*Nature* 297, 335–338, 1999). He says the company has had to overcome many technical challenges, including making sure the seals over the reservoirs would come off in reproducible ways, developing a reproducible way to load the reservoirs, reducing the size of the chip and encrypting the data.

Langer’s vision was for the device to carry multiple drugs—a “pharmacy-on-a-chip” as he described it 17 years ago. But that’s still in the future. “That’s not the first thing I want to take through the FDA,” says Blanchard. Separately, Langer and his colleagues are in the early stages of developing what he calls an “injectrode”: tiny electronically controlled implants for the brain that deliver drugs and record activity.

Privacy and security concerns

As digital health expands, the privacy concerns loom larger. “The privacy of all medical information of individuals is not at all assured today, and this just adds to it,” says Topol, referring to the suite of digital drug delivery technologies coming down the pike. Developers of devices say they have put extensive research into ensuring their devices will

protect electronic health information, are tamper resistant and not hackable. “We’ve engaged MIT cryptologists on our software and firmware to make sure our device isn’t interceptable,” says Blanchard. “That said, if somebody asked me: ‘Can you tamper with this device?’ My answer would be: ‘If someone is that devious, and they want to figure out how to do it, there’s always a way.’”

Indeed, electrical engineer Kevin Fu at the University of Michigan has demonstrated that it is possible to hack into implantable pacemakers and heart defibrillators and deliver a fatal shock, although the experiments required a team of experts and tens of thousands of dollars in equipment. And last March, the Department of Homeland Security released an alert identifying hacking vulnerabilities in hospital server software that manage intravenous pumps. An implanted dispenser carrying a year’s worth of drugs presents the potential risk of delivering to patients a toxic dose, whether due to hacking mischief or honest error.

Blanchard says hardware and safety precautions have been taken in the development of Microchips Biotech’s chip to ensure that doses cannot be released simultaneously, and that a dose cannot be administered unless a preprogrammed time has elapsed. A real-time clock chip ensures a certain amount of time lapses between each dose, she says. “The dose release circuitry cannot release more than one dose at a time as we have also limited the available power in the circuit which allows only one dose to be released at a time,” she says. To prevent hacking, the implant also has a unique serial number that the computer or remote control ordering a dose must identify. The wireless communication is encrypted, and the communication distance has been limited to one inch, she says.

Several bioethical considerations have been raised as well. Many of the patient populations that would be targeted by digital drug technologies are also the most vulnerable to coercion. Bioethicists say they wonder if the person signing up for the digital drug would be

competent enough to understand the privacy risks. “Mentally incapacitated adults are less able to make informed decisions about giving up their privacy and freedom,” says Amy McGuire, director of the center for medical ethics and health policy at Baylor College of Medicine in Houston. Art Caplan, director of the division of medical ethics at New York University, says another consideration is the possibility that employers, payers and others in positions of power might begin to require or coerce the use of digital adherence monitoring.

The bioethical considerations are valid, says Langer, “But I don’t see how it’s a new concern. If people in power want to abuse power and make people take a drug or make people do anything, they’re going to do it,” he says. Harassment in the workplace is one example of that abuse, he says. “So now with digital drugs it’s possible you have a method that may lower the bar a little bit. But the big problem is that some people abuse power. So we ought to have laws in place to deal with all of these things.”

Adds Karplus at Proteus: “This applies to our entire digital world. We also believe that consumers using technologies like ours have controls over important elements of data privacy. If they’re not careful with their own password, they could be responsible for their own leak. So the patient has some responsibility, too.”

It will take time to discern whether the bioethical considerations, along with digital drugs’ many challenges, will turn into obstacles for the industry. Consent and patient privacy issues are often sorted out reactively in the courts, rather than proactively by professional associations and regulators. The payer challenge will become clearer once the first products hit the market. “After you get a few approved and see how they are regulated by the FDA, you might see more aggressive approaches from other companies,” says Matthew Avery, an attorney at Baker Botts in Palo Alto, California. “It will turn the tide when Otsuka gets its approval.”

Emily Waltz, Nashville, Tennessee