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# PHARMA'S DIGITAL DIRECTIVE: Not If, But How





## PHARMA'S DIGITAL DIRECTIVE: Not If, But How

► By Rachel Laing, Alessia Deglincerti, Melinda Kutzing, Aurélie Deleforge, and Mark Ratner

- The engagement and connectivity of digital tools make them an easy fit into the clinical development infrastructure. Adding digital tools can provide additional product differentiation with the increased support they bring, and a partnering relationship could lead to rapid deployment in additional indications as evidence emerges.
- Making bets on a few flagship initiatives that tie into a company's existing portfolio makes sense, given the potential of digital tools to help improve outcomes and demonstrate value to payers.
- **So what?** Pharma companies should embrace digital technology, but as the extent of the clinical impact of digital therapeutics is not yet known, they must move ahead cautiously.

Digital technology, which includes the use of machine learning algorithms around large data sets and real-world data as well as digital measurement tools for collecting a wide swath of data in real time, has potential for impacting many parts of the pharma value chain. These methods can reduce time and cost to market through digitizing clinical trial operations and manufacturing; improve the understanding of how products perform in the real-world; and make products more competitive by improving patient outcomes through the use of a digital drug or companion digital solution.

"It will probably change every aspect of research and development," says Mathai Mammen, MD, PhD, global head of R&D for Janssen Pharmaceuticals Inc., a unit of Johnson & Johnson. "We at Johnson & Johnson and Janssen are not alone in appreciating that fact."

The payoff could extend well beyond operational benefits. Digital tools can increase access to health care and make the delivery of health care more efficient in several ways: by providing more tools to primary care



physicians; easing the burden on specialists by rapidly identifying patients who can benefit from certain interventions; or even substituting for a physician – the realm of clinical decision support tools, several of which have been cleared in the past year or so. They can also improve patient engagement and connectivity between patients and providers to improve outcomes and demonstrate value to payors. Digital therapeutics themselves – software that is therapeutically active either as a stand-alone drug or used in combination with molecular entities – are making their way onto the market.

The transformative potential of the digital revolution is apparent. However, pharma companies need to think pragmatically about how digital applies to what they already do.

### Digital Features

"There are many different ways to drive clinical outcomes that you can only do digitally," says David Klein, CEO of Click Therapeutics Inc. Increasing patient engagement is one way. "We are good at getting patients to do things," Klein says.

Click has attracted the attention of Sanofi Ventures, which led Click's recent \$17 million Series B financing.



The common element across Click's platform is its ability to engage patients in their therapy. The self-monitoring aspect of the treatment strategy, which uses a smart phone app to engage patients, the biological mechanisms it can target through behavioral intervention, the fact that the platform can target things drug compounds cannot and its potential application across different diseases are all important features. "I believe Click has modularity and potential for partnerships because its platform is not disease specific," says Sanofi Ventures SVP, Bernard Davitian. "Many internal stakeholders at Sanofi like the ability to combine with its products, whether in cardiovascular disease or insomnia," he says.

Digital therapeutics differ from other software cleared as a medical device – in particular, digital diagnostic and clinical support solutions – in that they deliver a therapeutic-like outcome either as a stand-alone or in conjunction with a drug. They presumably have a base of evidence and science behind them. It could be cognitive, behavioral, or coaching based. "It looks like we are able to modulate activities in key neural nodes using our technology," Klein says. Recent published research from a Phase II trial of Click's ClickEFMT app for treating major depressive disorder suggests it has a neuroplastic effect in the brain. "It is a very specific path that almost forces a patient to utilize emotion recognition and working memory at the exact same time," he says.

Some digital therapeutics sidestep the regulatory process: those from Omada Health Inc., Onduo LLC, Welldoc Inc. and Livongo Health Inc. in diabetes management, for example. Those companies partner with health plans and employers. Others, including Pear Therapeutics Inc. and Akili Interactive Labs Inc. and Click are going a different route. (Click's first product, Clickotine, for smoking cessation, did not go through a regulatory pathway but future products, led by ClickEFMT, will. Similarly, Cognoa, which has developed a Cognoa for Employers app to assist parents in spotting developmental delays in children, is also developing potential FDA-cleared products to diagnose and treat autism, ADHD and other disorders.)

In September 2017, Pear Therapeutics became the first digital therapeutics company to receive FDA clearance, for its mobile medical app, reSET, for treating substance abuse disorder. Novartis AG has inked several deals with the company, including participation in its January 2018 Series B round and two partnerships announced in the last nine months, including one to advance its THRIVE platform in schizophrenia and multiple sclerosis (MS; see Exhibit 1). Pear is also developing reSET-O, under review at FDA for opioid use disorder and potentially the first digital therapeutic to obtain an efficacy claim. (Also see "Novartis Teams With Pear Therapeutics In Neurological Digital Health Pact" - *Scrip*, 1 Mar, 2018.)

The Pear-Novartis relationship is about the belief that digital technology, as a means to develop a therapeutic agent, should be part of the product mix in the same way as small molecules, biologics, biosimilars, and gene therapies, says Novartis's VP, global head of digital business development and licensing, Jeremy Sohn. "People have to get their heads around understanding that an app can be cleared by the FDA, be prescribed by a physician, and can have efficacy equal to and in many cases better than the current clinical paradigm," he says.

Digital medicine technology also entails using technology "around the pill" to augment efficacy as well as maximize the commercial potential of an existing drug, be it digital or a more traditional form factor like a biologic or small molecule. In that context, use of the technology may lead to better adherence, a better diagnostic, or improved patient awareness and activation. "It is in this context where we are saying the industry has to take a more patient-oriented approach to how we think about our business," Sohn says.

Increasing patient engagement can improve the relationship researchers have with participants in clinical trials. That relationship has very much been one-dimensional, Sohn says – getting information from them but not necessarily giving back. "We need to be giving as much as we are taking, and we want to use the clinical trials opportunity to engage and inform as much as we can," he says. "We are trying to challenge our teams in terms of what data to collect and how to design our

### Exhibit 1: Selected Digital Medicine Deals With Pharma

Digital Company	Pharma Partner(s)	Deal Description (date)
Mindstrong	Takeda	Partnership to explore the development of digital biomarkers for selected mental health conditions, in particular schizophrenia and treatment-resistant depression. (Feb. 2018)
	Blackthorn Therapeutics	BlackThorn will use Mindstrong’s technology to passively collect digital behavioral biomarkers in a series of Phase IIa clinical studies of BTRX-246040, BlackThorn’s antagonist of the nociceptin receptor (NOPR), a target linked to multiple neurobehavioral disorders. (June 2017)
Pear Therapeutics	Novartis	Novartis’s Sandoz division is working with Pear to commercialize the latter’s FDA cleared app for substance abuse disorder and its app in development for opioid use disorder in patients who are currently receiving buprenorphine. (April 2018) Novartis also has a separate collaboration with Pear to develop prescription digital therapeutics for schizophrenia and multiple sclerosis. (March 2018)
Propeller Health	GSK	Agreement for Propeller to develop and manufacture a custom sensor for GSK’s Ellipta inhaler for use in asthma and COPD. (March 2015)
Verily Life Sciences	Sanofi	Joint venture, Onduo, focusing on developing integrated treatment and monitoring solutions for patient with diabetes. (Sept. 2016)
	GSK	Joint venture, Galvani Bioelectronics, focusing on medicines for neuromodulation of peripheral nerves. Initial focus is on inflammatory, metabolic, endocrine and respiratory disorders. (Aug. 2016)
Voluntis	AstraZeneca	Collaboration using Voluntis’s platform alongside AstraZeneca’s combination of cediranib and olaparib in ovarian cancer, now in late-stage trials. (Dec. 2015, extended Aug. 2018)
	Roche	Collaboration to develop medical and telemedicine services a companion solution to help breast cancer patients better manage their care. (Sept. 2015; extended to include solid tumors March 2018) Roche has also partnered with Voluntis in hemophilia to monitor warfarin therapy.
	Sanofi	Global expansion of 2011 partnership to use Voluntis’s Insulia basal insulin titration app with Sanofi drugs. (March 2017)

Sources: Strategic Transactions, company websites

clinical trials,” he says, emphasizing how to think more broadly about the drug itself – whether it should be the sole active agent or should a program also include some of these digital medicine capabilities.

Clinical development should be mindful of the patient’s journey, Sohn says, including practical matters like adherence. It is also important to realize that diseases may be exacerbated by indirect effects, making it a priority to be able to measure them. The symptoms of psoriasis, for example, may be made worse by depression, sleepless-

ness, anxiety and a range of other factors digital behavioral tools can capture and ameliorate. “We need to consider what we can do to reduce stress, improve state of mind, or help a patient get the right level of sleep,” Sohn says – factors that are important in cancer treatment, MS, and most chronic diseases. “Behavioral motivation is a big part of our patient engagement strategy and our longer-term product and business strategy,” he adds.

Pharma can leverage a range of biologic responses that are influenced by digital input, Sohn says. Game play,



digitized cognitive behavioral therapy, and virtual reality are all mediums for delivering biologic responses. “Our body is interpreting those inputs and having a physiologic or biologic response in the same way that I would take a drug that hits a target, causing downstream effect,” Sohn says. The subjective nature of current behavioral testing, which is prominent in diagnosing a range of mental health and neurodegenerative disorders, makes those conditions a special case for the application of digital tools.

For example, Janssen recently filed an NDA on its esketamine nasal spray for treatment-resistant depression, and its neuroscience R&D group has been actively working on a digital measurement tool, Mammen says. It is based on voice or sound that is a read-out of mood and is equivalent to and correlates with the Montgomery-Asberg Depression rating Scale, the standard in use for depression. Once esketamine is on the market, the tool can play a role in guiding the drug’s use – should it be continued, or should a patient go to see their doctor because the drug is not working anymore?

### **‘What’s needed to transform mental health is to create a bridge between clinic visits’ - Paul Dagum**

The approach is similar to that of Mindstrong Health, which has a tool for taking a variety of measurements of neurological function on a smart phone. Through its analysis of smart phone use, Mindstrong is providing new ways to measure brain health, and through that, improving a provider’s ability to select a treatment plan and titrate it appropriately. “What’s needed to transform mental health is to create a bridge between clinic visits,” says Mindstrong CEO Paul Dagum, MD, PhD. “The existing brick-and-mortar model is you come in, get seen, then go back again six months later. In between is when all the bad stuff happens,” he says. Through Mindstrong’s telemedicine service, providers can see when a patient starts to deteriorate between clinic visits, so they can intervene by changing medications or providing skilled training. Then if the patient continues to deteriorate, refer preemptively to the care provider before

the patient ends up in the hospital. “We need tools that can measure how someone functions and how resilient they are to their environment,” Dagum says. Whether the ultimate intervention is digital or pharmacological “is indifferent to us,” he says.

Mindstrong wants to provide pharma a platform to support therapeutics for psychiatric or nerve disorders. Its biomarker measurements could be bundled into a drug application in the same way as a companion diagnostic. The company also wants to look at how its continuous digital biomarker measures correlate with genetic variants linked to diseases like schizophrenia and depression.

### **Partnering Considerations: Ride The Wave**

The engagement and connectivity of digital tools make them attractive as supportive tools for a product launch. As part of its launch of the migraine drug Aimovig (erenumab), Novartis is using Healint’s Migraine Buddy, a migraine diary and tracking app that reaches a large community of migraine patients, notably those with a high variability of migraines throughout a given month. “It has been a great way to reach directly into the community,” Sohn says, especially as only about 11% of people with migraines get treated.

Adding a digital tool can provide further product differentiation with the increased support it brings, and a partnering relationship could lead to rapid deployment in other indications as evidence comes in. The ability to rapidly iterate software as new data are gathered also could offer considerable cost savings to pharma in both development and distribution.

That said, digital measurements may not be accurate enough right now, nor has the science of missing data and variance in the data been worked out enough, that they can be used to draw definitive conclusions about therapeutic efficacy and effectiveness on their own. “I would say we are in the early days,” says Robert Califf, MD, former FDA commissioner and currently an adviser to Verily Life Sciences (formerly a division of Google X). Plus, the process of iteration may be beneficial, but tricky. In other industries, consumer-facing devices can be sold, then undergo a series of iterations until they



are optimized. But in health care, a measurement that lets a drug get on the market or allows a disease-related advertising claim must be right before it goes on the market. “That’s a big difference,” Califf says.

As a result, pharmas should be pragmatic, dipping their toes in the water and making bets on a few flagship initiatives that tie into their existing portfolios. Part of that consideration should be whether to apply a digital therapeutic as a stand-alone or in combination with a drug in development. Either model could work, depending on the need: to expand a portfolio or differentiate a particular drug, for example. And given the economics and safety profile these tools have shown to date, pharma has little to lose by testing them out as widely as possible as part of a partnership.

Facilities housed at or near tech hubs and universities, such as Novartis’s just-opened Biome Lab in San Francisco and Pfizer Inc.’s Healthcare Hub in London, are already cropping up to connect with digitally-focused start-ups and innovators. As with like-minded pharma-academic tie-ups in the past, these initiatives could eventually lead to product-driven collaborations and licensing deals.

Pharma needs to start building the right teams and capabilities, Califf says, to be able to take advantage of what digital offers. But with the current reimbursement model, at the moment it can only go so far. Digital can make its biggest impact now in the drug discovery/systems biology/target area, he says, with the bigger area to come around value-based reimbursement and getting better clinical trials and measurement systems in place. Data analysis to help the health care system discern who (and what) is costing it money and analyzing and communicating health data are immediate innovations happening now. “My great hope is that as these analyses get more sophisticated, rather than current uses (which focus largely on claims data and billing), we will be figuring it out how to improve health more,” Califf says. Given 80% of death and disability is due to non-communicable chronic diseases and that those diseases are greatly affected by behavior, the big progress will be on the communication and sensor side, to move health improvement more into the home and workplace, he says.

Eventually, pharma might plug in a digital device in conjunction with its traditional therapeutics, either in series or side-by-side. At that frontier, the health care system will not think about whether it is digital software or a compound. “In that type of world, I think the economics for digital therapeutics companies partnering with pharma will look completely different,” says Ruchita Sinha, senior director of investments at Sanofi Ventures.

“There is a stepping stone where digital therapeutics are combined with traditional therapeutics,” Sinha says. That is the route Pear Therapeutics is taking – in fact, its name is a play on the notion of “pairing” with a compound. Some companies are already being more aggressive: some of the data from Akili, Click and even Pear, for example, suggest that their software could be efficacious for some patient populations as a stand-alone, or used where a traditional drug is not working or the population is resistant, she says.

### **‘We are looking for domain expertise and people who have a platform that can be leveraged to have an approvable drug’**

**- Jeremy Sohn**

For now, external arrangements can provide a valuable feedback mechanism. “They may inform about a friction point, and what you do with that failure in terms of attacking and hopefully not stopping a program but realizing maybe it was not the right time or right thinking to go into a different direction,” Sohn says. Initial deals may be similar to the molecular diagnostics model, where the profit pool is much smaller for the non-pharma partner. Overall, deal structures are likely to mirror those between pharma and biotech.

Like precision medicine, increased use of data analytics can help the pharmaceutical industry build better drugs, improve the efficiency of target identification, improve patient selection and recruitment of patients for trials using biomarkers, and even better identify patients once a drug is commercial. And as with preci-



sion medicine, where pharma tapped into the skill sets of diagnostics firms, it now must reach into the digital community to get access to core capabilities and resources. Digital health start-ups can play an important role because they bring not only talent but also targeted offerings for integration into a pharma's portfolio. "We are looking for domain expertise and people who have a platform that can be leveraged to have an approvable drug," Sohn says. "Many people can develop an app but not many can develop a GMP-class FDA-approvable drug."

Whereas most drugs tend to be static, digital therapeutics can be dynamic, Sohn says, in that they are continuously generating data, forming a tight connection with the user and engaging the patient. "We are looking for companies with that kind of agility and understanding and relationships with FDA to successfully manage that new aspect of the regulatory pathway," Sohn says. "Having a company that knows how to manage that relationship with providers and patients and do some of that change management is valuable."

The industry should also anticipate changes to the regulatory system as digital therapeutics seek efficacy claims, which will raise the bar above that currently needed for software cleared for use as a medical device. Pharma can benefit from partnering with companies already submerged in that dialog with FDA.

### Transformation Implications

In an interview earlier this year, published by *In Vivo's* sister publication *Scrip*, Novartis's chief digital officer Bertrand Bodson talked about the benefits of a shift from being a mainly product-oriented company towards one more focused on enhancing the customer experience. "Digital, data, and technology will be the key to making that happen," he said. Data science and digital technology touch on what Sohn characterizes as the "three horizons" of the company's strategy – to improve incremental and core elements of the business, and ultimately to transform it. "The digital transformation is about how to use technology – and for that matter, data – in a more meaningful way to improve how we do business today and how we prepare for tomorrow," he says.

"Making sure our teams have access to the expertise as we are thinking about these things is very much part of the digital transformation that is underway at Novartis," Sohn says. The goal is to brand Novartis "in the same way you think about great branded technology companies like Apple and Google," he says. "We are that good around the science and we should, and believe we can, be that good around technology as well." (Also see "New Novartis CDO Bodson Outlines Digital Health Ambitions" - *Scrip*, 6 Apr, 2018.)

The possible emergence of nontraditional players as drug developers – Google, Amazon, or 23andme, to cite a few examples – could influence the value chain both positively and negatively. They can provide data analytics infrastructure and tools to pharma. On the other hand, they could change the dynamics of the industry and create differences in pricing power and negotiating power, a shift between pharma and PBMs and pharma and payers. "A tech company coming in and changing the basic industry dynamic of who controls more lives and who has the pricing power could increase the speed with which drug pricing moves towards value-based pricing," says Sinha. Digital may carry with it a whole new way of branding a product – more akin to the way an Apple, Netflix, or Amazon operate – and a new go-to-market strategy based more on direct patient interaction.

"We want to lean into instead of be worried about a direct interaction with patients and families through our products," says Eddie Martucci, MD, CEO of Akili. "We strive to have a design that is on the highest end of captivating video game entertainment, which requires a relatively large investment on our part from the ground up, to do the medicine and the engagement very well." By virtue of how small and large molecules are developed and scaled to the world, that has not necessarily been a focus area for pharma, he says.

Pharma is very good at clinical validation, disease understanding and marketing, which could be very beneficial for the growth of digital therapeutics, Martucci says. But at this point, it is not yet clear that pharma will be a necessity for driving this industry, he believes. There is collaborative potential – areas where pharma will be



important in partnering for validation or scale. It is “to be determined whether pharma will be a critical part of that scaled medicine infrastructure as digital therapeutics become mainstream medicines,” he says.

The value split between a digital company and a pharma is far from clear cut and not as straightforward as, say, the companion diagnostics realm, where the diagnostics partner develops the test and pharma the drug. That leaves open the questions of to what extent will pharma want to be involved and do digital companies want that involvement? It is one more argument

in favor of pragmatism and for pharma to first apply digital tools within the realm of what it already does.

*Rachel Laing (rlaing@bionest.com) is a Managing Partner with Bionest Partners based in Basel; Alessia Deglincerti (ADeglincerti@bionest.com) is a consultant with Bionest Partners based in New York; Melinda Kutzing (mkutzing@bionest.com) is a Managing Partner with Bionest Partners based in New York; and Aurélie Deleforge (adeleforge@bionest.com) is a consultant with Bionest Partners based in Paris. Mark Ratner (mlratner@verizon.net) is a contributing editor to In Vivo.*