COMMENTARY

A regulatory framework emerges for digital medicine

Eric Elenko, Austin Speier & Daphne Zohar

Clear and logical regulatory guidelines on the process and requirements for approval of health apps and wearable sensors will be essential for the digital medicine sector to unleash its full potential.

Although government regulation of medical products is a core pillar of healthcare, its role (if any) in the oversight of digital medicine is the subject of a wide-ranging debate. At the center of this debate is an inherent tension between the rapid, iterative development culture of software free from the shackles of regulatory oversight and the more methodical and capital-intensive process of validating and launching conventional healthcare interventions.

The discussion as to how to resolve this tension is ongoing, but a regulatory framework to handle digital medicine products is already emerging in the United States. This framework is defined by a combination of regulatory policy positions and emerging precedent as decisions are made in response to immediate needs. Here, we review the progress and current status of the regulation of digital medicine.

The existing framework

The stated mission of the US Food and Drug Administration (FDA) is to "promote and protect the public health." This mission echoes the tension at the crux of the digital health debate; FDA is equally responsible for promoting public health by approving innovative therapies and diagnostics as well as protecting public health, which entails high-cost and time-intensive testing of products to pass regulatory scrutiny. The FDA's role in regulating software stretches back to when Congress granted FDA authority over medical devices, including medical software, in the 1976 Medical Device Amendment to the Federal Food, Drug and Cosmetic Act. As a result, software has historically been regulated by the FDA's Center for Devices and Radiological Health (CDRH).

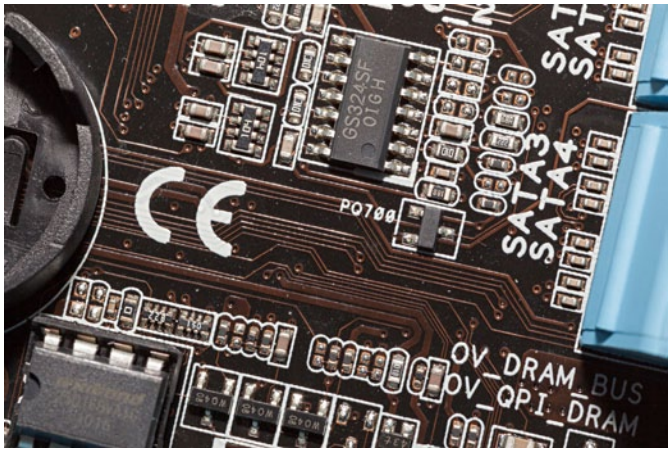
Debate is raging over whether regulatory oversight will limit innovation and adoption of digital health products or protect consumers from hawkers of digital 'snake oil.'

CDRH's regulatory framework is defined by a risk-based classification process: class I for the safest devices (e.g., tongue depressors, splints and braces), class II for moderate-risk or well-understood devices (e.g., physiologic monitors, X-ray systems) and class III for the most risky (e.g., pacemakers and cancer diagnostics). The majority of class II and all class III devices require FDA premarket review before being marketed. This occurs by two key review processes: the 510(k) premarket notification process for class II devices and premarket approval (PMA) for class III.

The vast majority of regulatory activity at CDRH occurs at the class II level along the 510(k) pathway. The 510(k) system is built upon historical precedent: in a 510(k), the sponsor claims "substantial equivalence" to an existing predicate device, and therefore cites the cumulative experience of safety and effectiveness with that product over time, meaning less original animal and clinical testing needs to be submitted for each product and/or filing. As a result, the 510(k) is often labeled the 'me too' pathway. A PMA, in contrast, is a much more involved pathway, which is typically closer to a new drug approval and must contain stand-alone evidence of safety and effectiveness. Companies are encouraged to fit within an existing class II category to be eligible to cite a predicate device and thus use the shorter, more efficient 510(k) pathway to market. In a key idiosyncrasy of how the 510(k) system is defined, any product for which there is no suitable predicate device defaults to a class III PMA, even if its risk profile is more similar to that of a class I or II product. Arguably, providing an easier path to market for "me too" products while making the path harder for safer innovative products discourages innovation and provides exactly the wrong set of incentives.

A partial solution to the problem came in 1997 when Congress established the *de novo* pathway—a risk-based classification request—that allowed devices lacking a predicate to be labeled as class I or class II and therefore have lower regulatory requirements than a PMA.

Eric Elenko & Daphne Zohar are at PureTech, Boston, Massachusetts, USA, and Austin Speier is at Precision for Medicine, Bethesda, Maryland, USA.
e-mail: DaphneNB@puretechhealth.com



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Digital health products will need to obtain the CE mark for marketing in Europe.

However, as originally envisioned, the process was time consuming which limited use of the new pathway. Further Congressional legislation in 2012 allowed sponsors to request a class I or class II designation earlier in the regulatory process, which made the *de novo* pathway a viable alternative (see **Box 1** for other Congressional initiatives). The emergence of a quicker *de novo* pathway has had great importance for the regulation of digital medicine products and enabled several software-based products to come to market that may not have been economical otherwise.

Software and health apps pose challenges

Historically, medical software has been regulated across all three classes based upon the intended use of the product. Because CDRH's regulatory system is based upon both risk classification and the gradual accumulation of historical precedent, an assortment of product categories have emerged for medical software, often dissociated from the actual nature of the products. This is a symptom of the fact that sponsors have historically had incentives to keep their products within existing class I and class II product categories, so as to avoid having them regulated as class III PMA devices. As a result, most FDA-regulated, stand-alone software has ended up in one of a few categories: calculator/data processing module for clinical use, picture archiving and communication systems, physiological signal transmitters and receivers, and a select few others, or, as something of a catch-all for class III software requiring a PMA, medical device data systems (MDDS).

Through the 1990s and early 2000s, this system was manageable and for the most part established a navigable and consistent, if not necessarily clear, pathway to market for medical software. More recently, with the advent of mobile technology and the emergence of what we term digital medicine, an explosion in the number and diversity of healthcare-focused software apps has occurred. According to IMS Health (Danbury, CT, USA), an estimated 40,000 health-related apps are now available, many of which were developed primarily for the consumer. With everything from simple wellness apps to diagnostic apps for the remote display and analysis of medical images, this new era of medical software has posed a challenge for the FDA's system of categories and precedents. The emerging category of stand-alone therapeutic and diagnostic apps further strains the previous regulatory paradigm.

FDA moves to adapt

Initially, there was concern and skepticism over whether the FDA could keep up with innovation without stifling it. The key turning point, however, was in 2011 with two events: the release in draft form of an FDA guidance document clarifying FDA's position on mobile medical apps; and the classification of MDSS to class I from class III which is a much lower regulatory burden[1]. The Mobile Medical Apps Guidance established a clear position whereby FDA would regulate mobile medical apps as medical devices based on the claims the mobile medical apps made and the risk associated with the software. In fact, in this Guidance, FDA took the position that most of the digital health software, including some apps that may historically have been class II, will not be regulated; this position was further established with the final Mobile Medical Apps Guidance in 2013 and an updated Guidance in 2015 (ref. 2). Importantly, FDA also clarified that it will not regulate the actual mobile platforms themselves (e.g., an iPhone). Similarly, the down-classification of MDDS removed substantial regulatory risk for developers, as MDDS had historically been a frequent 'default' classification for novel medical software.

More recently, FDA has clarified through additional guidance that it will not regulate software making general wellness claims[3] and elaborated on the exemption for MDDS and other data-handling software[4]. The FDA guidance on wellness, titled "General Wellness: Policy for Low Risk Devices," is applicable to a number of wearable devices and fitness apps. The draft guidance is aimed largely at devices and associated software "that promote a healthy lifestyle" but which "do not make any reference to diseases or conditions" which the FDA does not intend to regulate. Examples of devices promoting healthy lifestyle would include those keeping track of calories expended or consumed and monitors that track pulse rate during exercise. FDA even provided a specific decision algorithm to determine if a product would be considered a "general wellness product" and therefore not subject to FDA regulation.

Whether or not an app falls in the FDA-regulated or FDA-exempt category is determined by what claims the app makes and the perceived level of risk. If an app claims to diagnose or treat a disease or condition (e.g., treat depression), then it would be regulated as a medical device. On the other hand, the same app could make a related health claim (e.g., improves mood) and would not be considered a medical device. As a point of reference, the situation is analogous to the difference between a drug and a dietary supplement with the former making a claim around disease treatment and the latter making a general health claim.

In terms of risk, the key question is, what is the risk to the patient if this software fails? For a wellness app (e.g., measuring number of steps walked to track fitness), the impact on health is unlikely to be significant. In contrast, for an app that remotely displays a critical health alert (e.g., from a real-time bedside pulse oximeter), a missed alert could have fatal consequences. FDA has clearly exempted the former type of app but communicated that it plans to continue regulating the latter. In doing so, the agency has said that it will exercise "enforcement discretion" for most low-risk software, meaning that although it retains the authority to regulate a piece of software, FDA elects not to do so because there are no significant safety concerns. Examples of apps for which FDA will exercise enforcement discretion include those that help patients with psychiatric diseases by providing them with therapeutic behavioral techniques; provide guidance and motivation to people quitting an addiction (e.g., cigarette smoking); track use of asthma inhalers; and give guidance on the potential interaction of herbs and drugs. FDA also reserves the right to exercise enforcement discretion for other categories of apps, and in fact, the agency regularly updates a website where it provides current examples of regulated and exempt apps[5,6]. The sum result of these policy positions has been to give what this nascent and rapidly growing

field needs: some level of certainty as to what is, and what is not, regulated by FDA.

This leaves us with the final missing piece to this puzzle: an area that the FDA has termed "clinical decision support" (CDS) software. This is a diverse category of software that interfaces between patient data and clinical decision making. Often this software exists at the nexus of Health IT (hospital information technology) systems, electronic health records (EHRs) and medical devices, further adding to confusion of what is regulated, and by whom, because historically, the first two were exempt from FDA regulation. In a 2014 joint statement with the Office of the National Coordinator and the Federal Communications Commission, FDA began to define its position on CDS software[7], which is expected to be further clarified by a draft FDA guidance to be issued later this year. As with other medical software, FDA's guiding principle is risk. For example, CDS software that automates otherwise routine manual operations (e.g., updating EHRs, calculating risk scores and medication dosages) will be exempt. CDS software that performs complex analysis (e.g., automatic analysis of radiological images) will be regulated by FDA. Once the final guidance is published, FDA will have addressed most of the unknowns that have arisen around digital health over the past decade and thus lay the groundwork for adapting its historical software regulatory framework to the new reality of digital health.

Outside the United States

In Europe, a regulatory framework is emerging that shares several important elements with the approach being implemented by FDA. The European Commission (Brussels) released guidelines on "stand-alone software" that is being used for healthcare purposes[8]. Digital medicine interventions are going to be regulated as medical devices depending on their claims and functions. Software that makes a claim to diagnose or treat a condition could be considered a device, which is consistent with the basic definition of a device under European law. Neither telecommunication devices, such as phones, nor their associated infrastructure will be considered medical devices. The European Commission guidance needs to be implemented on a country-by-country basis.

Some countries, such as the United Kingdom and Sweden[9], have put out their own formal guidance, which thus far has been largely in line with the European Commission document. For example, the guidance from the UK's Medicines & Healthcare Products Regulatory Agency (London) included a list of words that, when appearing in a digital product's claims, make it more likely to be regulated as a device, including "detects," "measures" and "diagnose." As with other European medical devices, digital medicine products would need to obtain a CE Mark.

The case for government oversight

Thus far, FDA has cleared or approved numerous digital medicine products, including over 100 mobile medical apps. The apps include ones that allow data from more traditional medical devices to be read, disease management tools (e.g., medication reminders) and tools to help physicians (e.g., display medical images; see **Table 1** for more examples of approved software). Interestingly, some of these apps are now under FDA enforcement discretion and will no longer need to submit 510(k)s for future versions. Companies may prefer the certainty of being cleared by FDA and erring on the side of caution in submitting their products for FDA review. This distinction may also serve as an important differentiation point for those products.

In our first column, we defined digital medicine as "those products that are undergoing rigorous clinical validation and/or that ultimately have a direct impact on diagnosing, preventing, monitoring or treating a disease, condition or syndrome"[10]. We sought to distinguish the digital medicine category from the broader field of digital health that contains products aimed at consumers. The stamp of FDA marketing authorization itself could help distinguish true digital medicine products because obtaining FDA authorization necessitates making a disease claim. Enforcement actions by the Federal Trade Commission (FTC) help weed out and discourage the hawking of digital snake oil that can sully the perception of digital medicine in the eyes of physicians and consumers (**Box 2**). For digital medicine to continue into more mainstream medicine, it needs to have credibility, particularly with physicians. Although companies may choose to make consumer claims to avoid doing the work needed to obtain FDA approval and to get to market more quickly, there are potential economic benefits from being a medical product as opposed to a consumer product, which could make the stamp of FDA authorization worth obtaining.

FDA deserves credit for both the decision to exercise enforcement discretion for low-risk digital health products and for establishing and updating guidelines about what is considered a regulated medical device or an exempt mobile app or wellness product. The stance is consistent with the original intent of how the law defined a medical device, which is a reasonable one and is in line with clinical practice. FDA's attitude toward enforcement discretion for mobile apps is unusual compared with other categories of medical devices and reflects FDA's desire to err on the side of not over-regulating. Given its finite resources, the FDA cannot focus its attention everywhere, nor should it. By taking the stance that it will focus its resources mostly on products that might pose a threat to safety, FDA is prioritizing its resources in a reasonable manner.

Box 1 Congressional voices on digital health

Two major pieces of legislation are currently in Congress: The Medical Electronic Data Technology Enhancement for Consumers' Health (MEDTECH) Act introduced by Senators Orrin Hatch (R-Utah) and Michael Bennet (D-Colo.) and the Sensible Oversight for Technology which Advances Regulatory Efficiency (SOFTWARE) Act introduced by Representative Marsha Blackburn (R-Tenn.) and Gene Green (D-Texas). Versions of both the MEDTECH Act and the SOFTWARE Act were introduced in previous sessions of Congress. The SOFTWARE Act is being rolled into a larger 21st Century Cures Act, which covers a diverse range of healthcare topics. Both the SOFTWARE and MEDTECH Acts seek to clarify which types of software will be subject to FDA regulation and to further set boundaries around the area FDA has the authority to regulate. Other bills have been previously circulated in Congress around regulation of digital health, most notably the Preventing Regulatory Overreach To Enhance Care Technology (PROTECT) Act introduced in 2014 by Senator Debra Fischer (R-Neb.) which was co-sponsored by Angus King (I-Maine) and now-presidential candidate Marco Rubio (R-Fla.).

Given the continued gridlock in Congress and the myriad high-profile issues facing Congress, the fate of currently pending legislation is uncertain. However, the fact that there are bipartisan supporters of the legislation increases the chance of passage. What is clear is that FDA is under congressional scrutiny, which could influence how much of its enforcement discretion FDA decides to exercise. Further congressional interest could also be stirred up if large tech companies decide to flex their large lobbying muscles. As mobile health and digital health become increasingly lucrative, so will the willingness of players to take an active role in making their voices heard.

There is a danger that where the FDA decides to draw the line on enforcement discretion could shift depending on who at FDA is making the decision. To provide clarity, it will be important for FDA to be consistent and explain its actions to the community when it takes necessary enforcement actions. Currently, digital health products go to the divisions within FDA based on their use (e.g., neurology). It will be important for the various divisions to be cognizant of the positions that other divisions are taking with regards to digital health products to maintain a consistent overall FDA stance. Before formal FDA guidance on mobile medical apps and low-risk devices, Representative Mike Honda (D-Calif.) proposed the idea of creating a specific office within the FDA to oversee mobile medical apps. The idea remains an intriguing one and could be valuable, even if the only role of such an office was to make sure that the FDA was undertaking regulatory actions consistently and communicating them in a coherent manner.

Regulatory challenges

Even for people who think digital health should be regulated, the area poses several challenges. We detail these challenges below.

Human testing. Although double-blind, placebo-controlled studies are the gold standard

Table 1 Selected examples of digital health products and how they were classified by FDA

Product	Company	Intended use	Features contributing to FDA classification	Review time
Enforcement discretion (no FDA review)				
Prevent Companion App	Omada Health (San Francisco)	Prevent diabetes in prediabetic patients	Enforcement discretion per FDA Guidance	N/A
MediSafe	MediSafe Project (Boston)	Medication management and adherence	Enforcement discretion per FDA Guidance	N/A
WebMD	WebMD (New York)	Mobile health information app with health questionnaires	Enforcement discretion per FDA Guidance	N/A
Thync System	Thync (Los Gatos, CA, USA)	Noninvasive nerve stimulation to modify mood (energy and calm)	All product claims relate to mood modification only	N/A
Class II 510(k) premarket notification				
Glooko	Glooko (Palo Alto, CA, USA)	Diabetes management apps	Interfaces with traditional FDA-cleared glucose monitors (class II 510(k) products)	5 months
ResolutionMD Mobile	Calgary Scientific (Calgary, AB, Canada)	Picture archiving and communication system	Remote display of radiology images on mobile devices	4 months
AliveCor	AliveCor (San Francisco)	Electrocardiogram (ECG)	App plus accessory; attaches to a smartphone to provide ECG capability	1 month
iExaminer	Welch Allyn (Skaneateles Falls, NY, USA)	Ophthalmic camera vision test	App plus accessory; attaches to a smartphone to provide vision testing	1 month
Ieva Pelvic Floor Trainer	Remendium Labs (Baton Rouge, LA, USA)	Pelvic muscle–guided exercises	Mobile app training program for the treatment of stress urinary incontinence in women	1 month
Blood Pressure Monitor	Withings (Issy-les-Moulineaux, France)	Blood pressure monitor	Standard blood pressure monitor with iPhone connection; part of Withings suite of digital health products	4 months
***De novo* classification request**				
Dexcom Share	Dexcom (San Diego)	Secondary display of continuous glucose monitor (CGM) information	Interfaces with newer FDA-approved CGM (class III PMA product)	1.5 months
Accessory to a PMA device with a multiyear FDA history				
Dexcom STUDIO Cloud	Dexcom	Diabetes management app for CGM	Interfaces with newer FDA-approved CGM (class III PMA product)	4 months
Accessory to a PMA device with a multiyear FDA history				
NEBA System	NEBA Health (Augusta, GA, USA)	Neuropsychiatric interpretive electroencephalograph (EEG) assessment aid	Algorithm that analyzes EEG signals to report a comparison to reference norm, as aid in the diagnosis of attention deficit hyperactivity disorder (ADHD; clinical decision support)	19 months
Proteus Ingestible Event Marker (IEM)	Proteus Digital Health (Hayward, CA, USA)	Ingestible event marker (IEM)	Although medication adherence tracking is the ultimate claim, the IEM requires consumption by the patient and interfaces with another, regulated medical device (sensor-enabled wearable patch)	2 months
Preceded by multiple years of FDA negotiations				
Pixel 3 System	Gauss Surgical (Los Altos, CA, USA)	Image-processing device for estimation of external blood loss	Algorithm that analyzes images and produces clinically actionable information as an output Expanded features for existing 510(k)-cleared app with a multiyear FDA history	3 months
Class III PMA				
Minimed 530G with Threshold Suspend	Medtronic (Minneapolis)	Artificial pancreas system with threshold suspend	Algorithm that automatically monitors glucose levels and temporarily suspends or reduces insulin infusion from an insulin pump based upon specified thresholds of measured glucose levels	15 months
Merlin Conduct Mobile Software Application	St. Jude Medical (St. Paul, MN, USA)	Cardiac rhythm management mobile app	Portable, dedicated programming system designed to interrogate, program, display data and test St. Jude Medical implantable devices	21 months

N/A, not applicable.

in healthcare research, blinding a digital medicine intervention study is sometimes quite difficult. Medical device regulatory authorities have historically been less concerned about having a sham control or issues regarding blinding compared to drug regulators. When it comes to many devices (e.g., implantable devices), controls are often both impractical and unethical because they necessitate an invasive procedure. Although the need for controls will vary on a case-by-case basis, arguably some type of control arm should be included in pivotal studies when a product is making a therapeutic claim. What standards regulatory authorities will require remains an unanswered question. As digital medicine products begin to be tested in clinical studies, the consent process has also been a matter of concern—how effectively can a consent form on a mobile phone communicate the study intent and risks? Is tapping "OK" sufficient to signify consent? To date, this issue has not been a subject of regulatory policy or guidance but is being handled on a study-by-study basis by the study sponsor, primary investigator and supervising institutional review board.

Manufacturing. Establishment of quality systems as part of current good manufacturing practices (CGMPs) is another key area of FDA regulatory requirements that also applies to software-based medical devices. Although strict manufacturing standards are understandable for a physical medical device, the necessity of imposing CGMP standards on products that are software-only raises questions. Software products can conform to CGMP standards through the correct formal documentation and procedures. However, in a rapidly moving world where hardware devices are evolving constantly and where programmers are used to a more creative culture, the imposition of CGMP standards could cause consternation for companies going down the FDA route.

Software updates. Similarly, versioning can present challenges for digital medicine products. Although FDA has offered guidance on how to handle software documentation and validation[11,12], these documents are somewhat dated and geared toward integral medical device software, not stand-alone mobile medical apps. Furthermore, the FDA regulates software updates (including both minor and major version changes) the same way as any other device change (e.g., the change of a material in a surgical implant). Minor changes do not require FDA review, whereas changes having a significant effect on safety or effectiveness may require submission of a 510(k). In addition, FDA suggests that manufacturers review changes both individually and collectively since the prior submission. The result is that manufacturers can make small changes in products, then bundle the accumulated changes and submit them for FDA review (e.g., every few years, or as appropriate).

Combination products. Other questions revolve around combination products that marry digital medicine with therapeutics—what would regulation of a combination product with a drug entail? The guidance on combination products states that a product will be regulated as a drug or a device, depending on which mode of action is more responsible for the effect of the product[13]. How digital interventions that claim to work synergistically with drugs will be regulated remains to be determined. Companies, such as Proteus Digital Health (Redwood City, CA, USA), which markets a device-drug combination product intended to track and encourage medication compliance, have successfully navigated the process. The well-established precedent for digital accessories to the monitoring and administration of insulin for diabetics may also serve as a guidepost for such products.

Hardware. Although hardware devices (e.g., smart phones) themselves are not subject to regulation, the rapid pace of hardware development raises questions. For instance, new technologies, such as immersive virtual reality and augmented reality, may be integrated in the not-too-distant future, and the user experience will undoubtedly be completely different from current mobile technology. Will the FDA allow software that was cleared for use on one platform to be used on a completely novel platform?

Box 2 FDA and FTC the regulatory watchdogs

FDA's CDRH has an Office of Compliance that is tasked with the enforcement of FDA regulations for commercialized products. Included within this authority is the review of marketing materials and product labeling to ensure that claims are not being overstated. In response to excessive claims, FDA may issue a 'Warning Letter' to the manufacturer (or app developer) citing the issues with a product and requiring the company to rectify the issues or face enforcement action. Enforcement actions may include civil and criminal penalties, injunctions and seizures (or in the case of apps, forced removal from the app store). The Warning Letter is published online and becomes a matter of public record. To date, FDA has only used the less-severe 'Untitled Letter' for a mobile medical app.

In contrast, the FTC has taken stronger action when it comes to companies exceeding claims based on evidence. The FTC's mission is to protect consumers from deceitful, unfair practices and guard against anti-competitive trade. Historically, FTC has been willing to crack down on what it perceives as false health claims made by dietary supplements. In an analogous situation to digital health products, the same compound might be classified as a drug or a supplement depending on the claims that are being made. Similarly, the FTC has made it clear that it intends to take enforcement action against mobile medical apps that it believes are making false claims. In 2011, even before the FDA issued its guidance concerning mobile medical apps, the FTC cracked down on apps that claimed they could treat acne[14]. Last January, FTC told a company to stop making claims that a game it was marketing could improve cognition, including helping children with attention deficit hyperactivity disorder (ADHD)[15]. More recently, FTC moved against apps making unsubstantiated claims around the diagnosis of melanoma[16].

Given that detection of melanoma and treatment of ADHD are medical claims, arguably FDA would also have the power to regulate the apps in question and take legal action against their makers. The move by the FTC to start to regulate products that fall under FDA's purview is different from its historic enforcement pattern. Going forward, it's not clear if more enforcement actions will be coming from FTC or FDA and if the FTC will concentrate more on 'digital supplements'—those apps that position themselves as 'wellness products' not requiring FDA premarket review or around apps that make actual disease claims.

As is the case for dietary supplements, given the large number of health-related apps that are currently available, it will not be possible for the FTC to crack down on every app making false claims. The FTC has not publicly stated how it intends to prioritize which apps to select for enforcement, but its actions serve as a clear warning that digital health marketers must bear in mind both agencies.

Perspective

As digital health moves more into mainstream medicine and a greater number of people use both consumer digital health as well as digital medicine products, regulation will become an area of increasing interest. Thus far, FDA and regulators in Europe have taken reasonable

positions that have managed to walk the line between protecting the public and avoiding over-regulation. In fact, these agencies should be lauded for moving relatively quickly to establish a 'light' approach to oversight and for taking steps to clarify their approach. This has established a regulatory environment that is understandable and that can bridge the culture gap between digital innovation and medical progress. The result is greater certainty for innovators and their investors, allowing digital medicine business models to be developed with more confidence.

Given that several digital health products have no predicate but are safe enough to be considered class I or II, the *de novo* pathway is a logical choice for digital medicine products. The enhanced utility of the *de novo* pathway since 2012 has made it feasible for truly novel software products to be developed for more ambitious, FDA-regulated health claims, without resulting in the undue burden of a PMA. Once a *de novo* classification has been granted, the product can serve as a predicate device and future devices in that category can use the 510(k) process. The initial innovator takes on greater regulatory burden, only to establish a precedent for follow-on competitors. Arguably the greatest innovation would be encouraged by allowing truly novel devices, including software, to go down the *de novo* pathway while granting a period of exclusivity preventing competing "me too" products from using the first-in-class devices as a predicate—a regulatory practice already well-established for therapeutics.

Physical medical devices will become increasingly connected to digital interfaces, particularly ones on mobile platforms. The addition of a digital component has the potential to greatly increase innovation in the medical device field, even in areas where innovation has historically been more incremental in nature. The combination of regulatory certainty and the correct regulatory incentives are important contributing factors that could drive not only stand-alone software products, but also connected devices. The 'internet of things', in which objects emit information in a connected way to provide continual information, is an emerging area that has generated considerable excitement. A similar ecosystem of interfacing digital and physical medical devices could create a connected digital medicine network opening up new possibilities for medical devices.

Going forward, there will likely be a continued tug of war between those wanting less regulation and government authorities who feel obligated to enforce the law and protect the public. In meccas of digital innovation like Silicon Valley there is often a desire to move rapidly with less tolerance for regulations. Some of the most successful consumer startups, such as Uber (Long Island City, NY, USA) and Airbnb (San Francisco), are based on ideas that bring them in constant conflict with established rules. In our view, however, allowing unregulated claims has the potential to backfire by further detracting from the credibility of this emerging sector.

The direction of the debate will depend on certain future events. For instance, if somebody is injured using a digital health app, there will be calls for more regulation. On the other hand, if large tech players feel that regulation is getting in their way, they won't be shy about pushing for regulatory change. What is clear is that the rapid pace of innovation will continue, which will no doubt end up posing important regulatory questions hard to conceive today. For now, however, digital health regulation is finally reaching a mature and manageable state, and as it does so, it offers the potential to validate the clinical utility of digital medicine as it seeks to establish itself as a central player in clinical practice.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.3284).

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