21st Century Cures Act driving FDA changes

President Barack Obama signs the 21st Century Cures Act into law on Dec. 13, 2016. The sweeping legislation had broad bipartisan support.

AP PHOTO

By Jessica Kim Cohen

THE FOOD AND DRUG ADMINISTRATION last year approved its first autonomous, artificially intelligent medical device.

In a decision that seemed to take a page from science fiction, the FDA gave the OK to the IDx-DR, a device that uses artificial intelligence to analyze images of the back of a patient's eye to detect if they have diabetic retinopathy.

It's the first FDA-approved device to provide a screening decision without requiring a clinician to interpret the results—which means providers who aren't eye specialists, such as primary-care physicians, can rely on it to screen for the eye disease.

"Today's decision permits the marketing of a novel artificial intelligence technology that can be used in a primary-care doctor's office," Dr. Malvina Eydelman, director of the division of ophthalmic and ear, nose and throat devices at the FDA's Center for Devices and Radiological Health, said at the time. "The FDA will continue to facilitate the availability of safe and effective digital health devices that may improve patient access to needed healthcare," she added.

IDx sells the system in a bundle that costs around $20,000, which includes hardware installation, training and the retinal camera; the company does not manufacture the camera.

THE TAKEAWAY

When the 21st Century Cures Act passed in 2016, changes to the FDA's approval process were controversial and continue to be.

But in part because of the way the device was approved—using a fast-track approach established by the 21st Century Cures Act—the device was met with some skepticism. In the wake of the approval, researchers—mainly those involved with other healthcare AI projects—questioned aspects of the clinical study the FDA reviewed to evaluate IDx-DR, criticizing its sample size of patients from 10 primary-care sites, and whether longer-term studies would in fact illustrate a clin-

ical benefit to patients.

IDx-DR moved through the FDA's approval process in 85 days under the agency's de novo pre-market review pathway. The device was part of the agency's Breakthrough Device Program, which was established as part of the Cures Act—a landmark piece of legislation signed into law during the final month of the Obama administration.

At more than 300 pages, it contained a number of moving parts—funds for the National Institutes of Health, a new HHS assistant secretary for mental health and substance use, and an interoperability framework, not to mention dozens of measures meant to streamline a supposedly outdated regulatory process at the FDA.

"It has enabled the FDA to think more broadly and more strategically about how it can adapt to a very rapidly changing world in terms of the drug developments, the device developments, the digital health developments that are happening," said Hannah Bornstein, deputy practice group leader for government investigations and white collar defense at the law firm Nixon Peabody.

Despite its broadly bipartisan backing, the law faced criticism from consumer advocates and some well-known figures, including Democratic presidential hopefuls Sens. Bernie Sanders and Elizabeth Warren.

The Cures Act passed with strong support from both Democrats and Republicans. But despite its bipartisan backing, the law faced criticism from consumer advocates and some well-known figures, including Democratic presidential hopefuls Sens. Bernie Sanders and Elizabeth Warren.

Those critiques tended to center on changes to the FDA.

"There were some positive things in the legislation, such as the additional monies for NIH and opioid treatment," said Jack Mitchell, director of health policy at the National Center for Health Research, a not-for-profit that conducts and assesses public health research. But the Cures Act also included provisions that he said would "loosen standards" at the agency.

That's a key point of contention: Whether getting potentially life-saving treatments into the hands of patients is worth possible safety risks associated with approving them more quickly. That balance hits at the heart of the FDA's mission, according to Dr. Anupam Jena, a healthcare policy researcher at Harvard Medical School.

"The central role of the FDA is really managing this trade-off between getting drugs to market sooner, because that benefits patients who have a disease earlier, versus ensuring the safety of whatever products they approve to be introduced to the market," he said. "There's theory for and against both arguments. The real issue is: Net, how do patients fare?"

But while the healthcare industry may be divided on whether the Cures Act's vision aligns with what's best for patient care, most agree on one thing: The agency has been meeting its deadlines, for the most part.

"With the passage of the Cures Act in 2016, the FDA was tasked with a somewhat onerous set of responsibilities and projects, but ones that are worthwhile," said Monica Chmielewski, a partner at law firm Foley & Lardner. "The FDA continues to push forward to meet the requirements under the act and implement the necessary programs and changes."

Former FDA Commissioner Dr. Scott Gottlieb, who resigned in March, oversaw much of the agency's work on the Cures Act. Dr. Ned Sharpless, director of the National Cancer Institute, has been serving as acting commissioner. While the White House has yet to nominate a permanent replacement for Gottlieb, an agency spokesperson in an email said work continues on "advancing FDA priorities," including ongoing implementation of the Cures Act.

Read on for a look at the Cures Act's most-hyped provisions involving the FDA and their possible implications for hospitals and patient care.

Faster approval for treating debilitating diseases

The Breakthrough Devices Program, an expansion and replacement of previous FDA programs—the Expedited Access Pathway and the Priority Review Program—was part of an effort to accelerate and prioritize the development of devices for certain diseases, as outlined under the law. It's meant to "expedite the development of, and provide for the priority review for, devices ... that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions," as well as treatments and diagnoses for diseases for which no alternatives exist, according to the law.

The program, for which final guidance was published in December, primarily involves the agency working more closely with companies creating breakthrough-designated devices during the development and review process, to guide them on how to establish more efficient clinical study designs to get products approved more quickly.

"It allows you to have different interactions with the FDA, which are intended to help accelerate the development process," Chmielewski said. That could involve setting specific clinical trial endpoints and determining whether it's appropriate to use post-market data, rather than data collected prior to market authorization, to assess benefits and risks.

Some healthcare experts have taken issue with certain aspects of the program, one of which is the possible use of "surrogate endpoints," or study outcomes that measure a correlation to an intended outcome, rather than the outcome itself. In the case of cancer, that might involve measuring biomarkers such as tumor shrinkage, which are thought to be linked with mortality rate, instead of measuring mortality rate itself.

Those surrogate endpoints lead to quicker results, but don't guarantee patient outcomes, said Diana Zuckerman, president of the National Center for Health Research. Under this approach, it can take "five or 10 years to find out a drug isn't

really working, or is not as safe as we thought," she said.

The FDA also raised the cap on its Humanitarian Device Exemption, which exempts devices designed to benefit patients of rare diseases from certain regulatory requirements. Initially, the exemption applied to devices meant to benefit conditions that affect fewer than 4,000 people in the U.S. annually, but the Cures Act raised the cap to 8,000. The agency also published draft guidance on the Humanitarian Device Exemption in June 2018.

Meanwhile, as of July, there were 178 devices in the FDA's Breakthrough Devices Program, 11 of which have received marketing authorization, according to the FDA.

Scott Whitaker, CEO of the Advanced Medical Technology Association, said he credits the legislation, as well as the Medical Device User Fee Amendments, with reducing the time it takes to gain marketing authorization under the 510(k) and pre-market approval pathways.

That time's "gradually gone down a little bit," Whitaker said. And he argued it's not because the program has less-stringent standards. The FDA is more transparent about requirements, leading to more efficiencies—particularly in the Breakthrough Devices Program, he said.

"The communication from the FDA to companies about the exact needs to determine safety and effectiveness has been very, very clear," Whitaker said.

Drugs for new, off-label treatments

Much of the Cures Act's plan to modernize drug approvals has involved promoting the use of so-called "real-world evidence," which has led to a particular point of contention regarding off-label use of drugs.

Real-world evidence involves the analysis of patient health data collected routinely from sources like electronic health records, claims and billing systems, and product and disease registries. That contrasts with data collected through randomized controlled trials, which are considered the gold standard for medical research.

Under the Cures Act, the FDA was charged with producing a draft framework on the use of real-world evidence, primarily for two purposes: to support approvals of new uses for existing drugs, as well as to support collecting evidence for post-approval studies. The FDA successfully published the framework for a Real-World Evidence Program in December.

Findings from the Real-World Evidence Program will inform future draft guidance on the topic, which the agency is required to publish by 2021. "Real-world evidence has a lot of promise for expediting drug development," said Lucy Vereshchagina, vice president of science and regulatory advocacy at the Pharmaceutical Research and Manufacturers of America, which has voiced support for the Cures Act. That includes applying information to support approvals of off-label uses for drugs, which she called "low-hanging fruit for the use of RWE."

But while FDA leadership characterizes its goal for the Real-World Evidence Program as helping to "answer questions that may not have been answered in the trials that led to the drug approval—for example how a drug works in populations that weren't studied prior to approv-

5 Major provisions of the 21st Century Cures Act

1 Naming a new HHS assistant secretary for mental health and substance use

To lead a spate of mental healthcare and addiction treatment reforms included in the act, the law required President Donald Trump to appoint the first HHS assistant secretary for mental health and substance use. Dr. Elinore McCance-Katz, a former chief medical officer for the Substance Abuse and Mental Health Services Administration, was named to the role in 2017.

2 Beginning the push for Medicare price transparency

The CMS was charged with releasing a consumer-facing website providing Medicare beneficiaries with estimated prices for various services, based on the site of care. With the site-of-service price tool, launched in November 2018, users can compare Medicare payments for procedures performed in hospital outpatient departments and ambulatory surgery centers.

3 Releasing public data on antimicrobial resistance and stewardship

The law required HHS to publicly post data on aggregate national and regional trends of antimicrobial resistance within one year of enactment, and "annually thereafter." The Centers for Disease Control and Prevention's Patient Safety Atlas, a web app that predates the law, provides data on the topic. The web app displays antibiotic resistance data from 2011 to 2014, as well as more recent data on healthcare-associated infections and outpatient antibiotic use. HHS was also asked to release information on antimicrobial stewardship, including educational materials on how healthcare organizations can implement programs to tackle the issue. The CDC has published reports on antibiotic stewardship programs and resources including data through 2017.

4 Defining interoperability and information-blocking

HHS' Office of the National Coordinator for Health IT was charged with defining "reasonable and necessary activities" that do not constitute information-blocking, building on the act's definition of the term, as well as providing guidance on common barriers to data exchange. The agency is currently working to finalize its proposed rule on information-blocking, which was released in February after several delays.

5 Establishing the Trusted Exchange Framework and Common Agreement

The ONC was tasked with publishing its first draft of TEFCA within one year of convening a group of public and private stakeholders to develop the framework, which outlines principles for promoting nationwide interoperability. The ONC published its first draft of the Trusted Exchange Framework in early 2018 and released a second draft this past April.

al" in the framework—others have raised concerns that this move, again, falls short of gold-standard evidence.

The National Center for Health Research has raised concerns that while real-world evidence can provide a useful supplement to randomized controlled trials, there are still challenges to ensuring findings from real-world data are generalizable to an intended patient population.

The FDA is assessing whether real-world evidence can be used to inform regulatory decisions about the effectiveness of drugs, such as changes in labeling or dose regimens, as well as to add new indications. As drug companies study this under the Real-World Evidence Program, it means hospitals might become more involved in the regulatory process.

Drug companies, after all, will need access to key sources of real-world data, such as EHR, medical claims and billing data, opening up possible privacy and compliance concerns.

"One of the key issues for the hospital, in particular, to address is how they can get that data over to the pharma or device company," said Valerie Montague, a partner at law firm Nixon Peabody who focuses on health information privacy and security issues. That might involve de-identifying data, setting up data use agreements, getting patient consent or requesting a consent waiver.

Getting new products to patients

There's also the issue of whether patients will actually be able to access newly approved drugs and devices, despite supposedly more streamlined regulatory review. Some healthcare groups have suggested accelerated approval pathways would put more of a burden on physicians and patients to vet drugs and devices for safety and efficacy. But nearly three years after the Cures Act went into effect, most hospital concerns tend to center around financial, not clinical, considerations.

From a legal perspective, Chmielewski—the lawyer with Foley & Lardner—said she hasn't observed cases that attempt to ascribe liability to a hospital if a drug or device that has been approved under an accelerated pathway doesn't work as intended. The responsibility to review products is still on the FDA, she said. Hospitals and physicians often rely on the FDA's approval and clearance processes, and it's not standard or appropriate for hospitals to perform an independent review, she said, although providers should use their judgment to determine whether an FDA-approved drug or FDA-cleared device is appropriate for a particular patient's needs.

"It's not up to the hospital or the physician to second-guess the approval process," Chmielewski added.

Officials at UPMC in Pittsburgh said despite moves to accelerate FDA approvals, the health system hasn't changed how it determines which drugs to use in its facilities. That process already involves a clinician panel reviewing safety and efficacy of new drugs, as well as cost and insurance coverage.

"The 21st Century Cures Act has increased new drug approvals nationwide, as expected," said Jessica Daley, a vice president at UPMC who oversees pharmacy and supply chain. "However, UPMC's processes for evaluating the safety and efficacy of new drugs—and then monitoring their longer-term impact on patients—has not changed."

Clint Hinman, chief pharmacy officer at Centennial, Colo.-based Centura Health, said the health system's standard policy is to wait six months after a new product is released to review available research on patient outcomes and safety before determining whether to use it, although there are some case-by-case exceptions for novel therapies, based on patient needs. But alongside clinical outcomes, he highlighted another consideration: total cost of care, including assessing whether there are appropriate billing codes available after a new product is approved.

Recent CMS decisions may provide some relief. As part of its inpatient prospective payment system rule for fiscal 2020, the agency finalized a new technology add-on payment pathway for devices considered breakthrough technologies by the FDA. If these devices receive marketing authorization from the agency, they won't be required to demonstrate evidence of "substantial clinical improvement" to qualify for Medicare new technology add-on payments.

That's a step in the right direction; without reimbursement from insurers, many patients likely won't be able to afford the new drugs and devices—regardless of approval status.

"The biggest challenge," Hinman said, "is making sure CMS and the payers are on the same train with the FDA." ●

Timeline of the FDA's progress on 21st Century Cures Act provisions

2017

OCTOBER: Draft guidance for the Breakthrough Devices Program.

NOVEMBER: Draft guidance for expedited programs for regenerative medicine therapies for serious conditions.

JUNE: Draft guidance for patient-focused drug development.

2018

JUNE: Draft guidance for the Humanitarian Device Exemption program. Deadline for final guidance not specified.

DECEMBER: Final guidance for the Breakthrough Devices program.

DECEMBER: Framework for the Real-World Evidence Program.

2019

FEBRUARY: Final guidance for expedited programs for regenerative medicine therapies for serious conditions.

DECEMBER: Deadline for draft guidance on the qualification of drug development tools. Deadline for final guidance is six months after the public comment period for the draft closes.

2020

JUNE: Deadline for revised or final guidance for patient-focused drug development.

2021

DECEMBER: Deadline for draft guidance on the Real-World Evidence Program. Deadline for revised or final guidance is 18 months after the public comment period for the draft closes.

Sources: Food and Drug Administration, Modern Healthcare research