Health Law Daily Wrap Up, STRATEGIC PERSPECTIVES: Will the Cures Act address what ails the FDA approval process?, (Mar. 9, 2017)

Health Law Daily Wrap Up

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President Barrack Obama signed the 21st Century Cures Act (Cures Act) (P.L. 114-255) into law in December 2016 nearly three years after it was first introduced. The bipartisan legislation includes a slew of provisions intended to benefit various sections of the health care industry. In addition to the boon to the health care industry, the Cures Act includes provisions to address mental health treatment in the U.S., including administrative positions at the Substance Abuse and Mental Health Services Administration and state funding to combat opioid addiction.

Implementing provisions of the Cures Act will result in spending approximately $6.3 billion over the next decade including provisions that will expedite FDA approval of new drug and medical devices development via $500 million in funds to the agency. However, under President Donald Trump, some aspects of the Cures Act may not come to fruition because of the current administration's stated goals of reducing the volume of federal regulations. As the drug and device industries are heavily regulated, any regulation reductions may impact consumers' confidence in the safety and efficacy of newly FDA approved drugs and devices under the Cures Act accelerated review model.

Real-world evidence and priority reviews. The general goal of the Cures Act accelerated review model is to bring drugs and devices to market more quickly and at less cost by reforming the FDA, including: expedited review for breakthrough devices, increased patient involvement in the drug approval process, a streamlined review process for combination products that are both a drug and device, and freedom from red tape for software (see Faster, please: expedited drug approval pathways increasingly popular, July 2, 2015). Although there is new funding for the FDA to expedite review, the Cures Act retains some controversial provisions affecting how regulators evaluate certain types of medical products. Despite lawmaker assurances and the insertion of language that would keep the FDA's approval standards intact, these provisions could be interpreted to afford the FDA considerable discretion in applying those standards.

There are, however, two areas of concern with an accelerated review model in relation to drugs and devices: (1) the effectiveness of "real-world evidence" usage in lieu of controlled, clinical trials, and (2) the safety of using priority review for medical devices normally subject to the requirements of Federal Food, Drug, and Cosmetic Act (FDC Act) Sec. 510(k), also known as a 510(k) clearance. Real-world evidence could be used in support of new indications for existing drugs. This is defined as information on drug outcomes derived from nonclinical trial sources. As such, this type of data is problematic and less reliable because it would likely not have been uniformly collected. The second problematic area for the FDA under the Cures Act is the provision to speed up medical device approvals, such as formalizing an ongoing pilot program that allows high-risk medical devices priority review if considered a "breakthrough." The Cures Act opens priority review to device types subject to FDC Act Sec. 510(k) clearance and not just premarket application (PMA) approval or de novo requests. Thus, under the Cures Act, it would be possible to classify a medical device as a breakthrough even if the advantages to the device are not "clinically meaningful." In turn, this could lead to post-market safety problems.

This Strategic Perspective will examine some of these problematic areas that arise under the Cures Act and the impact on industry and consumers alike.

Real-World Evidence Takes a Prominent Role
Real-world evidence appears in section 3022 of the Cures Act, which creates Sec. 505f of the FDC Act. For the purposes of the Cures Act, real-world evidence is defined as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials." The new provisions require FDA to establish a program to evaluate real-world evidence for the following purposes: (1) help to support the approval of a new indication for a drug approved under Sec. 505(c); and (2) help to support or satisfy post-approval study requirements.

While the FDA historically has supported the controlled, randomized clinical trial as the gold standard for generating data to support all regulatory determinations, the agency recently acknowledged that real-world evidence meeting certain criteria could be used to support some regulatory decisions in the medical device sphere (see FDA sees real-world data as useful tool, July 27, 2016). In this real-world evidence draft guidance (RWE guidance), however, the agency remained silent about applying real-world evidence to pharmaceutical and biologic regulatory considerations. Now, the Cures Act requires that the FDA meet an accelerated timeline for developing a regulatory framework for real-world evidence that applies to drug applications as well. Much of the discussion on real-world evidence under the Cures Act can be seen originating in this earlier medical devices draft guidance on real-world data and evidence, along with subsequent agency commentary.

Provisions. Sec. 3001 of the Cures Act amends the FDC Act to require the FDA to make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of an approved new drug application (NDA) or biologics license application (BLA). The statement would include the following:

- data that are collected by any persons, e.g., patients and caregivers, patient advocacy groups, drug manufacturers, that provide information about the patients’ experiences with a disease or condition, including related to the impact of the disease on patients’ lives and patient preferences with respect to treatment;
- information on patient-focused drug development tools; and
- other information the FDA determines to be relevant.

The FDA must establish a framework for a real-world evidence program, which must be developed in collaboration with relevant stakeholders in the drug industry, and implement that framework within two years after the enactment date of the Cures Act. In addition, within five years of the enactment date, the FDA must issue draft guidance describing (1) the circumstances under which sponsors of drugs may rely on real-world evidence, and (2) acceptable standards and methodologies for collecting and analyzing real-world evidence.

RWE draft guidance. In the RWE draft guidance, the agency listed many potential sources of medical device real-world data, including "large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and health care claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries," and stated that validated data from these sources can provide valuable insight into the performance of medical devices used in actual clinical settings and in routine medical practice.

The RWE draft guidance explained how the agency planned to evaluate real-world data to determine whether it may be sufficiently relevant and reliable for various regulatory decisions and clarified when an investigational device exemption (IDE) may be needed to prospectively collect and use real-world data for the purposes of determining the safety and effectiveness of a device. The RWE draft guidance also defined real-world evidence, which may potentially be used to understand device performance at different points in its life cycle, including but not limited to:

- generation of hypotheses to be tested in a prospective clinical study;
- a historical control, a prior in a Bayesian trial, or as one source of data in a hierarchical model or a hybrid data synthesis;
• a setting where a registry or some other systematic data collection mechanism exists and the data can potentially be used as a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance;
• some circumstances where real-world use of a device is in a broader patient population or wider set of circumstances than described in the device labeling, it may be possible to use existing systematically collected real-world data to expand the labeling; or
• support public health surveillance efforts and to understand the evolution of the benefits and risks of devices after they have been approved or cleared in the U.S.

Proceeding with caution. The language in the medical device draft guidance, along with the FDA’s comments in the New England Journal of Medicine, support the culmination of using real-world evidence in both drug and device regulations. Industry should expect that real-world evidence usage under the Cures Act will be based largely on the FDA’s stance in its devices’ draft guidance. Although the drug clinical use context is starkly different from medical devices, real-world data sources for both are relatively comparable. Industry should be cautious, though, as the medical devices’ draft guidance was only issued in the summer of 2016. As such there has not been much time for industry to provide the FDA with feedback on the effectiveness of the criteria described in the guidance. Additionally, the FDA does not have much experience applying the use of real-world evidence in regulatory processes.

Priority Review of Breakthrough Medical Devices
The FDA’s Center for Devices and Radiological Health (CDRH) previously created an Expedited Access Pathway (EAP) program for medical devices and Section 3051 of the Cures Act takes this a step further by requiring the establishment of a breakthrough device pathway, which builds on the existing priority review device pathway. Unlike the EAP program, the Cures Act opens priority review to device types subject to 510(k) clearance and not just premarket application (PMA) approval or de novo requests. The Cures Act also codifies criteria for determining what constitutes a breakthrough device, and provides specific examples of significant, clinically meaningful advantages that reflect the guidance document.

Under the program, a manufacturer or sponsor may request priority review designation before submitting its FDA registration application. The bill authorizes the HHS to develop and issue additional guidelines specifying parameters and requirements of the program. It is speculated that the FDA will build on its already-established EAP, because of the initial work in creating it.

Benefits. The expansion of FDA’s existing priority review program for breakthrough devices for which there is no approved or cleared device currently on the market will benefit sponsors that receive a breakthrough designation. In a new and significant change for industry, the Cures Act provides that the FDA may enter into a binding agreement with breakthrough device sponsors that addresses clinical protocols that could support an application for premarket approval or a 510(k) or de novo submission—and once the agency and a sponsor reach an agreement on trial design, the FDA will encounter procedural hurdles if it decides to require changes to the protocol. Changes must be agreed to by both parties or the FDA must meet with the sponsor to discuss a substantial scientific issue essential to determining the device’s safety or effectiveness and issue a decision that such issue exists.

The procedures set forth in the Cures Act potentially expedite, by several years, the effective date of any FDA decision to not require premarket notification. As a result, the Cures Act appears to incorporate by statute the policy that FDA set forth in a 2015 guidance, which explained the agency would not enforce 510(k) requirements for Class I or II devices listed in the guidance, though FDA had not issued a final rule to amend its classification regulations (see FDA updates list of devices exempt from 510(k) premarket notification requirements, August 14, 2015).

Cures Act and the FDA’s Future
According to the FDA, the Cures Act will greatly improve the agency’s ability to hire and retain scientific experts. The law emphasizes the role of patients in the development of drugs and devices to diagnose and treat their
disease, since patients are in a unique position to provide essential insights about what it is like to live with and fight their disease. The Cures Act will likely enhance the FDA’s efforts to better incorporate the patient’s voice into decision-making. In the U.S., the FDA uses expedited programs (fast track, priority review, accelerated approval, and breakthrough therapy) for drugs and biologics more than comparable drug and biologic regulators in other countries. The first full year of operation for FDA’s EAP program was 2016 and 24 devices were given access. The FDA will look to increase this number for breakthrough devices with the Cures Act.

President Trump’s executive order directing federal agencies to cut two regulations for every new one adopted, however, could have significant implications for the FDA. The executive order noted that agencies must ensure that the "cost of planned regulations be prudently managed and controlled through a budgeting process." Under the executive order, for fiscal year 2017, the cost of all new regulations, including repealed regulations, is to be "no greater than zero," unless otherwise required by law or approved by the Office of Management and Budget. Consequently, the executive order may be too simplistic in its approach. The problems with current regulations are not that there are necessarily too many regulations, but that some are simply not needed. Some regulations are actually deregulations, which reduce existing burdens, while other regulations implement spending programs or are technical amendments correcting errors. Thus, it may not be as simple as cutting two regulations for every implemented regulation.

Looking into the near future, the FDA will need to continue its support of product development. There are various areas of import where underlying scientific knowledge is still lacking. The agency is at the early stage in building a national evidence generation system based on registries, claims data, and electronic health records that will be a source of post-market data and an avenue for conducting more efficient research. The Cures Act provides this support for continued exploration of the use of real-world evidence in the regulatory context.