Health Affairs Blog

21st Century Cures Act Lowers Confidence In FDA-Approved Drugs And Devices

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Editor's note: *This post was corrected to remove an earlier erroneous reference to decisions in the* Caronia *and* Amarin *cases as Supreme Court decisions.*

President Barack Obama signed the 21st Century Cures Act on December 13, 2016, bringing into law a piece of health care policy legislation that some describe as landmark. The Act is the result of years of debate on how best to approach a wide range of health care policy goals, from funding for and approval of new drugs to the growing nationwide problem of opioid abuse.

First introduced in the House in January 2015, the new law went through seven iterations and grew to more than 1,000 pages before landing on the President's desk. The final version invests in new therapies, injects money into health research and named initiatives, and changes standards for drug and device approval by the Food and Drug Administration (FDA). Many legislators who supported the bill have hailed it as a boon to innovation, but others are less optimistic.

In a time characterized by political stalemate, the bipartisan passage of the 21st Century Cures Act is noteworthy, but achieving support from both sides of the aisle necessitated a variety of trade-offs. For example, the Act allocates $4.8 billion to the National Institutes of Health (NIH) and provides $1 billion over two years for a response to the opioid crisis in the form of prevention and treatment activities; it provides additional funding for the Precision Medicine Initiative and $1.8 billion for former Vice President Joe Biden's Cancer Moonshot; it also invests in mental health treatment and the President's BRAIN initiative to help prevent and treat Alzheimer's and traumatic brain injuries. However, the subtle changes to the approval procedures for new drugs and medical devices included in the Act could weaken the FDA's regulatory oversight, as could a provision that permits off-label promotion of health care economic information.

Obama and the White House provided strong support for the Act. But others, such as Senators Elizabeth Warren (D-MA) and Bernie Sanders (I-VT), believe that the provisions that may compromise the FDA's ability to ensure the efficacy and safety of medical products outweigh the law's positives. We focus here on the potential changes the Act will have on the regulation of medical products and the resulting effects on physician and patient trust in the safety and efficacy of those products. Consumers need to be aware of these changes and must understand that the evidence required for drug approval may be less rigorous that it has been in the past. This primarily affects newly approved drugs, or drugs with newly approved indications.

What Might The Bill Do To Prescriber And Patient Confidence In FDA-Approved Drugs And Devices?

The 21st Century Cures Act changes the standards of evidence required for drug and device approval. Many of the changes are discretionary but may have the result of weakening the traditional standards required by the FDA, with an unpredictable long-term effect on drug safety and efficacy. Bringing new medical products to market efficiently is a laudable goal, but the government must carefully walk the fine line between speed of drug approval and the rigor of the approval process. The next FDA commissioner, along with Health and Human Services Secretary-Designate Price, will have a large role in interpreting the language on drug and device regulation in the 21st Century Cures Act, and President Trump's choice of commissioner will therefore have an especially great impact on the regulatory process.

Modified Standards Of Evidence For Drug Approval

One notable example of subtle deregulation in the 21st Century Cures Act is Section 3022, requiring that the FDA consider lower standards of evidence, including "real-world evidence." Real-world evidence is broadly defined as "data regarding the usage, or the potential benefits or risk, of a drug derived from sources other than randomized clinical trials." Section 3022 of the act requires that the Secretary consider whether to permit this evidence to support the approval for a new indication of a previously approved drug and to satisfy post-approval study requirements.

This gives substantial discretion to the Secretary to accept, limit, or reject the use of ambiguous "real-world evidence."

Randomized clinical trials, the traditional gold standard, may not be required for the approval of some new indications. Even worded as it is—giving regulators discretion rather than mandating the use of looser standards—this provision is a novel departure from the traditional view of the level of evidence that would be required.

Similarly, Section 3011, Qualification of Drug Development Tools, establishes review pathways, including the use of biomarkers and patient-reported outcomes, to shorten the time and reduce the failure rate in drug development. Acceptable biomarkers for supporting investigational use and obtaining drug approval include surrogate endpoints, which may not necessarily reflect or directly correlate with the clinical outcome of interest.

The act also provides industry with a faster route to approval for antibiotics and antifungals through the new and faster "limited population antibacterial drug" pathway. Section 3042 allows the FDA to approve antimicrobial drugs, alone or in combination, for limited populations of patients with "unmet medical needs" if the drug treats a serious or life-threatening infection, even when those drugs have not been tested in those subgroups. This allows smaller studies to go forward than previously would have been allowed, helping to speed new antimicrobial drugs to market. The act also enables faster updating of "breakpoints," used for the development of antimicrobial susceptibility tests, by allowing the FDA to use work done by other standard-setting organizations.

Widening of the antibiotic pipeline is quite important as the pathway for new antibiotics has not been robust; drug companies have not been financially incentivized to develop new antimicrobial agents. One hopes section 3042 will bring much-needed new antimicrobial agents to market, but there may be an impact on patient safety, particularly if "limited population" and "unmet medical need" are not interpreted conservatively and cautiously.

Finally, the Section 3014 of the act reauthorizes and expands the Priority Review Voucher (PRV) program. PRVs are vouchers issued to drug companies that have invested in the development of drugs for neglected tropical diseases or orphan diseases. These vouchers allow companies to expedite the review of another new drug product of their choosing.

PRVs are meant to encourage development for drugs for neglected diseases, but they also expedite the review of lower priority drugs, particularly since drug manufacturers can sell them to other companies. In this way PRVs reduce the FDA's traditional authority and control over the drug approval process.

Simpler And Easier Approval For Medical Devices

Another notable feature of the 21st Century Cures Act is the shift toward easier medical device approval. For example, Section 3056 provides for centralized institutional review boards (IRB) for medical device trials. Specifically, it eliminates the previous requirement that the sponsor of a medical device trial always use a local IRB. The rationale for using local IRBs is that they not only approve trial protocols, but also perform various site-specific tasks for clinical trials, such as training staff, and ensuring compliance with research protocols, and HIPAA privacy rules.

Additionally, Section 3058 of the act clarifies that FDA reviewers will consider the "least burdensome means" of approving a medical device, and it requires an audit to ensure that the least burdensome review standard is being applied for medical devices. Further, it clarifies that post-market information can be used to determine "the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness."

The statute (Section 3051) also establishes a pathway to accelerate the development of devices considered “breakthrough” technologies. This new program builds on the current Expedited Access Pathway (EAP) program. Breakthrough devices include those that provide more effective treatment or diagnosis of life-threatening conditions. The program is open to devices proceeding through clearance by the 510(k) pathway, as well as the pre-market approval (PMA) pathway.

Section 3060 recasts certain types of medical software as separate from devices subject to FDA review — a provision of considerable interest to industry stakeholders. This section exempts from review five categories of medical software based on the low level of risk to patients. Types of software exempt from review as a device include: software meant to serve as an electronic patient record; software for maintaining or encouraging a healthy lifestyle; and software for transferring, storing, or converting formats, or displaying clinical laboratory tests or device data.

The act does provide the FDA with the authority to regulate software in these categories if the software also includes functions that operate as reviewable medical devices, or if there are serious safety concerns with the software.

Off-Label Promotion Of Health Care Economic Information

Of particular concern to us is Section 3037 of the statute, which provides a safe harbor for the promotion to payers of off-label health care economic information, as long as the information relates to an approved indication of a drug. In effect, this provision allows drug manufacturers to promote to payers’ economic information, including clinical data, about uses of drugs that go beyond product claims within the FDA-approved label.

This provision builds on recent court decisions (*Caronia* and *Amarin*) that provide First Amendment protection for promotion of off-label uses, as long as the promotion is based on scientific information and is neither false nor misleading. On the one hand, the provision is disturbing to some stakeholders because off-label uses may potentially expose patients to safety concerns. On the other hand, proponents argue that off-label uses may be beneficial to patients when drugs are prescribed on the basis of good scientific data.

Looking Forward

While it is difficult to ignore the positive aspects of the 21st Century Cures Act, such as the Cancer Moonshot and widened pipeline for antibiotics, there is also legitimate cause for concern that the traditional regulatory standards we have come to rely on may be modified, with unknown long-term effects on the safety and efficacy of new drugs and devices. How these modified regulatory standards are interpreted and applied will depend significantly on the new FDA commissioner, and this critical appointment will be closely watched.

On January 30, President Trump introduced another variable into the mix by signing an Executive Order requiring federal agencies, including the FDA, to eliminate two regulations for each new regulation the agency introduces and to offset the incremental cost of new legislation. This Executive Order may seriously hinder the implementation of portions of the 21st Century Cures Act — much of the Act directs the FDA to create new review pathways for drugs and devices, and the FDA would effectuate this mandate by promulgating new regulations.

There will likely be no guidance on how the Executive Order will be implemented until a director of the White House Office of Management and Budget (OMB) is confirmed. The director of the OMB is tasked with evaluating the cost of regulations and has broad discretion in how to do so.

DRUGS AND MEDICAL INNOVATION

ASSOCIATED TOPICS: DRUGS AND MEDICAL TECHNOLOGY, QUALITY

TAGS: 21ST CENTURY CURES ACT, DRUG APPROVAL, FDA, MEDICAL DEVICES, OFF-LABEL PROMOTION, PATIENT SAFETY