

21st Century Cures Act: Key Provisions Related to Medical Devices

July 30, 2015

Food & Drug

The 21st Century Cures Act (“the Act” or “HR 6”) was passed by the House of Representatives on July 10, 2015, by a vote of 344-77. The Act includes proposals that stem from the 21st Century Cures Initiative that was launched in April 2014 by House Energy and Commerce Committee Chairman Fred Upton and Representative Diana DeGette. The Act contains four titles that are spread over more than 350 pages and includes provisions that would significantly affect the regulation of pharmaceuticals, biological products, and medical devices.

A [summary](#) released in conjunction with the Act states that “HR 6 accelerates the discovery, development and delivery of life saving and life improving therapies, and transforms the quest for fast cures by,” among other actions:

1. removing barriers to increase research collaboration;
2. measuring success and identifying diseases earlier through personalized medicine;
3. modernizing clinical trials;
4. removing regulatory uncertainty for the development of new medical apps; and
5. helping the entire biomedical ecosystem coordinate more efficiently to find faster cures.

We previously summarized the medical device provisions of a discussion draft of the Act that was circulated in January 2015 (see [here](#)¹). The device provisions of HR 6 has been subject to many revisions since the discussion draft, including (i) the deletion of a placeholder for laboratory developed tests (LDTs), (ii) deletion of sections related to research use only products and surrogate endpoint qualification and utilization; and (iii) significant changes to the section relating to FDA authority over certain software.

This alert summarizes the key provisions relating to medical devices and combination products, presenting these provisions in the order of the titles in the Act.

¹ https://www.cov.com/~media/files/corporate/publications/2015/02/21st_century_cures_legislation_discussion_draft_key_provisions_related_to_medical_devices.pdf

Title II – Development

Section 2102. Facilitating Responsible Communication of Scientific and Medical Developments

This section would require FDA to issue draft guidance, no later than eighteen months from the date of enactment, to clarify how drug and device manufacturers can permissibly disseminate truthful and non-misleading scientific and medical information about a drug or device that is not included in the approved labeling for the product. FDA's policies regarding the dissemination of "off-label" information about drugs and devices has long been a controversial issue. The debate has accelerated in recent years as a result of the Second Circuit's decision in *U.S. v. Caronia* and recent developments in the *Amarin v. FDA* case. FDA has announced that it will hold a public meeting to discuss issues related to its policies on off-label use and promotion.²

Section 2122. Susceptibility Testing Interpretive Criteria for Microorganisms

The Act includes several provisions, including Section 2122, that seek to address concerns about antimicrobial drug resistance and stimulate the nation's pipeline of antimicrobial drugs. Section 2122 would amend section 511 of the Federal Food, Drug, and Cosmetic Act (FDCA), which required FDA to issue guidance on clinical trials for antibiotic drugs. The purpose of this new section would be to provide an "expedited, flexible method" for:

- "clearance or premarket approval of antimicrobial susceptibility testing devices utilizing updated, recognized susceptibility test interpretive criteria to characterize the in vitro susceptibility of particular bacterial, fungi, or other microorganisms to antimicrobial drugs;" and
- "providing public notice of the availability of recognized interpretative criteria to meet premarket submission requirements or other requirements under [the FDCA] for antimicrobial susceptibility testing devices."

This section would require FDA to establish and maintain an "Interpretive Criteria Website," which would include susceptibility test interpretive criteria established on the basis of preclinical data, clinical data, Bayesian and pharmacometric statistical methodologies, and other evidence and information deemed appropriate by FDA. Section 2122 would also require FDA to evaluate new or updated susceptibility test criteria standards established by nationally and internationally recognized standards organizations that meet certain criteria and to update the Interpretive Criteria Website accordingly.

Section 2122 would permit FDA to authorize the marketing of antimicrobial susceptibility testing devices if certain specified conditions are met, including that the device is used to make a determination of susceptibility using interpretive criteria that are (i) included in a recognized standard or (ii) otherwise listed on the Interpretive Criteria Website. The labeling for such devices must include a disclaimer that the device "provides information about the susceptibility of bacteria and fungi to certain drugs," and the drug's safety and effectiveness "in treating

² <http://www.reuters.com/article/2015/05/07/us-fda-pharmaceuticals-constitution-idUSKBN0NS00F20150507>

clinical infections due to such bacteria or fungi may not have been established in adequate and well-controlled clinical trials and the clinical significance of such susceptibility information is unknown.” The device’s labeling must also include a statement that health care professionals should consult the drug labeling for the drug’s approved uses.

Section 2181 Enhancing Combination Products Review

Under this section, FDA would be required to issue final guidance within 18 months of the enactment of the Act that describes the responsibilities of each agency center for reviewing combination products. FDA would be required to periodically review and update the guidance after obtaining public comment.

Section 2201. Priority Review for Breakthrough Devices

Section 2201 would strike section 515(d)(5) of the FDCA, which provides authority for FDA’s current medical device priority review program, and would add a new section 515B to establish a new priority review program for breakthrough devices. This section reflects [FDA guidance](#) that was issued on April 13, 2015, establishing an expedited access pathway for unmet medical needs for life threatening or irreversibly debilitating diseases or conditions and are subject to premarket approval applications (PMAs) or *de novo* requests (“EAP Program”). The new section 515B would expand FDA’s current EAP Program to include devices subject to 510(k) premarket notifications, in addition to PMA and *de novo* devices. This section would also expand the criteria for qualification as a “breakthrough device” so that a device qualifies if it has “the potential to, compared to existing approved or cleared alternatives, reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients’ ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies.”

This section would provide a process for designating devices for priority review. A denial of a designation determination would be considered a “significant decision” under section 517A of the FDCA, which includes statutory timeframes for processing of appeals.

Section 2201 includes a number of actions intended to facilitate the priority review process. For example, FDA would be required to assign a team of staff and a team leader with appropriate subject matter expertise and experience for the device, provide oversight of the team by senior agency personnel, adopt an efficient process for timely dispute resolution, provide for interactive communication with the sponsor of the device during the review process, and, as applicable, expedite the review of applicable manufacturing and quality compliance.

In order to expedite the development and review of devices designated for priority review, FDA may also collaborate with the device sponsor to (i) coordinate an early agreement on a data development plan, (ii) take steps to ensure that a design of clinical trials is as efficient as practicable, such as through shorter or smaller clinical trials or application of surrogate endpoints, (iii) agree to clinical protocols that FDA will consider binding on the sponsor and FDA, and (iv) facilitate expedited and efficient development and review of the device through utilization of postmarket data collection. FDA would also be required to publish guidance on implementation of the new section 515A.

Section 2221. Third-Party Quality Assessment

Section 2221 would require FDA to establish a new third-party quality system assessment program under which FDA would accredit third parties to “assess whether a [device manufacturer’s] quality system, including its design controls, can reasonably assure the safety and effectiveness” of cleared or approved devices subject to “device-related changes.”

“Device-related changes” would include:

- changes to a 510(k) cleared device that would otherwise be subject to a premarket notification, and do not alter the intended use of the changed device or the fundamental scientific technology of such device;
- manufacturing changes to a PMA approved device, otherwise subject to a 30-day notice;
- changes to a PMA approved device that otherwise qualify for a Special PMA Supplement; and
- other changes as the FDA determines appropriate.

If the accredited third party certifies to FDA that a device manufacturer’s quality system meets the criteria included in a FDA guidance document (which FDA must issue), the manufacturer would not be required to submit a new 510(k), 30-day notice, or Special PMA supplement. The accredited third party would be required to submit to FDA a summary of the quality system assessment indicating that the manufacturer has satisfied the criteria in the guidance document.

FDA’s review and acceptance of the assessment certification would be deemed complete 30 days after receipt, unless FDA provides written notice otherwise. A certification by the accredited third party would remain in effect for two years and may be renewed, but it may also be revoked if FDA determines that the manufacturer’s quality system no longer meets the criteria in the guidance document.

A manufacturer whose quality system is certified by an accredited third party would be required to describe the device-related changes made and effective dates of such changes in periodic reports submitted to FDA.

In addition, Section 2221 would require FDA to evaluate this third-party quality assessment program by January 31, 2021, based on analysis of information from device manufacturers and other information, and to issue a report with the agency’s findings and recommendations on continuing or expanding the program. The section includes a sunset clause under which the section would cease to be effective on October 1, 2022.

Section 2222. Valid Scientific Evidence

Currently, the FDCA permits FDA to determine the effectiveness of a device based on “valid scientific evidence” (rather than “well-controlled clinical investigations”) if (i) the evidence is sufficient to determine the effectiveness of the device, and (ii) qualified experts can fairly and reasonably conclude that the device will have the effect it purports or is represented to have under the labeled conditions of use.

Section 2222 of the Act would add a definition of “valid scientific evidence” that would include (i) well-documented case histories, including certain registry data, and (ii) studies published in peer-reviewed journals. Valid scientific evidence would also include data collected outside the

United States. In the case of a study published in a peer-reviewed journal, FDA may request data underlying the study as long as such a request is consistent with the “least burdensome” concept (described below) and the agency provides a written rationale for the request.

Section 2223. Training and Oversight in Least Burdensome Appropriate Means Concept

Under current law, FDA must consider the “least burdensome” means of evaluating device effectiveness or substantial equivalence for purposes of approval or clearance of a device. Section 2223 is intended to strengthen this requirement.

Section 2223 would require all FDA employees involved in the review of PMA or 510(k) submissions to receive training regarding the meaning and interpretation of the “least burdensome” principle. The section would also require FDA to issue draft guidance updating the 2002 FDA Least Burdensome Guidance within 12 months after enactment of the Act and after convening a meeting of stakeholders. Within 18 months after issuance of the final guidance, the Center for Devices and Radiological Health (CDRH) ombudsman is required to conduct an audit of the training described above. This audit would be required to include interviews of industry representatives regarding their experience in the device premarket review process.

In addition, Section 2223 would require FDA to consider the “least burdensome means necessary to demonstrate device safety and effectiveness” when FDA requests additional information regarding a PMA application. “Necessary” would be defined as the “minimum required information that would support a determination by the Secretary that an application provides a reasonable assurance of the safety and effectiveness of the device.”

Section 2224. Recognition of Standards

Section 2224 would amend section 514(c) of the FDCA, which concerns recognition of standards for devices. Upon request of any person, FDA would be required to make a determination within 60 days to recognize all, part, or none of a standard issued by a nationally or internationally recognized standard development organization. FDA would be required to issue a written response to the requester that states FDA’s rationale for the determination and would also be required to make the response and rationale publicly available.

In addition, FDA would be required to (i) provide training to all employees who review device premarket submissions on the concept and use of recognized standards to facilitate premarket review, and (ii) issue guidance identifying the principles for recognizing standards under this section.

Section 2225. Easing Regulatory Burden with Respect to Certain Class I and Class II Devices

Under current law, most Class I devices and some Class II devices are exempt from the 510(k) premarket notification requirement. Section 2225 would require FDA to identify, through publication in the *Federal Register* within 120 days of passage enactment of the Act, additional types of Class I devices that no longer require a 510(k). In addition, FDA would be required, within 60 days of passage enactment of the Act, to publish a list of Class II device types that FDA believes no longer require a 510(k). After public comment, FDA would be required to publish a final list of Class II devices that are exempt from the 510(k) requirement.

Section 2226. Advisory Committee Process

This provision would amend section 513(b) of the FDCA to stipulate new procedures for medical device classification panels. FDA would be required, whenever a device is specifically the subject of review by a classification panel, to ensure that “adequate expertise” is represented on the panel, and FDA would need to consider the recommendations of the device sponsor as part of this process. A panel would have “adequate expertise” if it consists of (i) at least two voting members with a specialty or other expertise clinically relevant to the device under review and (ii) at least one voting member who is knowledgeable about the technology of the device.

Section 2226 would also amend section 513(b) to require FDA to provide time at the panel meeting time for a designated representative of the sponsor (who may be accompanied by experts) to address the panel, correct misstatements, or provide clarifying information, subject to the discretion of the panel chairperson. FDA would also be required to provide adequate time for initial presentations by the sponsor of the device and by the agency.

Section 2227. Humanitarian Device Exemption Application

This section would expand the availability of a humanitarian device exemption (“HDE”). Section 520(m) of the FDCA currently limits HDE devices to those that are intended to treat or diagnose a disease or condition that affects no more than 4,000 individuals in the U.S. per year. Section 2227 would increase the limit to 8,000 individuals in the U.S. per year.

This section would also require FDA to issue draft guidance within 18 months of enactment that defines the criteria for establishing “probable benefit” to health from use of an HDE device, which is a key requirement for a sponsor to obtain HDE approval.

Section 2228. CLIA Waiver Study Design Guidance for In Vitro Diagnostics

Currently, certain home use tests and “simple” tests that have “an insignificant risk of an erroneous result” are eligible for a waiver of the requirements of the Clinical Laboratory Improvement Amendments of 1988 (“CLIA”). In January 2008, FDA issued a guidance document describing the agency’s approach to determining that a device meets the CLIA statutory waiver criteria. Section 2228 would require FDA to publish a new draft guidance within 12 months to revise Section V of the 2008 guidance, which describes the agency’s recommendations on the clinical studies to demonstrate that a test is accurate in the hands of the intended operator and therefore has an insignificant risk of an erroneous result.

The new guidance would be required to include recommendations on the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy. FDA would be required to issue a final guidance within 12 months after the closing of the comment period on the draft guidance.

Sections 2241 – 2243. Sensible Oversight for Technology Which Advances Regulatory Efficiency

The Act includes several sections that, collectively, would narrow FDA authority over certain health information technology. The prior discussion draft would have established two categories: “medical software” (subject to FDA regulation) and “health software” (not subject to FDA regulation).

HR 6 uses a different approach. The legislation defines “health software” -- which would be excluded from regulation under the FDCA -- but no longer defines “medical software.” The definition of “health software” includes software for the following functions:

- administrative or operational support or the processing and maintenance of financial records,
- clinical, laboratory, or administrative workflow and related recordkeeping,
- transfer, aggregation, conversion (in accordance with a preset specification), storage, management, retrieval, or transmission of data or information, but not active patient monitoring or controlling a device that is connected to such software³,
- organization and presentation of information for health or wellness education or for use in maintaining a healthy lifestyle, including medication adherence and health management tools, and
- analysis of information to provide general health information that does *not* include patient-specific recommended options to consider in the prevention, diagnosis, treatment, cure, or mitigation of a particular disease or condition.

However, “health software” does not include

- software that, through use of an in vitro diagnostic device or signal acquisition system, is used to acquire, process, or analyze an image or physiological signal,
- an accessory to a medical device⁴,
- software that is an integral part of a device necessary to support the use of the device, and
- software that is used in the manufacture and transfusion of blood and blood components to assist in the prevention of disease in humans.

The Act specifies that software used to analyze information that *does* include patient-specific recommended options to consider in the prevention, diagnosis, treatment, cure, or mitigation of a particular disease or condition, would also fall within the health software definition, but would be excluded from regulation under the FDCA *only if* FDA determines that the software does not pose a significant risk to patient safety. Section 2242 would require FDA to consider the following four factors when determining whether software poses a significant risk to patient safety:

- the likelihood and severity of patient harm if the product does not perform as intended,

³ The Act states that this type of software must utilize a connectivity software platform, electronic or electrical hardware, or a physical communications infrastructure.

⁴ Section 2241 would define an “accessory” as a product that is (1) intended for use with one or more parent devices; and (2) intended to support, supplement, or augment the performance of one or more parent devices. The Act would require FDA to classify an accessory according to its own intended use, independently of the parent device classification.

- the extent to which the product is intended to support the clinical judgment of a medical professional,
- whether there is a reasonable opportunity for a medical professional to review the basis of the information or treatment recommendation provided by the product, and
- the intended user and user environment, such as whether a medical professional will use the product.

This section further requires FDA to review existing regulations and guidance regarding the regulation of software, and authorizes FDA to implement a new framework for the regulation of software by issuing, after consultation with external stakeholders, new regulations, guidance, or administrative orders.

Sections 2261 – 2263 Clinical Trials

Section 2261 would require, to the extent possible, the Secretary of Health and Human Services to harmonize differences between the HHS Human Subject Regulations and the FDA regulations governing clinical studies. The legislation would direct the Secretary to reduce regulatory duplication and unnecessary delays, modernize these provisions in the context of multistate and cooperative research projects, and incorporate local considerations, community values, and mechanisms to protect vulnerable populations.

Regulations and guidance to implement the section would be required to be issued no later than 36 months after the Act's enactment and after consultation with stakeholders. The Secretary would be required to submit a report to Congress within 24 months after the enactment of the Act on the progress toward completing harmonization.

Section 2262 would streamline the clinical investigations of devices by removing the requirement for a local IRB at each site in a multi-site study to review and approve a device study. These provisions would make it easier for sponsors to use a centralized IRB to oversee clinical research, which could help to expedite the initiation of clinical studies, simplify IRB reporting, and ensure consistency of IRB review.

Section 2263 would amend sections 520(g)(3) and 505(i)(4) of the FDCA to exempt the requirement of obtaining informed consent from human subjects for medical device or drug trials where “the proposed clinical testing poses no more than minimal risk” to the human subject and includes appropriate safeguards “to protect the rights, safety, and welfare” of the human subject.

Conclusion and Next Steps

The Senate is currently working on parallel legislation to the Act. In addition, if not enacted during this Congress, it is possible that many aspects of the proposed legislation will be incorporated in the reauthorization of the Medical Device User Fee Amendments and associated legislation in 2017.

We will continue to monitor these legislative proposals as they are considered by the Senate.

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