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21st Century Cures Legislation Discussion Draft: Key Provisions Related to Medical Devices

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Food & Drug

A discussion draft of the highly anticipated legislation, 21st Century Cures Act, was released on January 27, 2015 ("Draft Act"). The Draft Act includes proposals that stem from the 21st Century Cures Initiative that was launched in April 2014 by House Energy and Commerce ("E&C") Committee Chairman Fred Upton and Representative Diana DeGette. The draft bill contains five titles that are spread over almost 400 pages and includes provisions that would significantly affect the regulation of pharmaceuticals, biological products, and medical devices. A white paper released in conjunction with the Draft Act states that the proposed legislative changes are intended to:

1. incorporate patient perspectives into the regulatory process and help address their unmet medical needs;
2. build the foundation for 21st century medicine;
3. streamline clinical trials;
4. support continued innovation at our federal public health agencies; and
5. modernize medical product regulation.

This alert summarizes the key provisions relating to medical devices, presenting these provisions in the order of the titles in the Draft Act. As stated in the white paper accompanying the Draft Act, discussion regarding the proposed changes is still ongoing, and the E&C Committee requests feedback on the proposals. Indeed, the Draft Act contains placeholders for some important provisions for which legislative language is still being developed, including a placeholder for "Modernizing Regulation of Diagnostics."

Title I – Putting Patients First by Incorporating Their Perspectives into the Regulatory Process and Addressing Unmet Needs

Sections. 1021 – 1023. Surrogate Endpoint Qualification and Utilization

Section 1021, which includes provisions related to both devices and drugs, would amend the Federal Food, Drug, and Cosmetic Act (FDCA) to require FDA to issue a guidance document to establish evidentiary standards (including study and data requirements) for qualifying "surrogate endpoints." The Draft Act defines a "surrogate endpoint" as "a biomarker that is intended to substitute for a clinical endpoint." A "biomarker" is defined to include "a physiologic, pathologic, or anatomic characteristic or measurement" that is objectively measured. Section 1021 also authorizes FDA to enter into a "public-private partnership" with private entities to review

requests and develop standards to qualify biomarkers for use other than as surrogate endpoints.

Section 1022 would amend the FDCA to add a new section 507A that would establish a process by which any person can request that FDA qualify a surrogate endpoint. When assessing the request, FDA may consult with external experts, subject to confidentiality protections, and at the requestor's request, must consult with external scientific experts in a public forum. Any surrogate endpoints qualified through this process are available for use "by any person" to support future investigational use or premarket submissions for a device, drug, or biological product, or for any other regulatory purpose. If the requestor provides consent, FDA must make available to the public information about the surrogate endpoint, supportive data, and determinations.

Section 1023 sets out transitional provisions for biomarker requests that are pending at the time of the enactment of the bill. In "the sole discretion of the requestor," the requestor may submit a request that the pending request be reviewed under the public biomarker qualification process of section 507A.

These sections, if enacted, would facilitate a more timely review of surrogate endpoints and could provide greater predictability for requestors.

Section 1062. Susceptibility Test Interpretive Criteria for Microbial Organisms

The Draft Act includes several provisions, including section 1062, that seek to address antibacterial drug resistance and stimulate the nation's pipeline of antibiotic products. Section 1062 would amend section 511 of the FDCA, which required FDA to issue guidance on clinical trials for antibiotic drugs to expand the types of susceptibility test interpretive criteria that can be used to analyze antibacterial and antifungal drugs.

Under this provision, FDA would be required 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. The section would also require FDA to evaluate new or updated susceptibility test criteria standards established by nationally and internationally recognized standards organizations and to update the Interpretive Criteria Website accordingly. The criteria published on the website would be recognized as a performance standard under section 514 of the FDCA and used by the agency for purposes of device classification.

Section 1062 would permit the marketing of susceptibility testing devices if they are based on the interpretive criteria. The labeling for such devices would need to include a disclaimer that the drug's safety and effectiveness in treating clinical infections was not established in adequate and well-controlled clinical trials and the clinical significance of the 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 1081. Priority Review for Breakthrough Devices

This section would expand FDA's current medical device priority review program to include devices subject to the de novo classification process and 510(k) clearance. This section builds upon the current priority review language in section 515(d)(5) of the FDCA that relates to

devices subject to premarket approval (PMA) as well as FDA's 2014 draft guidance, "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions." This section would also expand the criteria to qualify as a "breakthrough devices" under the current priority review program. Specifically, a device would be able to qualify if it "has the potential to, compared to existing approved 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."

Section 1081 also adds a process for designating breakthrough devices for priority review. Within 60 days of receiving a request, FDA must determine whether the device meets the criteria for a "breakthrough device" and provide a "written, substantive summary of the basis for the determination." If the request is denied, the sponsor may request, within 30 days of the denial, reconsideration by the Center Director. Section 1081 includes a number of actions intended to facilitate the priority review process. For example, FDA must assign a team of staff and a team leader with appropriate subject matter expertise and experience for each device, provide for interactive communication with the sponsor during the review process, and expedite the review of applicable manufacturing and quality compliance. If FDA intends to consult with external experts or an advisory committee, FDA must disclose to the sponsor the topics of any such consultation in advance and provide an opportunity for the sponsor to recommend external experts.

In order to expedite the development and review of devices designated as "breakthrough," FDA may collaborate with the device sponsor to coordinate an early agreement on a data development plan, to ensure that a design of clinical trials is as efficient as practicable, to agree to clinical protocols that FDA will consider binding on FDA (unless there arises an unreasonable risk to public health), and to facilitate expedited and efficient development and review of the device through utilization of postmarket data collection. FDA is also required to publish guidance on priority review for breakthrough devices.

Section 1101. Accelerated Approval for Breakthrough Devices

This section would add section 515C to the FDCA. Under this new section, FDA may approve a device that meets the new priority review criteria for a "breakthrough device" (described in the section above) upon a determination that the device has an effect on a surrogate endpoint that is "reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit." Approval of the device may be subject to a requirement that the sponsor conducts appropriate postapproval studies to verify clinical benefit or effectiveness.

Section 1161. Dissemination of Information about Medical Products Using the Internet

Section 1161 would require FDA to review its current regulations and guidance documents and update its policies for drug and device promotion using the Internet, including "social media platforms and character-limited applications."

FDA's current social media draft guidance[1] requires risk information to be included within the same character-space limited communication as any benefit claim (including the indication statement). Section 1161 would direct FDA to revise its regulations and guidance to recognize that companies may disseminate, in character-limited applications, an introductory paragraph including the product's name and approved uses, and a hyperlink to additional information about the safety and effectiveness of the product. FDA must treat the hyperlinked information as if it appeared in the introductory information.

Title II – Building the Foundation for 21st Century Medicine, Including Helping Young Scientists

Sections 2061 – 2063. Sensible Oversight for Technology Which Advances Regulatory Efficiency (Software)

These sections would limit FDA authority over health information technology. The Draft Act incorporates concepts from the SOFTWARE Act discussion draft (H.R. 3303).

Section 2061 of the Draft Act would amend section 201 of the FDCA to add new definitions relating to software. These sections would exclude "health software" from regulation as a medical device, and would require FDA to promulgate regulations to establish standards and procedures for regulating "medical software."

"Health software" is defined as software that is not "medical software" or a component of a medical device, is intended to be used for or in support of a health care purpose, and is intended for certain uses specified in the Draft Act. These specified intended uses include, in part:

(i) administrative or operational support;

(ii) clinical, laboratory, or administrative workflow, including electronic health records;

(iii) conversion, storage, and transmission of data from a device or other thing;

(iv) a platform for secondary software;

(v) patient self-management or self-monitoring of a disease or condition, including management of medications;

(vi) analysis of patient-specific information to provide patient-specific recommended treatments to inform a health care professional's treatment or diagnostic decision with the opportunity for additional interpretation or independent confirmation before taking a course of action; and

(vii) analysis of patient-specific information for purposes of providing general information related to prevention, diagnosis, prognosis, treatment, monitoring or management of a disease or condition.

[1] FDA, Draft Guidance for Industry: Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices (June 2014).

"Medical software" is defined as software that is not a component and not intended to provide a diagnosis, and that is intended to analyze patient-specific information to recommend to a health care professional a single treatment or course of action without the need for the professional to interpret or independently confirm the action. The new definition of an "accessory" provides that an accessory should be classified "based on its own intended use, functionality, and risk," instead of taking on the classification of the product with which it is used.

Section 2062 of the Draft Act would add a new section 524B to the FDCA, under which FDA would be required to promulgate regulations to establish a separate regulatory framework for medical software. This would include separate regulations for classification, standards for software development and validation/verification, review, modifications, manufacturing, quality systems, labeling and postmarketing requirements. FDA would also be required to hold several workshops that include patient and expert representatives to obtain input regarding the promulgation of these regulations.

Section 2092. Recommendations for Development and Use of Clinical Data Registries

This section stipulates that within one year of enactment of the 21st Century Cures Act, FDA would be required to make recommendations for the development and use of clinical data registries that are integrated with clinical practice guidelines and best practices or standards of care for the improvement of patient care. FDA would be required to consult with clinical experts in the development of these recommendations.

FDA would be required to provide recommendations on: (1) a set of standards that would allow the bidirectional, interoperable exchange of information between electronic health records of the reporting clinicians and the registries; (2) how clinical registries may be developed and used to evaluate care models and methods, including for management of diseases as measured by care parameters (e.g., A1c, blood pressure, and cholesterol for diabetes care); (3) how such registries should be structured to facilitate the recording and reporting of postmarket data for the purposes of monitoring safety and efficacy of FDA-approved devices and drugs, and the reporting of relevant clinical data to satisfy attestation requirement for coverage of prescribed devices and drugs; (4) how data from such registries may be used to inform physicians and other health care professional regarding clinical practices for the prevention of disease; and (5) how registries can be used to promote preventive health benefits that may reduce the risk of chronic disease.

Sections 2141 – 2142. Combination Products

Section 2141 attempts to clarify and streamline the review process for combination products (products with two or more FDA-regulated components).[2] This section would require the Office of Combination Products (OCP): (1) to coordinate communications with each FDA center involved in the review process and ensure that the FDA center with primary jurisdiction is the sole point of contact for the sponsor; (2) to ensure that each center involved in the review attends all meetings with the sponsor; and (3) to require that each consulting center completes its premarket review within timeframes that allow the lead center to meet its review goal.

[2] This section does not amend the definition of a combination product or amend the definitions of drug, device, or other product categories.

This section also provides that the communications and commitments from the lead center "shall be binding on all other centers involved in the review." FDA must issue (and biannually review and update) guidance describing the responsibilities of each center in the review of combination products.

In addition, Section 2142 would require the GAO to submit a report to Congress providing various combination product designation metrics and describing FDA's processes for combination products. GAO would also be required to include in the report any recommendations for improving the process for development and review of combination products.

Section 2161. Modernizing Regulation of Diagnostics

This section contains a placeholder for future legislative text.

Section 2181. Interoperability

This section contains a placeholder for future legislative text. According to the white paper accompanying the Draft Act, the goal of such text will be to develop a "national interoperable health information infrastructure."

Title III – Modernizing Clinical Trials

Section 3002. Use of Institutional Review Boards for Review of Investigational Device Exemptions

This section would streamline the clinical investigations of devices by removing the requirement for a local institutional review board (IRB) at each site in a multi-site study to review and approve a device study. This section would also require FDA to issue regulations or guidance to implement this new approach. 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 the IRB reporting process, and ensure consistency of IRB review.

Section 3021. Clinical Trial Modernization

Section 3021 would require FDA to establish and implement a framework through which sponsors of drugs, biologics or devices may submit a proposal for incorporating adaptive trial designs, Bayesian methods or alternative statistical methods into proposed clinical protocols and marketing submissions.

FDA would be required to update and finalize the FDA draft guidance on adaptive trial design for drugs and biologics, and issue draft guidance on the use of Bayesian methods in the development and regulatory review of drugs, biologics, and devices. These guidances must address standards for using such designs and methods in clinical trials and mechanisms for sponsors to obtain feedback from FDA. Prior to developing the guidances, FDA must hold a public meeting. Within four years of enactment of the 21st Century Cures Act, FDA must review and, as appropriate, revise the guidance documents to reflect developments in statistical methods.

Title IV – Accelerating the Discovery, Development, and Delivery Cycle and Continuing 21st Century Innovation at NIH, FDA, CDC, and CMS

Section 4301. Establishment of Manufacturer Opt-Out Program for Medical Devices

As a mechanism to speed the availability of new medical devices, section 4301 of the Draft Act would create a public "Accelerating Innovation in Medicine" (AIM) list of devices that have yet to receive FDA clearance/approval. A device would be eligible for the AIM list if the manufacturer has a pending PMA application or 510(k) submission with FDA, or if the device is exempt from 510(k) or PMA requirements. Patients can receive a device on the AIM list if they agree to pay personally for the device and the services related to furnishing the device, if no insurance payments are requested or made, and they provide informed consent. Under the program, a manufacturer would be able to request that its device be placed on the AIM list for a 3-year period.

The device could remain on the AIM list for subsequent 3-year periods unless it is removed or not renewed (1) at the request of the manufacturer or (2) if the manufacturer fails to submit published or publicly available clinical data on the device at the end of the previous 3-year period. In addition, if a physician or other entity fails to obtain a patient's informed consent to receive a device on the AIM list and accept liability for payment, the physician or entity would not be able to charge the patient for the device.

Section 4321. Medicare Pharmaceutical and Technology Ombudsman

This section would provide for the establishment of a pharmaceutical and technology ombudsman within the Centers for Medicare & Medicaid Services (CMS) to receive and respond to complaints, grievances, and requests from pharmaceutical and medical device companies regarding Medicare coverage, coding, or payment for their products. The section also requires the ombudsman to submit an annual report of its activities to Congress. The white paper accompanying the Draft Act states that this provision is intended to help companies "to appeal decisions and better understand the reasoning behind Medicare coverage decisions."

Section 4401. Clarification Regarding Research Use Only Products

This section would add section 520(o) to the FDCA to clarify that in vitro diagnostic products that are labeled for research use only (RUO) and not for use in diagnostic procedures may not be considered adulterated or misbranded on the basis that the manufacturer sells the product to an end user who uses the product in a manner inconsistent with the RUO labeling, or because the manufacturer communicates with the user about the functioning of the product or provides technical support, customer service, or communication to ensure product performance. This section also includes a sunset provision five years after the enactment of the section.

Title V – Modernizing Medical Product Regulation

Section 5061. Third-Party Quality System Assessment

Section 5061 would add a new section 524B to the FDCA to allow an accredited third party to "assess and certify a facility's capability to evaluate and implement" certain changes to a cleared or approved device. A manufacturer would not be required to submit a new 510(k) or PMA supplement for these changes if the accredited party determines that the facility has a

quality system (including the facility's design controls) that is capable of evaluating on a continuing basis certain types of device changes so as to provide reasonable assurance of safety and effectiveness, and provides a written determination that the change is in compliance with the FDCA. These changes are: technology changes to devices that were found to be substantially equivalent to a predicate device; changes in the manufacturing of a device; changes that do not alter a device's fundamental technology; and certain labeling changes. A determination by the accredited third party would remain in effect for two years and may be renewed.

Section 5062. Valid Scientific Evidence

This section would amend section 513(a)(3)(B) of the FDCA, which currently permits FDA to authorize the effectiveness of a device to be determined on the basis of valid scientific evidence (rather than the well-controlled clinical investigation required by section 513(a)(3)(A) of the FDCA) if the evidence is sufficient to determine the effectiveness of the device and from which 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 5062 would define valid scientific evidence for purposes of Section 513(a)(3)(B) of the FDCA to include well-documented case histories, including registry data, and studies published in peer-reviewed journals that are internationally recognized as authoritative sources. Valid scientific evidence would also include data collected outside the United States.

Section 5063. Training and Oversight in the Least Burdensome Means Concept

Under existing law, FDA must require the "least burdensome" appropriate means of evaluating device effectiveness or substantial equivalence for purposes of approval or clearance of a device. Section 5063 of the Draft Act is intended to ensure that FDA is complying with that requirement. The section would require all FDA employees involved in the review of PMA or 510(k) submissions to receive training on an annual basis regarding the meaning and interpretation of the least burdensome means concept.

FDA would also be required to ensure that adequate guidance documents describing the least burdensome means concept and its implementation are available to persons involved in the review of PMAs and 510(k) submissions. The ombudsman for the organizational unit of FDA responsible for the premarket review of devices would also be required to conduct an audit of that unit to determine the unit's performance in implementing the least burdensome means requirements.

Section 5064. Recognition of Standards

Section 5064 would amend section 514(c) of the FDCA, which concerns recognition of standards for devices. Under this provision, FDA may recognize, by publication in the Federal Register, any new standard issued by a nationally or internationally recognized standard development organization. Not later than 60 days after the organization makes the standard available, FDA must issue a Federal Register notice recognizing the standard or explaining the basis for refusing to recognize the standard. In addition, FDA must provide training to all employees who review device premarket submissions on the concept and use of recognized standards to facilitate premarket review and support determinations of reasonable assurance of safety and effectiveness.

Section 5065. Notification of Marketing of Certain Class I Devices

Under current law, most Class I devices are exempt from the requirement for submission of a 510(k) premarket notification before marketing. However, pursuant to section 510(l) of the FDCA, devices that are intended for a use of substantial importance in preventing impairment of human health or that present a potential unreasonable risk of illness or injury are still subject to the 510(k) requirement. Section 5065 of the Draft Act would provide a streamlined notification process for such devices. Under this new notification process, companies could market a device five business days after FDA receives a notification that includes an assessment by an FDA-accredited third-party reviewer that the company is in compliance with good manufacturing practice requirements.

Section 5066. General and Specific Uses

This section would require FDA to accept the manufacturer's stated indication for use in a 510(k) submission if that indication is the same as for the predicate device. Furthermore, the section would prohibit FDA from requiring information or data for an indication that is different from the proposed indication.

Section 5067. Humanitarian Device Exemption Application to In Vitro Diagnostics

This section would expand the availability of a humanitarian device exemption (HDE) by raising the 4,000 patient limitation in certain circumstances. Section 520(m) of the FDCA currently provides an exemption from the effectiveness requirements of a premarket approval application for a device that is intended to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in the U.S. per year. Section 5067 would amend section 520(m) to expand this exemption to include certain devices intended to treat or diagnose diseases that affect more than 4,000 patients in the U.S. per year if the applicant demonstrates, in addition to the existing requirements, that the public health requires a greater availability of the device, and that there is no satisfactory alternative.

The section also prohibits an HDE approval order from limiting the number of devices under the HDE if the devices are determined by FDA to be "medically necessary to treat, diagnose, or monitor individuals" with the diseases or conditions described in section 520(m) of the FDCA. The Draft Act would also require FDA to issue guidance defining the criteria for establishing "probable benefit" of a device, which is a key requirement for a sponsor to obtain HDE approval.

Section 5068. Advisory Committee Process

This provision would amend section 513(b) of the FDCA to stipulate new procedures for medical device classification panels. In particular, FDA would be required to: (1) convene these panels no later than 60 days after matters to be considered are "ready for panel review"; (2) provide the person whose device is subject to review any material on the matters to be considered no later than 30 days before the meeting; and (3) furnish these materials to the public no later than 14 days before the meeting.

Additionally, FDA would have to consult with the device sponsor about the "expertise" needed on the panel; this expertise shall include: (1) the disease or condition area the device is intended to cure, treat, mitigate, prevent, or diagnosis, and (2) the technology of the device.

The amendments to section 513(b) would also require FDA to provide at the panel meeting adequate time for the sponsor to make an initial presentation and to respond to FDA's

presentation, and to address the panel to answer any questions related to the review questions that were provided by FDA and agreed upon by FDA and the sponsor.

Sections 5081 – 5088. Supply Chain Security for Devices

Sections 5081 through 5088, entitled the "Device Distribution Licensing Act of 2015" (DDLA), would amend the FDCA to include provisions that parallel portions of the Drug Supply Chain Security Act, which was enacted in November 2013. The DDLA would require manufacturers, wholesale distributors, third-party logistics providers, and dispensers of prescription devices to trade only with "authorized trading partners" by January 1, 2016. "Authorized" is defined as referring to having a valid registration pursuant to section 510 of the FDCA (in the case of manufacturers) or a valid license under state law (in the case of wholesale distributors, third-party logistics providers, and dispensers). The DDLA would also establish national licensing standards for wholesale distributors and third-party logistics providers through which these trading partners could also qualify as "authorized." The DDLA, if enacted, would preempt any state or local standards, requirements, or regulations that are inconsistent with these national licensing standards. As shown by the implementation of the DSCSA over the past year, these provisions can present interpretive and logistical challenges for industry due to open issues that require guidance from FDA.

Conclusion

The provisions of the Draft Act could be far-reaching, and interested parties are encouraged to provide feedback to the E&C Committee. We will continue to monitor these legislative proposals.

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