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21st Century Cures Act: Key Provisions Related to Drugs

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Food & Drug

The House of Representatives recently passed the 21st Century Cures Act ("the Act" or "H.R. 6") 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 and biological products, as well as 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 things:

1. removing barriers to increased research collaboration;
2. incorporating the patient perspective into the drug development and regulatory review process;
3. measuring success and identifying diseases earlier through personalized medicine;
4. modernizing clinical trials;
5. providing new incentives for the development of drugs for rare diseases;
6. helping the entire biomedical ecosystem coordinate more efficiently to find faster cures; and
7. investing in 21st century science and next generation investigators.

We previously summarized the medical device provisions of the Act (see here). This alert summarizes the key provisions of H.R. 6 relating to drugs, presenting these provisions in the order of the titles in the Act. These provisions affect both the National Institutes of Health ("NIH") and the U.S. Food and Drug Administration ("FDA"), and they amend both the Federal Food, Drug, and Cosmetic Act ("FDCA") and the Public Health Service Act ("PHSA").

Title I - Discovery

Section 1121. Clinical Trial Data System

This section requires the Secretary of Health and Human Services ("the Secretary") to execute a seven-year cooperative agreement with one or more "eligible entities" to implement a pilot program for sharing of data from "qualified clinical trials" with registered users who will conduct further research on that data. "Qualified clinical trial" includes a clinical trial sponsored solely by an agency of the Department of Health and Human Services that involves: (1) an approved or cleared drug or biological product; (2) an investigational drug or biological product; or

(3) investigational product for which original investigations were discontinued, so long as the sponsor plans no additional development work and consents to inclusion of the data in the Clinical Trial Data System.

"Eligible entities" may be institutions of higher education or 501(c)(3) organizations. To be deemed eligible, an entity must submit an application that establishes, among other things, its proven track record of being "a neutral third party" in working with medical product manufacturers, academic institutions, and FDA, and of having the ability to protect confidential data. Furthermore, an applying entity must certify that it is not currently sponsoring, operating, or participating in another clinical trial or collaborating with another entity for these purposes, nor does it plan to do so.

The entity also must certify that it will allow only registered users to access and use data from qualified clinical trials. "Registered user" is defined as a scientific or medical researcher who has a legitimate biomedical research purpose for accessing the data, has appropriate qualifications to conduct the research, and agrees not to: (1) transfer the data to individuals who are not registered users; (2) use the data for reasons not specified in the research proposal; or (3) seek to re-identify study subjects.

At the end of the seven years, the Secretary may extend, expand, or terminate the pilot program.

Title II - Development

Section 2001. Development and Use of Patient Experience Data to Enhance Structured Risk-Benefit Assessment Framework

This section moves, from section 505(d) of the FDCA to new section 505(x) of the FDCA, language requiring FDA to implement a structured risk-benefit assessment framework in the new drug approval process. It also adds section 505(y) of the FDCA, which requires FDA to establish and implement processes for development and use of "patient experience data" to enhance the structured risk-benefit assessment framework, among other things. "Patient experience data" means data collected by patients, parents, caregivers, patient advocacy organizations, disease research foundations, medical researchers, research sponsors, and other "appropriate" parties that are intended to facilitate or enhance FDA's risk-benefit assessments, including information on the impact of a disease or therapy on patients' lives.

FDA also must publish guidance on implementation of section 505(y). The guidance must specify the timelines for FDA's review of submissions related to patient experience data and how FDA will use this information in developing or updating guidance. It also must address topics that include methodological considerations for collecting patient experience data and methodologies, standards, and study design for patient reported outcomes. FDA must issue the draft guidance within 3 years of enactment and final guidance within one year of the close of the period for comment on the draft guidance.

In addition, FDA must convene a series of public workshops with various stakeholders to inform FDA's development of the guidance and obtain input on the draft guidance.

Section 2021. Drug Development Tools

This section adds section 507 to the FDCA, which requires FDA to establish a process for the qualification of "drug development tools." The bill defines "drug development tool" to include a biomarker, a clinical outcome assessment (*i.e.*, a measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions), and "any other method, material, or measure" that FDA determines aids drug development and regulatory review.

Section 2021 requires FDA to establish a process for the qualification of drug development tools. The "requestor" seeking qualification of a drug development tool must initiate this process by submitting a letter of intent to the agency. If FDA accepts the letter of intent, the requestor may then submit a "qualification plan" that, if accepted by the agency, may be followed by a "full qualification package." If the full qualification package is accepted, FDA then reviews and determines whether to qualify the drug development tool for its proposed context of use. In determining whether to accept each type of qualification submission, FDA must consider the scientific merit of the submission and FDA's "available resources." A qualification package may be given priority on the basis of certain factors, including the severity, rarity, or prevalence of the disease or condition targeted by the drug development tool; the availability or lack of alternative treatments for the disease or condition; and the identification of the drug development tool and its proposed context of use as a public health priority. Section 2021 also authorizes FDA to consult with external experts for purposes of reviewing qualification submissions and consider the recommendations of these experts when reviewing qualification plans and packages.

If qualified by FDA, a drug development tool could then be used by any person for its proposed "context of use," which is defined as "the circumstances under which the drug development tool is to be used in drug development and regulatory review." Specifically, any person may use a drug development tool to support or obtain approval or licensure of a drug or biological product or to support the investigational use of a drug or biological product. Nothing in section 507 may be construed as authorizing FDA to disclose trade secret or confidential commercial information in a new drug application or biologics license application, however. FDA may rescind or modify a determination to qualify a drug development tool, based on new information or otherwise, if the agency determines that the drug development tool "is not appropriate for the proposed context of use specified by the requestor."

FDA must make publicly available on its website, among other things, the current status of each qualification submission; the submissions themselves (including data and evidence submitted); and a list of all drug development tools that have been qualified. Furthermore, FDA also must establish a taxonomy for the classification of biomarkers and make this taxonomy publicly available. Finally, to implement section 507, FDA must issue guidance that specifies standards and scientific approaches for development of biomarkers and outlines procedures and timelines for the qualification process.

Section 2022. Accelerated Approval Development Plan

This section amends section 506 of the FDCA to add section 506(g). Section 506(g) allows sponsors of drugs eligible for accelerated approval to request, after the submission of an investigational new drug application (IND), that FDA agree to an "accelerated approval development plan." An accelerated approval development plan includes agreement on the surrogate endpoint to be assessed, the design of the study that will utilize the surrogate endpoint, and the magnitude of the drug's effect on the surrogate endpoint that would be

sufficient to form the primary basis for a claim that the drug is effective. FDA may require a sponsor to modify or terminate an accelerated approval development plan if new information indicates that the plan as originally agreed upon is no longer sufficient to demonstrate the safety and effectiveness of the drug or the drug is no longer eligible for accelerated approval.

Section 2041. Precision Medicine

This section would add sections 591 and 592 to the FDCA. Section 591 requires FDA to issue guidance defining the term "precision drug or biological product" and to address issues related to development of precision medicines, including the evidence needed to support the use of biomarkers that identify subsets of patients as likely responders to therapies, recommendations for the design of studies to demonstrate the validity of a biomarker as a predictor of drug response, and the manner and extent to which a benefit-risk assessment may be affected when clinical trials are limited to patient subsets that are identified using biomarkers. The guidance also must address development of companion diagnostics in the context of a drug development program and when biomarker information may appear in drug labeling.

Furthermore, in the case of precision drugs that are intended for treatment of a serious or life threatening condition and designated as orphan drugs, section 592 provides that FDA may rely upon data previously submitted by the same sponsor or another sponsor (provided that the sponsor seeking to use the data has obtained a contractual right of reference) for the approval of a different drug or indication. This reliance would expedite clinical development of a precision drug that uses the same or similar approach as that used to support the prior approval. FDA must consider these drugs for accelerated approval. Nothing in section 592 may be construed to confer any new rights for sponsors to reference another approved application.

Section 2061. Broader Application of Bayesian Statistics and Adaptive Trial Designs

Section 2061 requires FDA to update and finalize the agency's 2010 draft guidance on adaptive trial design for drugs and biologics and issue a new draft guidance on the use of Bayesian methods in the development and regulatory review of drugs and biologics. These guidances must address use of these designs and methods in clinical trials, recommended analysis methodologies, and mechanisms for sponsors to obtain feedback from FDA on technical issues related to modeling or simulations. Prior to developing or finalizing the guidances, FDA must hold a public meeting to obtain input from stakeholders.

Section 2062. Utilizing Evidence from Clinical Experience

Under new section 505F of the FDCA, FDA must develop a program to evaluate the potential use of "evidence from clinical experience" for supporting the approval of a new indication for an approved drug or satisfying postapproval study requirements. Evidence from clinical experience means data regarding the usage or the potential benefits and risks of a drug derived from sources other than randomized clinical trials (*e.g.*, observational studies, registries, and therapeutic use).

This program must be implemented no later than two years after enactment based on a draft framework established within eighteen months after enactment and consultation with interested parties. Furthermore, within three years of enactment, FDA must issue draft guidance regarding the circumstances under which drug sponsors may rely on evidence of clinical experiences for the purposes of obtaining approval of a new indication or satisfying postapproval study requirements. This guidance, which must also discuss the appropriate standards and

methodologies for the collection and analysis of this evidence, must be finalized no later than four years after enactment.

Section 2063. Streamlined Data Review Program

Section 2063 adds a new section 505H to the FDCA, which requires FDA to establish a "streamlined data review program" under which an NDA or BLA holder may submit "qualified data summaries" to support a new "qualified indication" for an approved drug or biologic.

A qualified data summary is a summary of clinical data intended to demonstrate the safety and effectiveness of the qualified indication. Qualified indications are indications for the treatment of cancer, as determined appropriate by FDA, and any other types of indications qualified by FDA.

Even where a supplemental application may contain a qualified data summary, the full data sets used to develop the qualified data summary must also be submitted unless FDA waives this requirement. There must also be an existing database acceptable to FDA regarding the safety of the drug for one or more of its approved indications. FDA must issue final guidance for the implementation of the streamlined data review program no later than two years after enactment. This guidance must, in part, discuss the process for expanding the types of indications considered "qualified indications."

FDA must post on its website several statistics relating to the use of the streamlined data review program.

Section 2081. Sense of Congress Regarding Approval of Breakthrough Therapies

This section states that it is the sense of Congress that FDA should continue to expedite the approval of drugs designated as breakthrough therapies under section 506(a) of the FDCA, by approving these drugs as early as possible in the clinical development process, regardless of the development phase, provided that FDA determines the application meets the statutory safety and effectiveness standards.

Section 2082. Expanded Access Policies

Section 2082 adds a new section 561A to the FDCA, which requires manufacturers and distributors of investigational drugs for the diagnosis, monitoring, or treatment of serious diseases or conditions to make publicly available their policies on evaluating and responding to requests for expanded access under section 561(b) of the FDCA. This requirement may be satisfied by posting a policy applicable to all of the company's investigational drugs. The policy must include contact information, procedures for making these requests, the general criteria considered or used in approving these requests, and the length of time expected to be necessary to acknowledge the receipt of the requests. The policy must be posted on the later of the date that is sixty days after enactment or the first initiation of a phase two or phase three study with respect to the investigational drug. Manufacturers and distributors may revise their policies at any time. The section also clarifies that the posting of a policy will not serve as a guarantee of access to any specific drug by any individual patient.

Section 2083. Finalizing Draft Guidance on Expanded Access

This section requires FDA to finalize its 2013 draft guidance on expanded access Q&A's within twelve months after enactment. The final guidance must define how FDA interprets and uses adverse drug event data reported by investigators from expanded access use.

Section 2101. Facilitating Dissemination of Health Care Economic Information

This section amends Section 502(a) of the FDCA on drug manufacturer's dissemination of health care economic information. Under the revised provision, the audience for this information is "a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement." (The current provision refers to "a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations.") Under amended section 502(a), health care economic information is not considered false or misleading if it "relates" (rather than "directly relates" as in the current law) to an approved indication for a drug or biological product, among other things. Also, if the health care economic information materially differs from the approved labeling, a "conspicuous and prominent statement" describing the differences must be included.

The definition of "health care economic information" is broadened to mean "any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcome, of the use of a drug. Such analysis may be comparative to the use of another drug, to another health care intervention, or to no intervention." Any analysis "that relates only to" an unapproved indication is not considered health care economic information, however.

Section 2102. Facilitating Responsible Communication of Scientific and Medical Developments

This section requires FDA to issue draft guidance within eighteen months of enactment regarding the responsible dissemination of truthful and nonmisleading scientific and medical information not included in approved labeling of drugs and devices.

Section 2121. Approval of Certain Drugs for Use in a Limited Population of Patients

This section adds new subsection (z) to section 505 of the FDCA. Under this subsection, a sponsor of an antibacterial or antifungal drug that is intended to treat a serious or life-threatening infection may voluntarily enter into a written agreement with FDA regarding the process for developing data to support an application for approval of the drug for use in "a limited population of patients." Section 2121 also amends the Public Health Service Act ("PHSA") to provide that section 505(z) applies to biologics for serious or life-threatening bacterial or fungal infections.

If a written agreement is executed, FDA may approve the drug for use in a limited population of patients for which there is unmet medical need based on a streamlined development program, but the applicable approval standards under section 505 of the FDCA and section 351 of the PHSA must be satisfied. In approving such a drug, FDA may rely on traditional and alternate endpoints; a combination thereof; data sets of a limited size, "as appropriate"; other data, such as preclinical, pharmacologic, or pathophysiologic evidence; nonclinical susceptibility and pharmacokinetic data; data from phase 2 clinical trials; and such other confirmatory evidence FDA deems appropriate. Furthermore, the sponsor may request meetings with FDA to develop a written agreement and to obtain feedback that would help the sponsor design and conduct a drug development program "as efficiently as possible."

The labeling of an antibacterial or antifungal drug approved under section 505(z) must contain the statement "Limited Population" in a prominent manner adjacent to the product's brand name. Additionally, the prescribing information must include the statement "This drug is indicated for use in a limited and specific population of patients." Any promotional material for the antibacterial or antifungal also is subject to the pre-review requirements for accelerated approval drugs. Failure to follow any of these requirements would render the drug misbranded. If a drug is initially approved under section 505(z) but then later approved for the same indication "other than in accordance with [subsection (z)]," the drug will no longer be subject to these labeling requirements and postmarketing conditions. If instead FDA approves the drug for a different condition of use, the labeling requirement and postmarketing conditions under section 505(z) will not apply to the approval of the different condition of use.

The Act requires FDA to issue draft guidance describing the criteria, the process, and other general considerations for demonstrating the safety and effectiveness of antibacterial and antifungal drugs to be approved under section 505(z) within eighteen months of the bill's enactment. Within four years of enactment, FDA must publish an assessment of the pathway for public comment. If FDA determines that expansion of the limited-use pathway would be beneficial to the public health, the agency is authorized to expand the pathway in accordance with this determination.

Section 2141. Timely Review of Vaccines by the Advisory Committee on Immunization Practices

This section amends section 2102(a) of the PHSA to direct the Advisory Committee on Immunization Practices ("ACIP") to consider a vaccine's use at the next regularly scheduled ACIP meeting following the vaccine's licensure or the licensure of a new indication for the vaccine. If ACIP does not make a recommendation with respect to the vaccine's use at this meeting, then, at the vaccine sponsor's request, ACIP must make a recommendation on an expedited basis. Furthermore, if a licensed vaccine is designated as a breakthrough therapy under section 506 of the FDCA, ACIP must always make a recommendation on an expedited basis.

Section 2142. Review of Processes and Consistency of ACIP Recommendations

This section requires the Director of the Centers for Disease Control and Prevention ("CDC") to conduct a review of the processes used by ACIP to evaluate consistency in formulating and issuing recommendations pertaining to vaccines. The CDC's review must include an assessment of the criteria used to evaluate new and existing vaccines, the Grading of Recommendations, Assessment, Development, and Evaluation ("GRADE") approach to the review and analysis of scientific and economic data, and the extent to which the processes used by the working groups of ACIP are consistent among groups. The Director of the CDC must solicit input from vaccine stakeholders, and the Director's report to Congress on the results of the review and recommended improvements is due within eighteen months after enactment.

Section 2143. Meetings Between the CDC and Vaccine Developers

This section amends section 310 of the PHSA to establish procedures by which the CDC would provide advice and data to vaccine developers. Within 120 days of receipt of a vaccine developer's written request for a meeting (that includes a valid justification for the meeting), the CDC must convene a meeting of the vaccine developer and the CDC's experts in immunization programs, epidemiology, and other relevant areas, for the purpose of informing the vaccine

developer of public health needs and priorities. Furthermore, within 120 days of receipt of a vaccine developer's written request, the CDC must provide any requested age-based or other demographically assessed disease epidemiological analyses or data that have been published, have been performed by or are in the possession of the CDC, are not trade secret or confidential commercial information, and do not contain individually identifiable information.

Section 2151. Extension of Exclusivity Period for a Drug Approved for a New Indication for a Rare Disease or Condition

This section amends the FDCA to insert new section 505I. Section 505I provides a six-month extension of certain exclusivity periods for a drug designated by FDA as "a drug approved for a new indication to prevent, diagnose, or treat a rare disease or condition." To qualify for this 505I designation, the drug must have been previously approved but not for the new rare indication, and the application holder for the approved drug must file an application or supplement for approval of the new rare indication.

The six-month period extends (1) Hatch-Waxman exclusivities (including five-year new chemical entity exclusivity and three-year new clinical investigation exclusivity); (2) orphan drug exclusivity; and (3) reference product exclusivity for biologics. Also, the exclusivity extends the period during which FDA cannot approve an abbreviated new drug application (ANDA) or section 505(b)(2) application due to a listed patent. Any exclusivity extension granted under this section would be in addition to pediatric exclusivity and qualified infectious disease product exclusivity. However, the extension does not apply if the drug previously received an extension under section 505I.

Section 2152. Reauthorization of Rare Pediatric Disease Priority Review Voucher Incentive Program

Section 2152 amends the definition of "rare pediatric disease" to add that the disease must be "serious and life-threatening" with "serious and life-threatening manifestations" primarily affecting pediatric patients. The bill also provides that an application is not eligible for a rare pediatric disease priority review voucher if the drug or biological product has already received a tropical disease priority review voucher under section 524 of the FDCA.

This section also amends section 529 of the FDCA to authorize FDA to continue awarding rare pediatric disease priority review vouchers until December 31, 2018. The current text of section 529 terminates FDA's authority to award rare pediatric disease priority review vouchers one year after the agency grants its third such voucher, which the agency issued in March 2015. The bill also provides that the sponsor of a drug that is designated for a rare pediatric disease and is the subject of a rare pediatric disease product application submitted between enactment and December 31, 2018 remains eligible for a priority review voucher, regardless of when the rare pediatric disease product application is approved.

Section 2161. Grants for Studying the Process of Continuous Drug Manufacturing

This section authorizes FDA to award grants to higher education institutions and nonprofit organizations for the purpose of studying and recommending improvements to the process of continuous manufacturing of drugs and biologics and similar innovative monitoring and control techniques.

Section 2181. Enhancing Combination Products Review

Within eighteen months of enactment, FDA must issue final guidance describing the responsibilities of each agency center regarding its review of combination products. FDA also must periodically review and update the guidance after soliciting public comment.

Conclusion

The Senate is currently working on parallel legislation to the Act. If the Act is not enacted during this Congress, many aspects of the proposed legislation might be incorporated in the reauthorization of the Prescription Drug User Fee Act and associated legislation in 2017.

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

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug practice group:

Krista Carver	+1 202 662 5197	kcarver@cov.com
Richard Kingham	+1 202 662 5268	rkingham@cov.com
Michael Labson	+1 202 662 5220	mlabson@cov.com
Peter Safir	+1 202 662 5162	psafir@cov.com

Additional contributors to this alert included Grant Dixon, Christopher Hanson, Mingham Ji, Colleen Kelly, Christina Kuhn, and Grant Young.

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