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Much to Metabolize: The 21st Century Cures Act Introduces Numerous Changes to FDA's Drug Regulatory Framework to Spur Development of New Treatments

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With President Obama's signature, the 21st Century Cures Act (Cures Act) has become law, unleashing an expansive suite of measures designed to deliver new cures and treatments to patients. Among these measures are a wide-ranging set of changes to the U.S. Food and Drug Administration's regulation of drugs and biologics. Here, we highlight some key areas of the Cures Act that will affect pharmaceutical and biotechnology companies, including provisions related to clinical trials, use of real world evidence, patient-focused drug development, health care economic information, summary level review, combination products, expanded access, drugs for rare diseases, and regenerative therapies.

Modern Clinical Trial Design and Evidence Development

HHS/FDA guidance on novel clinical trial designs. Industry has sought the use of non-traditional study designs to provide reliable evidence of safety and effectiveness that FDA will accept in support of new drug approvals. Section 3021 of the Cures Act requires the Secretary of the Department of Health and Human Services (HHS) (who may act through FDA) to hold a public meeting regarding novel trial designs and to issue draft guidance on how sponsors should propose novel trial designs, how sponsors can satisfy the substantial evidence standard using novel trials, and how sponsors may obtain feedback from FDA regarding modeling or simulations. A particular type of novel trial design, referred to in the Cures Act as "complex adaptive" trial design, is already addressed in a 2010 draft FDA guidance.

Use of real world evidence (RWE) in drug application review. Earlier this year, FDA released a draft guidance regarding the use of real world data to support regulatory decision-making for medical devices. The PDUFA VI Commitment Letter also specified that the Agency would begin taking steps by no later than the end of FY 2018 to gather input regarding the use of RWE in regulatory decision-making for drugs and to publish draft guidance on this topic by no

later than the end of FY 2021. Section 3022 of the Cures Act reinforces these measures by requiring FDA to establish a draft framework to evaluate the potential use of RWE in the assessment of safety and efficacy for drugs, and to issue guidance within 5 years regarding acceptable uses of RWE to support drug applications.

Other Clinical Trials Provisions

Harmonization of FDA and HHS human subject protection regulations. Although HHS and FDA human subject protection regulations do not always both apply to a particular clinical study, Section 3023 of the Cures Act requires these regulations to be harmonized and updated (via changes to the HHS regulations, FDA regulations, or both) to the extent practicable and consistent with other statutory provisions. As a result, FDA regulations related to informed consent, institutional review board (IRB) review, and investigational new drugs could change. The goals of this provision are to reduce regulatory duplication and unnecessary delay, modernize and enhance human subject protections, and set forth a framework for regulatory review when both HHS and FDA regulations apply. FDA's website contains a comparison of the current FDA and HHS human subject protection regulations.

Exemption from informed consent regulations for clinical trials posing minimal risk. Section 3024 of the Cures Act amends Section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) and requires promulgation of certain new provisions in FDA's informed consent regulations to exempt clinical trials that pose no more than minimal risk to human subjects where appropriate safeguards protecting the rights, safety, and welfare of those subjects are in place. This exception would add to the exceptions from informed consent requirements that are already in FDA's regulations (e.g., where it is not feasible, or where it is contrary to the best interests of study subjects, to obtain consent).

Reports to Congress regarding required submissions to ClinicalTrials.gov. Section 2052 of the Cures Act requires the Secretary of HHS to report to Congress regarding its educational and enforcement activities related to the requirements to submit information on applicable drug clinical trials to ClinicalTrials.gov. This reporting requirement may lead to closer scrutiny of, and increased enforcement related to, required submissions to ClinicalTrials.gov.

Analysis of different effects in women and minority populations in clinical trials. Currently, the National Institutes of Health (NIH) must ensure—where women or minorities are study subjects in certain clinical trials—that the clinical trial is designed and performed in a manner to allow valid analysis of the different effect of the investigational product in those female and minority subjects. Section 2053 of the Cures Act adds the requirement that the entity conducting such a clinical trial must submit to ClinicalTrials.gov the results of its analysis of the different effects in women or minorities. NIH will consider an entity's compliance with this requirement when deciding on future grant requests, and NIH may establish additional incentives to encourage these analyses.

Patient-Focused Drug Development

Section 3001 requires FDA to publicly issue a brief statement of patient experience data and related information submitted and reviewed in conjunction with each drug application approved by the Agency, starting 180 days after enactment of the Cures Act. Over 5 years, FDA also must issue guidance regarding collection of patient experience data and use of such data and related information in drug development. Section 3002 specifies that among other things, the guidance must address methodologies for collecting patient experience data for submission to, and proposed use by, FDA in regulatory decision-making; how FDA intends to respond to submissions of such patient data; and how FDA, as appropriate, anticipates using patient experience data and related information to inform regulatory decision-making.

Qualification of Drug Development Tools

Although FDA's Center for Drug Evaluation and Research (CDER) has already established some drug development tool (DDT) qualification procedures under a 2014 guidance document, there are currently only three types of DDTs covered at this time. Section 3011 of the Cures Act requires FDA to publish guidance for a framework for qualification of DDTs, including a multi-step process of submitting a letter of intent, qualification plan, and full qualification package. FDA must determine whether to accept or reject each of these submissions based on a number of factors, which may include scientific merit; and FDA has authority to rescind or modify any qualification determination after such determination is made.

FDA must also publish on its website information regarding each qualification submission, including any data and evidence contained therein and FDA's decision on each submission. As a result, this qualification submission information may be accessed and used by others, and qualification of a DDT by one entity for a specific use allows other entities to use the DDT for that same use. Notably, this section specifies that public disclosure of information in a qualification submission is a permissible disclosure under the Trade Secrets Act; however, it underscores that nothing in this section authorizes FDA to disclose any confidential commercial or trade secret information contained in applications submitted under Section 505 of the FDCA or Section 351 of the Public Health Service Act.

Health Care Economic Information

Section 3037 of the Cures Act broadens the parameters of health care economic information (HCEI) that manufacturers may use to promote their products to formulary committees, payors, and similar entities. This provision expands the permitted audiences for HCEI to include payors (in addition to formulary committees and other similar entities previously listed in Section 502(a) of the FDCA) but clarifies that these entities must be "carrying out [ ] responsibilities for the selection of drugs for coverage or reimbursement." Section 3037 also specifies that HCEI may be "related" to an approved indication of a drug; previously, the statute required HCEI to be *directly* related to an approved indication. In addition, the definition of HCEI has been amended to include not only the HCEI analysis itself, but also the "clinical data, inputs, clinical or other assumptions, methods, results, and other components" of the analysis. Finally, Section

3037 retains the "competent and reliable scientific evidence" standard to substantiate HCEI claims, but also requires that where applicable, HCEI must be accompanied by a "conspicuous and prominent statement describing any material differences" from approved labeling.

Summary Level Review

Section 3031 of the Cures Act amends Section 505 of the FDCA and Section 351 of the PHSA to allow the Agency to rely on a "qualified data summary" to approve a supplemental application for a "qualified indication" of a drug or biological product. Section 3031 specifies that summary level review shall be available only if there is acceptable data demonstrating the safety of the drug and if all data used to develop the qualified data summary are submitted with the application. The term "qualified indication" is defined as an indication that the Agency determines to be appropriate for summary level review; and the term "qualified data summary" is defined as "a summary of clinical data that demonstrates the safety and effectiveness of a drug with respect to a qualified indication." These definitions leave the Agency significant discretion to determine the circumstances under which summary level review may be appropriate. Section 3031 of the Cures Act also directs FDA to post annual reports on its website disclosing the number of supplemental applications reviewed solely via summary level review, the average review times for supplemental applications where the Agency utilized summary level review and for those where it did not, and the number of supplemental applications reviewed under summary level review where the Agency used full data sets as well as the qualified data summaries.

Combination Products

Section 3038 of the Cures Act modifies and clarifies FDA's regulation of combination products. First, this provision addresses the concern that FDA too often regulates combination products as drugs by stating that FDA may no longer determine that a product has a drug primary mode of action so long as it has any sort of chemical action in the human body. At the same time, FDA retains authority to determine the primary mode of action of a combination product as a drug or device. Second, this provision creates a combination product determination and dispute resolution process that allows sponsors to propose studies to establish the relevance of chemical action in achieving the primary mode of action for a combination product. Third, Section 3038 implements provisions addressing applications for combination products for which a constituent part (whether drug or device) has already been approved or cleared by FDA.

FDA is required to issue a final guidance on combination products that describes the structured process for managing pre-submission interactions, best practices for the Agency in such interactions, and information that sponsors should submit with a combination product meeting request. FDA also must publicly identify types of combination products and manufacturing processes for which good manufacturing practices may be different than those required by existing regulations.

Expanded Access

Although pharmaceutical companies are not required to grant expanded access or compassionate use requests for their investigational drugs, Section 3032 of the Cures Act requires manufacturers or distributors of investigational drugs to make their expanded access policies publicly accessible (e.g., posted on the company's website). These policies must include contact information, request procedures, general criteria for evaluation of and responses to requests, the estimated length of time to acknowledge receipt of requests, and a link or other reference to the information on ClinicalTrials.gov for each of the drug's clinical trials. Importantly, companies must make their expanded access policies publicly accessible within 60 calendar days after enactment of the Cures Act, or upon the first initiation of a phase II or phase III study for an investigational drug. This provision allows a company to establish one overarching policy for all of its investigational drugs and to freely revise its policy at any time.

Drugs for Rare Diseases

Reliance on data and information from previously approved products for certain genetically- or protein-targeted drugs. Section 3012 clarifies FDA's authority to facilitate the development, review, and approval of genetically targeted drugs and variant protein targeted drugs to address unmet medical needs in one or more patient subgroups for rare diseases or conditions that are serious or life-threatening. For a genetically targeted drug or a variant protein targeted drug that uses the same or similar targeting technology as a previously approved drug, the sponsor may rely on data and information from the previously approved application—whether its own, or that of another sponsor if the sponsor has provided a right of reference. This provision will allow sponsors of therapies that treat different mutations in the same gene or protein, as well as sponsors employing a platform technology that targets different disease-causing genes, to incorporate relevant data and information from related approved products into subsequent applications, diminishing the need to generate duplicative information and allowing reliance on a safety database drawn from various applications.

Orphan drug grants for additional types of studies. Section 3015 of the Cures Act expands the types of grants and contracts FDA can make for development of drugs for rare diseases and conditions. Previously, FDA was authorized to make orphan grants and contracts for human clinical and preclinical testing. Section 3015 expands this list to include prospectively planned and designed observational studies and other analyses conducted to assist in understanding the natural history, developing a therapy, developing or validating a DDT, or understanding the full spectrum of disease manifestations for a rare disease or condition.

Reauthorization of rare pediatric disease priority review vouchers. Section 3013 reauthorizes for four more years the priority review voucher program for rare pediatric disease product applications, and Section 3014 requires the U.S. Comptroller General to study the effectiveness and overall impact of the neglected tropical disease, rare pediatric disease, and medical countermeasure priority review voucher programs. Congress has expressed interest in the incentive aspect of the programs, potential effects of the sunset provisions on priority review voucher programs, and assessment of potential changes to the incentives.

Regenerative Medicine Therapies and Regenerative Advanced Therapies

Accelerated approval for regenerative advanced therapies. Section 3033 of the Cures Act defines "regenerative medicine therapy" to include cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and 21 CFR 1271. A "regenerative advanced therapy" is defined as a regenerative medicine product intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, for which preliminary clinical evidence indicates the proposed product has the potential to address unmet medical needs for such disease or condition. Section 3033 establishes a designation process and amends Section 506 of the FDCA to make regenerative advanced therapies eligible for breakthrough therapy designation, priority review, and accelerated approval.

Guidance for medical devices in regenerative therapies. Section 3034 requires the Agency to issue draft guidance within 1 year for medical devices used in the recovery, isolation, or delivery of regenerative advanced therapies. The guidance should specify, among other things, attributes that would warrant classification of a device as Class III vs. Class II, and how to demonstrate that a device may be used with more than one cell type.

Regenerative medicine therapy standards. Section 3036 requires that within 2 years, FDA must initiate and lead a stakeholder engagement process, together with the National Institutes for Standards and Technology and other stakeholders (including regenerative medicine manufacturers, clinicians, and industry organizations), to develop standards for regenerative medicine.

Report on regenerative advanced therapies. Section 3035 requires FDA to provide an annual report to Congress on the number and type of regenerative advanced therapy applications filed, approved, licensed, withdrawn, or denied; and on the number of applications granted accelerated approval or priority review. This provision makes FDA accountable to Congress for its actions to accelerate development and approval of regenerative medicine products.

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Although not exhaustive, this alert provides an overview of the extent and variety of the Cures Act's key FDA regulatory provisions for drugs and biological products. In addition to these provisions, the Cures Act includes many measures that have implications for the pharmaceutical and biotechnology industry, such as the Precision Medicine Initiative, funding for the Cancer Moonshot and BRAIN Initiatives, measures to establish a national pediatric research network and global pediatric clinical study network, provisions related to antimicrobial products, and various delivery and payment reforms. We are continuing to analyze and examine the full impact of these provisions. If you have any questions about the 21st Century Cures Act and how it may affect your business or organization, please contact one of the authors of this alert or the Hogan Lovells attorney with whom you regularly work.

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