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CLIENT ALERT

Trump, Gottlieb, and the Cures Act: What Pharmaceutical Manufacturers Need to Know

By Kim Tyrrell-Knott, Bradley S. Davidsen, and Elena M. Quattrone

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I. Executive Summary

The 21st Century Cures Act ("Cures Act"),[1] signed into law by former President Obama on December 13, 2016, sets out a bold agenda for the Food and Drug Administration ("FDA"). Among other things, the Cures Act strives to streamline the drug development and approval process and create a more patient-focused regulatory framework—two things on which the Obama administration, the Trump administration, and President Trump's nominee for FDA Commissioner, Dr. Scott Gottlieb, all seem to agree. However, several of these changes still require additional regulation, guidance, and other regulatory action in order to be implemented by FDA.

We discuss below some of the key provisions of the Cures Act for pharmaceutical manufacturers and the impact that the Trump administration and an FDA led by Dr. Gottlieb would have on the implementation of the Cures Act.

II. Key Provisions of the Cures Act for Pharmaceutical Manufacturers

a. Clinical Trial Design

The average cost of developing a drug that is granted marketing approval is more than $2.5 billion, and the drug approval process takes, on average, over a decade.[2] Much of this money and time is spent during clinical development. One way that sponsors of clinical trials have advocated to reduce the cost and time is by avoiding the traditional lock-step progression of clinical trials from Phase I to III through creative clinical trial designs. The Cures Act encourages the use of novel clinical trial designs and new sources of data in the drug approval process and also requires FDA to investigate how patient experience data can be utilized in the drug development and approval process:

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[1] H.R. 34, 114th Cong. (2016) (enacted).

[2] *See* Pharmaceutical Research and Manufacturers of America, "2016 Profile Biopharmaceutical Research Industry" (April 2016), *available at* http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-profile.pdf.

- *Novel Trial Designs*. Section 3021 requires FDA to hold a public meeting to discuss the use of complex adaptive and other novel trial designs in the development, regulatory review, and approval of drugs and biological products. FDA also must publish draft guidance within 18 months of the meeting and finalize the guidance document within a year of the comment period closing. The guidance must address the following: the use of complex adaptive and other novel trial designs, including how such clinical trials proposed or submitted help to satisfy the substantial evidence standard to market new drugs; how to obtain modeling and simulation feedback from FDA; the types of quantitative and qualitative information that should be submitted for review; and any recommended analysis methodologies.

- *Real World Evidence*. Section 3022 calls for the evaluation of the use of real world evidence ("RWE") in support of applications for new indications and to satisfy post-approval study requirements. "Real world evidence" is defined as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials." The Cures Act requires FDA to create a draft framework for the use of RWE within two years that addresses the following: acceptable sources of RWE, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities; gaps in data collection activities; and standards and methodologies for the collection and analysis of RWE. The framework will also describe any other priority areas, remaining challenges, and potential pilot opportunities that the program will address. Additionally, within five years, FDA must publish draft guidance on when RWE may be used and how to collect and analyze such evidence when included within a submission.

- *Patient Experience Data*. Similar to RWE, Section 3002 requires FDA to publish within 18 months and finalize within five years draft guidance documents on the collection and use of patient experience data in drug development and regulatory decision-making. Section 3001 also requires the Secretary of Health and Human Services to publish a statement regarding any patient experience data that was reviewed as part of a drug approval. "Patient experience data" is defined as data that "are collected by any persons" and "intended to provide information about patients' experiences with diseases or conditions, including the impact of such disease or condition, or a related therapy on patients' lives, and patient preferences with respect to the treatment of certain diseases or conditions." Currently, this type of data does not carry tremendous value when included in an FDA submission. The implementation of these new initiatives may lead to a more patient-centric drug development and approval process.

These and other changes mandated by the Cures Act are likely to result in a regulatory framework for pharmaceutical manufacturers that both provides greater flexibility in how manufacturers create and submit data to support marketing applications and takes into account patient outcomes and preferences.

b. Pathways to Market

The Cures Act created or amended four pathways to market or programs for drugs that treat serious or life-threatening diseases that affect a smaller subset of the population or diseases that have significant public health risks:

- *Targeted Drugs for Rare Diseases.* Section 3012 facilitates the development and approval of "genetically targeted drugs and variant protein targeted drugs to address an unmet medical need" for diseases that are "serious or life-threatening," and enables the use of "scientific tools, or methods, including surrogate endpoints and other biomarkers." For drugs intended to treat serious or life-threatening diseases, this section explicitly promotes the use of previous data from other submissions by the same sponsor (or another sponsor if contractually permitted) related to "a drug that incorporates or utilizes the same or similar genetically targeted technology" or "for a variant protein targeted drug that is the same or incorporates or utilizes the same variant protein targeted drug" that was previously approved.

- *Antimicrobial Resistant Drugs for Limited Populations.* Section 3042 creates a program for the approval of certain antibacterial or antifungal drugs engineered to treat limited populations affected by "superbugs." The program allows an applicable drug to "be approved … notwithstanding a lack of evidence to fully establish a favorable benefit-risk profile in a population that is broader than the intended limited population." The drug would undergo a "benefit-risk consideration" in which the safety and the efficacy of the drug are assessed for the limited population in a manner that takes "into account the severity, rarity, or prevalence of the infection the drug is intended to treat and the availability or lack of alternative treatment in such limited population." Any drug approved under the program must adhere to special labeling requirements stating the drug's intended use for limited populations. The Cures Act specifically states that these limitations should not be construed as affecting a physician's prescribing authority or the practice of health care.

- *Orphan Drugs.* Funding available under the Orphan Drug Act was previously limited to support for clinical trials. The Cures Act, in Section 3015, expands the types of trials and activities that fall under the Orphan Drug Act's funding provisions by including observational studies and other analyses to enhance the understanding of rare diseases, and the development of drugs that target these diseases. These changes will likely incentivize additional research into novel therapies to benefit individuals suffering from rare diseases.

- *Voucher Program Review.* Section 3013 reauthorizes FDA's voucher program for rare pediatric diseases until September 30, 2020. Additionally, Section 3014 requires the Government Accountability Office ("GAO") to review the impact of FDA voucher programs by studying the drugs that have been approved to receive vouchers, the drugs that have utilized vouchers, and the prices that companies have paid for the transfer of a voucher, among other things. This provision appears to be in response to criticisms of voucher programs that have awarded

extended exclusivity for highly profitable drugs or that have allowed voucher awardees to sell vouchers for hundreds of millions of dollars.[3]

c. Expanded Access Programs

Current FDA regulations allow pharmaceutical companies to provide access to investigational medical products outside of a clinical trial for patients who have a serious or chronic disease or condition. While these programs are not required, many pharmaceutical companies have utilized expanded access programs in response to patient requests when patients do not meet inclusion/exclusion criteria for a clinical trial. Section 3032 of the Cures Act requires manufacturers of investigational drugs to make their expanded access program policies publicly available to patients, including providing information on how a manufacturer evaluates and responds to requests for investigational drugs under its expanded access program. Although manufacturers are not required to provide investigational drugs, increasing the transparency of the manufacturers' expanded access programs will help improve patients' ability to access novel therapies.

III. The Impact That the Trump Administration and an FDA Led by Dr. Gottlieb Would Have on the Cures Act's Implementation

a. Dr. Gottlieb's Views on the Drug Approval Process

Although Dr. Gottlieb is not yet the current FDA Commissioner, his confirmation appears imminent based on his confirmation hearings. By all accounts, Dr. Gottlieb appears to embrace flexible systemic approaches to shorten review timelines and bring more products to market, especially for rare diseases affecting small populations. In 2012, Dr. Gottlieb authored an oft-cited opinion article in *National Affairs* in which he criticized the culture of FDA, particularly in regard to the agency's approval process for certain enzyme-replacement therapies in the 1990s.[4] He mainly criticized the fact that FDA did not apply its prior experience approving and regulating enzyme-replacement drugs when new enzyme-replacement drugs were submitted for review. Dr. Gottlieb also criticized what he described as unnecessary requests by FDA for additional data and to add more patients to studies conducted for approval of enzyme-replacement drugs where the population of individuals who could be treated with the drug, if approved, was very small.[5] These criticisms echo the Cures Act's approaches in creating and amending pathways to market for antimicrobial drug approvals for limited populations and other programs for the treatment of diseases affecting small populations. Dr. Gottlieb's criticisms also suggest that he may have a favorable view of submitting RWE data from alternative sources, like data from previous trials of similar drugs, to support the submission for approval of a new drug.

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[3] *See, e.g.,* "Congress tries to fix a drug voucher program, but critics say it's not enough," STAT (June 9, 2016), *available at* https://www.statnews.com/pharmalot/2016/06/09/congress-vouchers-rare-diseases/.

[4] Scott Gottlieb, *Changing the FDA's Culture*, NATIONAL AFFAIRS (Summer 2012), https://www.nationalaffairs.com/publications/detail/changing-the-fdas-culture.

[5] *Id.*

With a focus on bringing greater patient access to drugs, Dr. Gottlieb will likely embrace Cures Act initiatives, such as the use of novel clinical trial designs and alternative sources of data, which are meant to reduce drug approval timelines and provide additional data for FDA review. In a recent article in *Forbes,* Dr. Gottlieb criticized FDA as insisting on "trying to force [complex drugs] down its traditional, misapplied, and dead-end approval routes" because the agency "lacks the scientific and regulatory framework to efficiently approve [generic versions of] complex drugs under its existing rules."[6] While this article focused on the development of generic versions of branded drugs, it demonstrates a willingness and desire to seek flexibility in clinical trial designs. He also has long advocated a better approach to implementing the Hatch-Waxman Act, which allows generic versions of drugs to become approved by showing equivalence rather than by providing all the information that branded drugs are required to provide within an application.[7]

Historically, Dr. Gottlieb has shown support for expanded access programs, touting their value at speeches given while he was a deputy commissioner at FDA.[8] During his confirmation hearing, Dr. Gottlieb stated that he was "uniquely positioned … because of [his] background" to address the purported abuse of the Orphan Drug Act through systemic changes that would likely involve further acts by Congress. This aligns with the Cures Act's requirement of a GAO study addressing the voucher program based on criticisms that some manufacturers take advantage of the program.

b. Hurdles to Implementing the Cures Act

The biggest hurdle that Dr. Gottlieb may face in implementing the Cures Act is the Trump administration's "two for one" executive order ("EO").[9] This EO requires any "significant regulatory action" that an agency wants to implement—including, in some instances, guidance documents—to be counterbalanced by the removal of two other regulations. As the majority of the Cures Act's provisions call for guidance documents to be proposed, the EO could present a significant challenge to the effective implementation of critical pieces of the Cures Act. There are three ways FDA may circumvent this restriction in connection with the Cures Act. First, any regulations promulgated or guidance issued under the Cures Act would be exempt from the "two for one" requirement under Section 2(b) of the EO to the extent that they are "required by law."[10] Second, FDA could argue that the regulation or guidance is deregulatory and, thus, does not trigger the requirement in accordance with the EO's implementing guidance from the Office of Management and Budgets.[11] However, in order to qualify as

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[6] Scott Gottlieb, *EpiPen Shows a Path to Solve the Bigger Drug Pricing Challenge*, FORBES (Oct. 24, 2016 7:50AM), https://www.forbes.com/sites/scottgottlieb/2016/10/24/epipen-drug-pricing-challenge/4/#55858f3c46ad.

[7] Scott Gottlieb, *How Obama's FDA Keeps Generic Drugs Off the Market*, WALL ST J (Aug. 20, 2016), at A13.

[8] Scott Gottlieb, *Speech before National Coalition for Cancer Survivorship: Industry Roundtable on Expanded Access* (Jan. 6, 2006), https://www.fda.gov/NewsEvents/Speeches/ucm052366.htm.

[9] Exec. Order No. 13,771, *Reducing Regulation and Controlling Regulatory Costs*, 82 FR 9339 (Jan. 30, 2017).

[10] *Id.* at § 2(b); *see* Office of Info. & Reg. Affairs, *Interim Guidance Implementing Section 2 of the Executive Order of January 20, 2017, Titled "Reducing Regulation and Controlling Regulatory Costs,"* p. 5 (Feb. 2, 2017), *available at* https://www.whitehouse.gov/sites/whitehouse.gov/files/briefing-room/presidential-actions/related-omb-material/eo_iterim_guidance_reducing_regulations_controlling_regulatory_costs.pdf.

[11] *Id.* at p. 4.

deregulatory, the action must provide cost savings for all affected parties. Third, FDA can consult with its Office of Information and Regulatory Affairs Desk Officer regarding significant guidance on a case-by-case basis to determine if the EO applies.[12] However, if this "two for one" EO proves applicable to the Cures Act and Dr. Gottlieb is confirmed, he may face a difficult path trying to implement key provisions of the Cures Act and other initiatives consistent with his policy positions.

Another hurdle will be funding. Whether FDA will have the necessary budget to implement these provisions of the Cures Act is unclear based upon the budget proposals from the White House that limit FDA funding, and the looming reauthorization of the prescription drug user fees. Therefore, despite the bipartisan support behind passing the Cures Act, FDA may still lack the resources to effectively support all of the initiatives required under the Cures Act.

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This Client Alert was authored by **Kim Tyrrell-Knott, Bradley S. Davidsen,** *and* **Elena M. Quattrone.** *For additional information about the issues discussed in this Client Alert, please contact one of the authors or the Epstein Becker Green attorney who regularly handles your legal matters.*

[12] *Id.* at p. 3.