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Evidentiary Standards for Drug Approvals in the 21st Century Cures Act: A Continued Trend Towards Valuing Access over Safety for Pharmaceutical Drugs

Farrah R. Raja

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**EVIDENTIARY STANDARDS FOR DRUG APPROVALS IN THE 21ST
CENTURY CURES ACT: A CONTINUED TREND TOWARDS
VALUING ACCESS OVER SAFETY FOR PHARMACEUTICAL DRUGS**

*Farrah R. Raja**

The Food and Drug Administration (“FDA”), tasked with promoting and protecting public health, has long been recognized as the gatekeeper for drugs. However, the agency has not been immune from criticism from patients and industry stakeholders over its time-consuming and clinical data-driven approval processes, alleged to hinder potentially effective drugs from reaching the market as quickly as they could. In December of 2016, the signing of the 21st Century Cures Act (“Cures Act”), a piece of “landmark” legislation that alters the rigorous approval processes for drugs by allowing data other than those derived from clinical trials into the approval process consideration, came as a triumph to these critics. These critics lauded the legislation as a win for both patient access and innovation. However, this “triumph” may come at an expense: safety. This Recent Development examines the key, relevant provisions of the Cures Act relating to the different standards of evidence required for drug approvals, and how the implementation of these provisions will impact the future of safe and effective drugs, given our current framework for drug approvals.

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I: INTRODUCTION

The recent enactment of the 21st Century Cures Act¹ into law has ignited a sense of hope and optimism in patients and other industry stakeholders who are disillusioned with regulatory obstacles that impede the ability of drugs to enter the market in an expeditious manner.² The legislation is acclaimed for its attempts to advance new therapies and treatments by accelerating the

* J.D. Candidate, University of North Carolina School of Law Class of 2018. The author would like to thank the North Carolina Journal of Law and Technology staff and editors for their hard work and feedback. The author would also like to thank Professor Joan H. Krause and Justin Mann for their helpful guidance and insightful comments.

¹ 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016).

² Elaine Schattner, *Why Patients Support the 21st Century Cures Act*, FORBES (Nov. 30, 2016, 9:54 AM), <http://www.forbes.com/sites/elaineschattner/2016/11/30/why-patients-support-the-21st-century-cures-act/#12a60850ac37>.

Federal Drug Administration (“FDA”) approval³ process for new drugs.⁴ Patients like Janet Freeman-Daily, a sixty-year-old woman who has been living with advanced lung cancer for the past five years, see the bill as a victory over “paperwork” hurdles that prevent potentially effective drugs from reaching the market.⁵ For Freeman-Daily, the Cures Act represents an opportunity to accelerate drug approval for oncogene-driven cancers.⁶ Given the complexity surrounding drug discovery, including the inherent risk involved in scientific uncertainty, approving a new drug for market, by no means, is a simple process.⁷ It can take anywhere from ten to fifteen years to approve a new drug, and the estimated costs can run into the hundreds of millions of dollars.⁸ The Cures Act should alleviate the many concerns patients and industry stakeholders have about a lengthy and time-consuming approval process. Critics, like law professor Ana Santos Rutschman,⁹ however, worry that hastening the drug approval process will not come without costs.¹⁰ According to Santos Rutschman, the Cures

³ It is important to distinguish between drug approval and the FDA’s review process for drugs at the onset. Drug approval encompasses all of the time that goes into the development of the drug, including initial research, the discovery of the medicine, preclinical development testing, and clinical trial testing. Drug review, on the other hand, refers to the FDA’s review of all of the data submitted with the new drug’s application for market approval. *The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective*, U.S. FOOD AND DRUG ADMIN., <https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>. (last visited Mar. 20, 2017).

⁴ 130 Stat. 1033.

⁵ Schattner, *supra* note 2.

⁶ *Id.*

⁷ BERNARD LO & MARILYN J. FIELD, CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE, 23 (2009) (ebook).

⁸ *Id.*

⁹ Professor Santos Rutschman is the Jaharis Faculty Fellow in Health Law and Intellectual Property at DePaul University College of Law. Ana Santos Rutschman, DEPAUL UNIV. COLL. OF L., <http://law.depaul.edu/faculty-and-staff/faculty-a-z/Pages/ana-santos-rutschman.aspx> (last visited Mar. 20, 2017).

¹⁰ Ana Santos Rutschman, *Faster Drug & Medical Device Approvals Under 21st Century Cures Act Raises Patient Safety Concerns*, DRUG DISCOVERY & DEV. (Jan. 16, 2017, 8:54 AM), <http://www.dddmag.com/article/2017/01/faster->

Act may represent a sacrifice between safety and efficacy of drugs in exchange for quicker delivery to patients.¹¹

President Obama signed the Cures Act into law in December of 2016 after it passed both the House and the Senate with bipartisan support. The bill, spanning almost 1,000 pages in length, champions several initiatives in addition to providing funding for these initiatives.¹² The bill authorizes funding for countering the opioid epidemic,¹³ cancer research through the “Moonshot Initiative,”¹⁴ mental health parity implementation,¹⁵ and precision medicine efforts.¹⁶ The aforementioned initiatives have garnered praise from the majority of people, however, the most contentious parts of the Cures Act are those that address the evidentiary standards that can be used in the FDA’s approval process for drugs.¹⁷

This Recent Development argues that while the Cures Act’s provisions that relax the evidentiary standards used in the FDA approval processes for drugs may help patients access drug treatments and therapies more quickly and might appear to further innovation by removing regulatory barriers, the hastened process authorized by these provisions poses a threat to both patient safety and innovation in developing *effective* treatments. This paper proceeds in six parts. Part II examines the FDA and how its regulatory drug standards have evolved since its inception, and increased utilization of expedited drug development and approval programs. Part III explores the legislative history behind the Cures Act. Part IV discusses the likely impact of the Cures Act’s FDA provisions that encourage the use of real-world evidence, surrogate endpoints, patient outcome data, and data summaries in drug

drug-medical-device-approvals-under-21st-century-cures-act-raises-patient-safety-concerns.

¹¹ *Id.*

¹² 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016).

¹³ *Id.* § 1003.

¹⁴ *Id.* § 1001.

¹⁵ *Id.* § 13001–07.

¹⁶ *Id.* § 2011.

¹⁷ Jerry Avorn & Aaron S. Kesselheim, *The 21st Century Cures Act—Will it Take Us Back in Time?*, NEW ENG. J. MED. 2473, 2474 (2015).

approvals. Part V examines the broader policy implications of the Cures Act on patients, stakeholders, and the legitimacy of the FDA. Finally, Part VI will conclude.

II: THE FDA - TRACING ITS EVOLUTION

In an effort to place the significance of the Cures Act's drug alteration provisions into context, this section introduces the reader to the FDA and the historical evolution of its regulations and control. Part A provides background information about the FDA and its role in the development and marketing of drugs. Part B supplies a more thorough discussion of the agency's review processes for approving drugs than was mentioned in the Introduction.¹⁸ Part C gives an overview of special approval pathways that have been used by the FDA. Part D examines past instances of less than rigorous drug approvals, the negative repercussions that subsequently resulted, and what these past situations can teach us about what the Cures Act may hold for the future of drug safety and efficacy.

A. *The FDA: The Gatekeeper*

The FDA has long been regarded as the gatekeeper of the American pharmaceutical industry.¹⁹ The FDA has the power “to sculpt medical and scientific concepts,”²⁰ to determine which drugs can enter the market, to determine how medical success is defined, and to “influence how citizens live and die.”²¹ Undoubtedly, the agency's impact on patients' lives and the entire pharmaceutical industry is far-reaching.

While the FDA was originally formed in 1906 with the passage of the Pure Food and Drug Act of 1906—that was aimed at preventing the adulteration and mislabeling of food and drug products—the scope of the agency's regulatory authority over the pharmaceutical industry was not fully realized until the passage of

¹⁸ See *supra* PART I.

¹⁹ DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 1 (2010).

²⁰ *Id.*

²¹ *Id.*

the Federal Food, Drug, and Cosmetic Act (“FDCA”)²² in 1938.²³ The FDCA was passed in the aftermath of the elixir sulfanilamide tragedy²⁴ that took the lives of approximately one hundred people.²⁵ The drug was not tested for safety, as was the case for many new drugs, since prior to the enactment of the FDCA, new drugs did not undergo safety scrutiny.²⁶ The FDCA gave the FDA stricter control over drugs.²⁷ The FDCA also further strengthened the agency’s ability to enforce the new law.²⁸

While the enactment of the FDCA addressed safety concerns associated with drugs, there was still no requirement that drug firms prove the effectiveness of the drugs for which they sought approval.²⁹ This changed with the monumental passage of the 1962 Kefauver-Harris Drug Amendments³⁰ to the FDCA. Under the 1962 Amendments, drug companies now had to prove not only that the drug was safe for its intended use, but also provide “substantial evidence of effectiveness for the product’s intended use.”³¹ The most sweeping change that the 1962 Amendments brought, however, was the requirement that evidence supporting the drug come from “*adequate and well-controlled studies*.”³² Without a

²² Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-17, 52 Stat. 1040 (1938).

²³ CARPENTER, *supra* note 19, at 1.

²⁴ During the *elixir sulfanilamide* tragedy, 105 individuals died after taking the drug *elixir sulfanilamide*, intended to treat infections. The drug was later found to have a toxic ingredient in its solution. Carol Ballentine, *Taste of Raspberries: Taste of Death: The 1937 Elixir Sulfanilamide Incident*, U.S. FOOD AND DRUG ADMINISTRATION (Jun. 1981), <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/>.

²⁵ *Id.*

²⁶ *Id.*

²⁷ *See* 52 Stat. 1040.

²⁸ *Id.*

²⁹ Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, U.S. FOOD AND DRUG ADMIN. (Jan.—Feb. 2006), <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/>.

³⁰ Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

³¹ Meadows, *supra* note 29; *see also* 76 Stat. 781.

³² Meadows, *supra* note 29 (emphasis added).

doubt, the Amendments thrust the importance of relying on thorough and controlled effectiveness studies into the forefront.³³ As Part B discusses, this reliance on clinical data from controlled trials is fundamental for drug approval.³⁴

B. FDA Review Processes for Drugs

The process of getting a new drug approved on the market is a process that is rigorous and time-consuming for both the agency and for drug sponsors. Following its initial manufacture and before it can enter the market for sale, a drug must demonstrate “substantial effectiveness”³⁵ and safety for its intended use.³⁶ The FDA makes this determination after reviewing results from clinical trials submitted by the drug manufacturer at various stages in the process.³⁷

There are roughly seven stages for new drug development and review.³⁸ The first stage, a very crucial one, begins when drug sponsors submit an Investigational New Drug Application (“IND”). During this stage in the process, sponsors must submit results from “preclinical” testing in laboratory animals, in addition to a proposed plan for human testing.³⁹ If the results do not demonstrate “reasonable safety,”⁴⁰ the FDA can reject the drug for testing in humans, thereby ending its review.⁴¹ Review of the IND

³³ Jeremy A. Greene et al., *Reform, Regulation, and Pharmaceuticals – The Kefauver-Harris Drug Amendments at 50*, NEW ENG. J. MED 1481 (2012).

³⁴ See *infra* FDA Review Processes for Drugs.

³⁵ “Substantial evidence of effectiveness” is shown when qualified experts have reviewed data from adequate and well-controlled studies, and can conclude from the results of the data that the drug will have its intended effect for its prescription and labeling uses. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-17, 52 Stat. 1040 (1938).

³⁶ *The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective*, *supra* note 3.

³⁷ *Id.*

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ Reasonable safety is demonstrated when, based on scientific evidence, the probable benefits from using the drug for its intended use outweigh the probable risks associated with using the drug. 52 Stat. 1040.

⁴¹ *The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective*, *supra* note 3.

is a joint collaborative process that involves both the FDA and an Institutional Review Board,⁴² a panel of scientists and non-scientists whose main objective in studies involving human research subjects is to review and assess the study itself, the study's consent procedures, and the study's safety protocols.⁴³

Once the FDA deems the study "reasonably safe" for testing in humans, the sponsor may begin clinical testing, consisting of three phases: Phase 1, Phase 2, and Phase 3.⁴⁴ During Phase 1 testing, studies are conducted on the drug's impact on healthy volunteers, with the main objective targeted at finding out the drug's side effects on humans.⁴⁵ Once Phase 1 testing is completed and reviewed, if the results do not show "unacceptable toxicity," the drug may move on to Phase 2 testing.⁴⁶ While Phase 1 testing is concerned with a drug's safety, Phase 2 testing is most concerned with the drug's effectiveness.⁴⁷ The subjects involved in Phase 2 testing are individuals with certain illnesses or diseases.⁴⁸ During this Phase, through controlled trials, researchers compare similar patients who are given a placebo or different kind of drug in place of the drug being tested.⁴⁹ Through Phase 2 testing, the drug's safety is *still* evaluated, in addition to the short-terms side effects of the drug.⁵⁰ Once Phase 2 testing is complete and has demonstrated that the drug is effective, the FDA and drug sponsors must come to an agreement on how Phase 3 testing will proceed.⁵¹

⁴² "[Institutional Review Board]s approve the clinical trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives, and other details. IRBs make sure the study is acceptable, that participants have given consent and are fully informed of their risks, and that researchers take appropriate steps to protect patients from harm." *Id.*

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ *Id.*

⁴⁶ *Id.*

⁴⁷ *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, *supra* note 3.

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *Id.*

Phase 3 studies are targeted at gathering additional information about the drug's safety and effectiveness by (1) studying the drug's effects on different populations, (2) using different dosages, and (3) studying the drug's effects when used in combination with other drugs.⁵² Phase 3 testing concludes with a review meeting between the drug sponsor and the FDA.

After the three phases of testing are complete, the sponsor seeks the approval of the FDA for marketing the drug in the United States by submitting a New Drug Application ("NDA").⁵³ The NDA must include all evidence gathered from the three phases of clinical testing, including all animal and human data, the procedure by which the drug is manufactured, and information about how the drug behaves in humans.⁵⁴ The FDA can refuse to "file" an NDA for review, but must do so within a sixty-day period, though refusing to file occurs infrequently.⁵⁵

Once the FDA approves a drug and it is ready for the market, the FDA's scrutiny of the drug continues.⁵⁶ The FDA can require drug sponsors to submit additional data from studies after drug has obtained market approval.⁵⁷ These studies are particularly important because some safety concerns can only come to light after patients have taken the drugs and have reported adverse outcomes. The FDA's management and handling of post-marketing studies, however, have been the subject of numerous concerns.⁵⁸ According to the a 2015 report by the Government Accountability Office,⁵⁹ these concerns included that (1) the FDA's

⁵² *Id.*

⁵³ *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, *supra* note 3.

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ *Step 5: FDA Post-Market Safety Monitoring*, U.S. FOOD AND DRUG ADMIN., <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405579.htm>. (last visited Mar. 20, 2017).

⁵⁷ *Id.*

⁵⁸ *See* H.R. REP. GAO-16-192 (2015), <http://www.gao.gov/assets/680/674183.pdf>.

⁵⁹ The Government Accountability Office is an independent and nonpartisan government agency that is primarily tasked with investigating how public funds

data on tracked issues was not complete, and (2) post-market study data was often outdated and contained inaccuracies.⁶⁰ While post-market studies can be extremely helpful, especially when it comes to using them to support withdrawing a drug from the market, they are ineffective if not properly managed.

C. Special Approval Pathways: An Overview

As Part B⁶¹ of the paper illustrates, there are a rigorous set of procedures that must be followed before a drug can be marketed for sale in the United States. While these procedures are in place to ensure safety and effectiveness and to weed out drugs that pose great risk and little benefit, these procedures can also cause great delay in allowing potentially effective drugs to be reviewed and marketed.⁶² This is particularly problematic for the individual living with a life-threatening disease, for which there is not any other treatment available.⁶³ Recognizing this dilemma, the FDA has worked with Congress to create “special approval pathways”⁶⁴ that speed up the development and review process for drugs that meet certain criteria.⁶⁵ Since the late 1980s, the number of special approval pathways has routinely been increasing.⁶⁶

Over the past two decades, five programs have been created to speed up drug approvals and reviews for illnesses that are either rare or life threatening, and for which no other treatment is available or for which the new drug suggests greater therapeutic

are used. U.S. GOV'T ACCOUNTABILITY OFF.,
<https://www.gao.gov/about/index.html> (last visited Mar. 20, 2017).

⁶⁰ H.R. REP. GAO-16-192, *supra* note 58, at 23.

⁶¹ See *FDA Review Processes for Drugs*, *supra* Part B.

⁶² Aaron S. Kesselheim et al., *Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987-2014; cohort study*, 1 BRIT. MED. J. 2 (2015), <http://www.bmj.com/content/bmj/351/bmj.h4633.full.pdf>.

⁶³ *Id.*

⁶⁴ Special approval pathways have typically been applied to drugs that treat “serious” diseases, and are more readily used when a drug is the first treatment for the serious disease or is advantageous over existing treatments for the disease. *Id.*

⁶⁵ *Id.*

⁶⁶ *Id.*

advantage over existing therapies.⁶⁷ The five programs are (1) orphan drug,⁶⁸ (2) fast track,⁶⁹ (3) priority review,⁷⁰ (4) accelerated approval,⁷¹ and (5) breakthrough therapy.⁷²

The number of drugs approved within one of these special approval pathways has been increasing over the past two decades, perhaps beyond what the FDA intended.⁷³ According to studies, in 2013, 56% of twenty-seven new drugs were approved under a special pathway approval program, and twelve of these drugs qualified for more than one program.⁷⁴ The same study revealed that despite the increase in approvals under these programs, many of the drugs did not meet the qualifying criteria as being “innovative.”⁷⁵ In fact, many suggest that approvals under special pathways have become the *rule* and not the exception.⁷⁶ The dilemma posed by the Cures Act is whether additional methods for expediting drug development and delivery are needed, when

⁶⁷ *Id.*

⁶⁸ Under the orphan drug program, a drug qualifies only if it is intended to treat a disease that occurs in less than 200,000 people per year in the United States. This designation does not change the statutory standards, however orphan drugs have been shown to be approved based on “small, non-randomized, unblended, single arm trials.” Kesselheim et al., *supra* note 62 at 2.

⁶⁹ A drug qualifies for fast track designation if it treats a “life threatening” or “severely debilitating” disease. This designation allows qualifying drugs to be approved after just one Phase 2 study. *Id.*

⁷⁰ A qualifying drug under priority review designation is one that “seems to offer therapeutic advance over available therapy.” This does not change the statutory standard for approval. *Id.*

⁷¹ Under accelerated approval designation, a qualifying drug is one that treats “serious or life threatening illnesses,” allowing surrogate endpoints that are “reasonable likely to predict patient benefit” to be used. *Id.*

⁷² A drug is eligible for breakthrough designation if it is one that “treats a serious disease for which preliminary clinical evidence suggests substantial improvement over existing therapies on one or more clinically important endpoints.” This does not change the statutory standard for approval. *Id.*

⁷³ *Id.*

⁷⁴ Kesselheim et al., *supra* note 62 at 2.

⁷⁵ *Id.*

⁷⁶ Margot Sanger-Katz, *Speedy Drug Approvals Have Become the Rule, Not the Exception*, N.Y. TIMES (May 1, 2015), <https://www.nytimes.com/2015/05/02/upshot/speedy-drug-approvals-have-become-the-rule-not-the-exception.html>.

approval pathways already exist, and evidence shows they are utilized very frequently.

D. A Trends Towards Increased Expedited Drug Development and Approval Programs

While special approval pathways have resulted in revolutionary drugs, they have also caused great controversy.⁷⁷ Their increase has brought about more drug applications and approvals, but for the most part, most of the drugs approved under these expedited development programs have not shown “noticeable clinical advances.”⁷⁸ This debunks the belief that the FDA’s clinical-data driven process hinders innovation. The FDA’s history is laced with tragedies that have brought great scrutiny to the agency’s actions.⁷⁹ These tragedies have motivated the FDA to implement regulatory reforms.⁸⁰ In particular, many argue that the pharmaceutical industry’s “capture” of the FDA and an increase in special approval pathways are what have led to some of the country’s worst drug disasters at the hands of the FDA.⁸¹

There are many problems associated with special regulatory designations that allow for drug approvals based on less rigorous data.⁸² Notably, there are two problems: (1) basing approvals on less rigorous data, and (2) inadequate post-approval procedures for these drugs.⁸³ For instance, the case study of gemtuzumab, known by its brand name “Mylotarg,” illustrates the dangers of using surrogate endpoints⁸⁴ under accelerated approval pathways.⁸⁵ Mylotarg was approved in 2000 for acute myeloid leukemia based

⁷⁷ Kesselheim et al., *supra* note 62, at 2.

⁷⁸ *Id.* at 1.

⁷⁹ Sue McGrath, *Only a Matter of Time: Lessons Unlearned at the Food and Drug Administration Keep Americans at Risk*, 60 FOOD DRUG L.J. 603 (2005).

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² Kesselheim et al., *supra* note 62, at 2–6.

⁸³ *Id.*

⁸⁴ “Surrogate endpoints consist of markers such as laboratory measurements or radiographic images, and contrast with clinical endpoints such as reduction in patient symptoms or mortality.” *Id.* at 2.

⁸⁵ *Id.* at 2.

on surrogate endpoints,⁸⁶ however a *decade* later, it was removed from the market after confirmatory post-approval studies found it showed “no efficacy and increased mortality.”⁸⁷ However, the issue is that the FDA often delays or fails to complete post-marketing studies.⁸⁸ Much of the information about a drug’s effectiveness is learned *after* the drug has been approved through post-approval studies.⁸⁹

Expedited approval processes are often created with the belief that they will allow new and innovative drugs to reach the market.⁹⁰ While special approval pathways have led to more approvals, they have also been used for drugs that present no special advantage, thereby presenting greater risk and little benefit to patients.⁹¹ Given the startling number of drugs approved each year based on limited data, the Cures Act drug provisions will exacerbate this problem.

III: LEGISLATIVE HISTORY OF THE CURES ACT: A SUSPECTED HOST OF SPONSORS, SUPPORT FOR THE ACT, AND OPPOSITION TO THE ACT

This section will introduce the reader to a very brief legislative history behind the Cures Act to include its supporters and its critics. This legislative history of the Cures Act is included in order to give the reader insight into the circumstances that catapulted the passage of the law.

The strongest proponents of the Cures Act drug provisions were pharmaceutical industry stakeholders.⁹² Almost 1,300

⁸⁶ *Id.*

⁸⁷ *Id.* (“Approving drugs on the basis of surrogate endpoints, for example, can be risky, since promising surrogates may later be found not to accurately predict actual changes in patient health outcomes.”).

⁸⁸ Kesselheim et al., *supra* note 62, at 5.

⁸⁹ *Id.*

⁹⁰ *Id.* at 1–2.

⁹¹ *Id.* at 6.

⁹² Dennis Thompson, *Congress Passes 21st Century Cures Act with Billions for New Research, Treatment*, CBS NEWS (Dec. 8, 2016, 12:34 PM), <http://www.cbsnews.com/news/21st-century-cures-act-congress-health-care-passed/>.

lobbyists from pharmaceutical companies were largely responsible for the passage of the entire bill, not shocking, given the financial incentive the bill provides for pharma companies.⁹³ Proponents of the Cures Act routinely presented the Cures Act in a compassionate light, arguing that patients with life-threatening illnesses could wait no longer.

Critics of the Cures Act, however, painted a very different picture of the Act. Critics were vocal in their opposition and even sent Congressional members a letter to urge them to reconsider hastily passing the bill.⁹⁴ They argued that (1) the bill, as written, threatened the ability of the FDA do its job by ensuring safety and quality, and (2) that the provisions were unnecessary, given that the FDA already used expedited pathways, and even their use was raising “serious concerns”⁹⁵ In the end, however, the pharmaceutical industry came out with a victory. Given the Cures Act’s support and funding for other noteworthy causes,⁹⁶ one can see how the FDA provisions managed to sneak their way in. Other critics of the Cures Act, including Diana Zuckerman, the president of the National Center for Health Research, a non-partisan think tank, took a stab at the bill, citing the irony of its name.⁹⁷ Zuckerman was quoted as saying, “The irony is calling this 21st Century Cures, when they’re talking about standards that were left behind in the 20th century, because they were found to not be good.”⁹⁸

One reason often cited for making the FDA’s drug approval process less rigorous is that in its current state, it stifles the discovery of new drugs and innovation. Critics of this reason,

⁹³ *Id.*

⁹⁴ *21st Century Cures Act Letter* (Oct. 26, 2016), <https://morningconsult.com/wp-content/uploads/2016/10/21st-Century-Cures-Act-letter.pdf>.

⁹⁵ *Id.*

⁹⁶ See INTRODUCTION, *supra* PART I.

⁹⁷ Carolyn Y. Johnson, *This Bill Promises to Speed up Drug Approvals So Much That It’s Making People Uncomfortable*, WASH. POST, (Jul. 10, 2015), https://www.washingtonpost.com/news/wonk/wp/2015/07/08/this-bill-promises-to-speed-up-drug-approvals-so-much-that-its-making-people-uncomfortable/?utm_term=.801765c95739.

⁹⁸ *Id.*

however, offer different explanations. Jerry Avorn, a professor at Harvard Medical School presented his theory on the lagging innovation in drug development.⁹⁹ Avorn was quoted as saying,

If there's a shortfall in drug development, it is mostly because the companies have lost their verve in their ability to discover new drugs . . . Lowering FDA standards for approving drugs and antibiotics without evidence of clinical benefit -- I don't think that's going to help, but it could also harm patients. What we don't need is more drugs approved based on lab tests instead of patient benefit.¹⁰⁰

The Cures Act presents a stark contrast in viewpoints, with patients and pharmaceutical industry stakeholders on one side, and on the other, physicians.

IV: THE FUTURE OF DRUG REGULATION: AN ANALYSIS OF HOW THE CURES ACT'S EVIDENTIARY STANDARDS FOR DRUG APPROVALS WILL UNDERMINE SAFETY AND INNOVATION

This section provides an in-depth discussion and analysis of the key provisions of the Cures Act relating to evidentiary standards for drug approvals and the impact of these provisions on safety and innovation. Part A discusses the use of real-world evidence to support the FDA's decisions. Part B discusses the use of patient experience data in the review process. Part C discusses the Act's mandate on drug development tools in drug development and review. Part D discusses the overall implications these three provisions will have on drug regulation.

A. "Real-World" Evidence: Waning Significance of the Clinical Trial

As discussed in Part II,¹⁰¹ when determining whether a certain drug will be approved during the NDA period, the FDA makes its determination based on data from clinical trials. Under the Cures Act, for drugs that have already been approved by the FDA but are

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ See THE FDA: TRACING ITS EVOLUTION, *supra* PART II.

now being considered for a new indication, the agency can utilize real world-data in its assessment.¹⁰² This provision, however, though it provides flexibility in gathering data for review, may prove to be ultimately harmful in the end. In its attempt to incorporate real-world evidence into the FDA's regulatory approval process, the Cures Act represents perhaps one of the most significant moves in clinical trial flexibility in the agency's history.

Real-world evidence can come in a variety of forms, and its use in the drug approval process can pose noteworthy concerns. Real-world evidence, according to the Cures Act, is "evidence from clinical experience, mean[ing] data regarding the usage, or the potential benefits or risks, of a drug derived from sources *other than randomized clinical trials*, including from observational studies, registries, and therapeutic use."¹⁰³ While the Cures Act does not purport to do away with the clinical trial requirement, it does bring into question the future of randomized clinical trials, given that real-world evidence can now be used as a tool for review by the FDA, and can quicken the approval process.¹⁰⁴

For some patients, incorporation of real-world evidence into the FDA's review process seems like a victory.¹⁰⁵ As Freeman-Daily¹⁰⁶ points out, clinical trials are not always convenient or even *possible* to conduct due to the low volume of people living with a particular rare disease.¹⁰⁷ According to Freeman-Dailey's account,

They're [referring to the Cures Act] talking about accelerating approval of drugs for patients with rare diseases and oncogene-driven cancers like mine. Many of these are conditions are infrequent; it would be extremely difficult if not impossible to collect sufficient numbers of patients for separate clinical trials of each drug in each condition. The nearest trial for me is one thousand miles away, in Denver . . . Many patients can't travel. That's why

¹⁰² 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033 (2016).

¹⁰³ *Id.* § 3022(b)–3022(c)(2)(A) (emphasis added).

¹⁰⁴ *Id.* § 3022(2)(A).

¹⁰⁵ Schattner, *supra* note 2.

¹⁰⁶ *See supra* PART I.

¹⁰⁷ Schattner, *supra* note 2.

greater flexibility in trial design for evaluating precision medicine drugs is needed . . . ¹⁰⁸

The use of “real-world evidence” in the drug approval process, though wrought with controversy in many ways, however, could be useful in a number of areas, including its use in tracking observational data, a major issue that often arises in the area of off-label drug use.¹⁰⁹ Under the current framework, physicians who prescribe off-label are not required to record the purpose for which a particular drug is prescribed.¹¹⁰ Under the Cures Act, however, medical professionals may be incentivized to share data from observational studies for drug-promotion if the data can help in the approval process for a drug. Tracking observational data is particularly important because it can provide additional information to researchers, including what purposes doctors are prescribing the off-label drug for, and who they are prescribing it to.¹¹¹ This information could then be used by researchers to evaluate whether the drug is safe and effective for the prescribed uses, which would save researchers both time and expenses in beginning with clinical trials.¹¹² Alternatively, tracking observational data also serves a policing function for improper off-label drug promotion. Particularly, the ability to track observational data becomes useful in situations where doctors are prescribing off-label drugs when the drug presents little benefit, yet high risk, or if there are actual safe and effective *existing* therapies.¹¹³ However, tracking observational data may alternatively be achieved by incorporating diagnostic codes that

¹⁰⁸ *Id.*

¹⁰⁹ “This practice includes prescribing for a different therapeutic purpose, using a different dose or a different duration of use, using a different mode of administration than the one indicated on the label, and prescribing the drug for patients in a different age cohort or gender than the population on which it was tested.” Marc Rodwin, *Managing Off-Label Drug Use*, HEALTH AFFAIRS BLOG (Dec. 17, 2013), <http://healthaffairs.org/blog/2013/12/17/managing-off-label-drug-use/>.

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ Rodwin, *supra* note 109.

include the particular purposes for which a drug is being used into Medicare claims.

Despite the potential incentive to track data from observational studies, many argue that the incorporation of real-world evidence into approval processes will do more harm than good.¹¹⁴ According to scholars, assessing efficacy based on observational data is “subject to numerous forms of bias and unmeasured confounding, which would obscure the true benefits and risks of drugs and devices.”¹¹⁵ Real-world evidence can largely be problematic because it is not collected with the intent to support research, and thus is not “optimized” for research support.¹¹⁶ Another issue posed by using real-world evidence is privacy issues.¹¹⁷ Sharing electronic health information from patients who have not consented can present significant issues for both the disclosing entities and those receiving the data.¹¹⁸

Assessing the benefits of incorporating real-world evidence into the drug approval process, however, requires further addressing the limitations of clinical trials. Among a number of concerns that have been identified include, patient recruitment and

¹¹⁴ Ameet Sarpatwari & A.S. Kesselheim, *The 21st Century Cures Act: Opportunities and Challenges*, 98 CLINICAL PHARMACOLOGY AND THERAPEUTICS 575 (2015).

¹¹⁵ *Id.* at 2 (“This potential is particularly true for data derived from insurance claims databases—a likely source of clinical experience information—owing to their lack of information on such critical variables as laboratory test results, smoking status, and body mass index.”).

¹¹⁶ Rachel E. Sherman et al., *Real-World Evidence—What Is It and What Can It Tell Us*, NEW ENG. J. MED. 2293, 2294 (2016).

¹¹⁷ *Id.*

¹¹⁸ See The Health Insurance Portability and Accountability Act of 1996, Pub. L. 104–191, 110 Stat. 1936 (1996) (“HIPAA is the acronym for the Health Insurance Portability and Accountability Act, which became law in August 1996. The Secretary of HHS was mandated to produce a regulation to protect the privacy of certain health information. This mandate resulted in the publication of the regulation (45 C.F.R. 160 and 164) Standards for Privacy of Individually Identifiable Health Information, more commonly referred to as the ‘Privacy Rule.’ By the compliance date of April 14th, 2003 (April 14th, 2004 for small health plans) covered entities were required to have standards implemented to protect individually identifiable health information (usually referred to as ‘protected health information’ or ‘PHI’) from misuse.”).

retention, informed consent issues, gaining Institutional Review Board approval, a “shrinking” clinical research workforce, and the costs of clinical trials.¹¹⁹

Real-world evidence, indeed, from patients like Freeman-Daily and others, may seem to be valuable in that data would be more easily generated than it could be from a clinical trial. This provision of the Cures Act could also save researchers a lot of time and money when it comes to gathering data. On the other hand, however, ease in generating data using real-world evidence will come at an expense, and that expense is ensuring that the drug’s safety and effectiveness is supported by *reliable* data. Ancillary concerns include the privacy ramifications of using data from patients who have not consented to sharing of that data. Further, it will delay the development of drugs that have gone through the rigorous clinical data-driven review process that presents a greater guarantee of effectiveness.

B. Incorporating Patient Experience into the Review Process

The Cures Act also aims to incorporate “patient experience” into the review process for drugs.¹²⁰ For the purposes of the provision, “patient experience data” is defined as including data that,

- (1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and
- (2) are intended to provide information about patients’ experiences with a disease or condition, including—
 - (A) the impact of such disease or condition, or a related therapy, on patients’ lives; and

¹¹⁹ See Rebecca A. English et al., *Transforming Clinical Research in the United States: Challenges and Opportunities* (2010), INST. OF MED. 20, https://www.ncbi.nlm.nih.gov/books/NBK50892/pdf/Bookshelf_NBK50892.pdf

¹²⁰ 21st Century Cures Act, Pub. L. No. 114-255, § 3001, 130 Stat. 1033 (2016).

(B) patient preferences with respect to treatment of such disease or condition.¹²¹

Upon examination of the definition provided in the Cures Act, “patient experience” data seems to be very broad.

Patient experience data can be useful, but as a supplement to clinical trials. Patient-reported outcomes (“PROs”) can play an important function in the drug approval process.¹²² FDA statisticians have described some of the advantages, including the ability of PROs to capture “how a patient feels and functions directly from the patient.”¹²³ Another benefit derived from patient experience data includes the ability for the patient to be more involved in their care.¹²⁴ Dr. Janet Woodcock, the director of the U.S. FDA Center for Drug Evaluation and Research was cited as saying that the Cures Act would allow researchers to “collect data from a broad range of patients in a ‘structured way,’ including details about the burden of their disease and what matters to them. This reflects the ‘societal shift from the doctors telling you what you have . . . to the patient as a navigator.’”¹²⁵ Indeed, patient experience data could allow for approving drugs based on data from more broad patient bases, which is not always possible in a clinical trial setting.

On the other hand, patient experience data also has severe downsides. One critique of patient experience data is that including personal experience data collected by family members, caregivers, and the patients themselves can improperly bias the FDA’s otherwise objective review process.

¹²¹ *Id.* § 3001(1)(C)(c).

¹²² Rima Izem, Lisa A. Kammerman & Scott Komo, *Statistical Challenges in Drug Approval Trials That Use Patient-Reported Outcomes*, 23 STATISTICAL METHODS IN MED. RESEARCH 398, 407 (2013).

¹²³ *Id.*

¹²⁴ Judy Stone, *21st Century Cures Act: Pork or Promise?*, FORBES, (Sept. 22, 2016, 6:30 AM), <https://www.forbes.com/sites/judystone/2016/09/22/21st-century-cures-act-pork-or-promise/#3a593cc51b2d>.

¹²⁵ *Id.*

C. *Qualification of Drug Development Tools*

Under the Cures Act, another provision that has raised concerns is Section 3011, which mandates the Department of Health and Human Services (“DHHS”) Secretary to certify “drug development tools.”¹²⁶ This section of the paper will briefly mention the other drug development tools mentioned in the Cures Act under Section 3011, but it will focus on biomarkers, specifically surrogate endpoints. According to the provision, a “drug development tool” is defined as a “(A) biomarker, (B) a clinical outcome assessment, (C) and any other method any other method, material, or measure that the Secretary determines aids drug development and regulatory review for purposes of this section.”¹²⁷ The Act previously defined a “biomarker,” as “a characteristic (such as a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention; and includes a surrogate endpoint.”¹²⁸

First, it is important to recognize that using surrogate endpoints does, in fact, offer significant benefits, and Section 3011 of the Cures Act can help realize these benefits. One of the reasons biomarkers are used is because they are cheaper and easier to use than clinical endpoints.¹²⁹ The measurements from biomarkers can also be measured more quickly.¹³⁰ Another advantage with using surrogate endpoints is that they can avoid many of the ethical issues posed by measuring clinical endpoints.¹³¹

¹²⁶ 21st Century Cures Act, Pub. L. No. 114-255, § 3011, 130 Stat. 1033 (2016).

¹²⁷ *Id.* § 3011(a)(e)(5).

¹²⁸ *Id.* § 3011(a)(e)(1).

¹²⁹ J.K. Aronson, *Biomarkers and Surrogate Endpoints*, 59 BRIT. J. CLIN. PHARMACOL. 491 (2005) (“For example, it is easier to measure a patient’s blood pressure than to use echocardiography to measure left ventricular function, and it is much easier to do echocardiography than to measure morbidity and mortality from hypertension in the long term.”).

¹³⁰ *Id.*

¹³¹ *Id.* (“For example, in paracetamol overdose it is unethical to wait for evidence of liver damage before deciding whether or not to treat a patient;

Surrogate endpoints, however, have been found to be very problematic.¹³² Surrogate endpoints, despite their benefits, are like the Cures Act itself: sacrificing safety and reliability for speed.¹³³ The FDA has even acknowledged the problem with using surrogate endpoints, citing that the use of surrogate endpoints alone fail to capture the total “picture of benefit and risk of a therapy.”¹³⁴ Some of the limitations of using surrogate endpoints, according to the FDA, include:

For example, surrogate endpoints may sometimes fail to predict the overall benefit and/or risk for a medical product. These limitations underscore the importance of continued evaluation in the post-market phase when products are approved based upon surrogate endpoints that have not been validated, as well as the need to rigorously evaluate and sometimes re-evaluate surrogate endpoints clinically.¹³⁵

Under the Cures Act, however, a much greater use of surrogate endpoints is encouraged.¹³⁶ Researchers also point to the harms associated with relying too much on surrogate endpoints, including medical and financial harm, citing that surrogate endpoints are not useful in studying all disease, rather only in cases where the “pathophysiology of the disease and the mechanism of action of the intervention are thoroughly understood.”¹³⁷

instead a pharmacological biomarker, the plasma paracetamol concentration, is used to predict whether treatment is required.”).

¹³² *Id.* at 493.

¹³³ *See id.* at 494.

¹³⁴ *FDA Facts: Biomarkers and Surrogate Endpoints*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/AboutFDA/Innovation/ucm512503.htm>. (last visited Mar. 20, 2017).

¹³⁵ *Id.*

¹³⁶ 21st Century Cures Act, Pub. L. No. 114-255, § 3011(a)(e)(5), 130 Stat. 1033 (2016).

¹³⁷ Aronson, *supra* note 129, at 492.

D. Summary Level Review

Section 3031 of the Cures Act also allows for data summaries to be used in the drug approval process.¹³⁸ According to Section 3031:

(A) The Secretary may rely upon qualified data summaries to support the approval of a supplemental application, with respect to a qualified indication for a drug, submitted under subsection (b), if such supplemental application complies with subparagraph (B).

(B) A supplemental application is eligible for review as described in subparagraph (A) only if--

(i) there is existing data available and acceptable to the Secretary demonstrating the safety of the drug; and

(ii) all data used to develop the qualified data summaries are submitted to the Secretary as part of the supplemental application.¹³⁹

Data summaries are defined as a “summary of clinical data that demonstrates the safety and effectiveness of a drug with respect to a qualified indication.”¹⁴⁰ In randomized clinical trials, “meta-analysis of individual patient data is regarded as the gold standard in systematic reviews.”¹⁴¹ However, researchers are incentivized to deviate from analysis of individual data for three key reasons, including the cost, time, and difficulty associated with obtaining individual-level data.¹⁴²

According to critics, however, data summaries present great potential for manipulation by manufacturers. According to Aaron Kesselheim, Associate Professor of Medicine at Harvard University,

At present, the FDA usually examines all data put forward to support drug approval, including supplemental

¹³⁸ 21st Century Cures Act § 3031.

¹³⁹ *Id.* § 3031(a)(5)(A).

¹⁴⁰ *Id.* § 3031(a)(5)(D)(ii).

¹⁴¹ D.Y. Lin & D. Zeng, *On the Relative Efficiency of Using Summary Statistics Versus Individual-Level Data in Meta-Analysis*, 97 *BIOMETRIKA* 321, 321 (2010).

¹⁴² *Id.*

indications. This herculean effort has proven necessary because manufacturers have sometimes been found (often through litigation) to summarize their data in ways that excessively emphasize benefits of their products and minimize risks.¹⁴³

Greater use of data summary in the approval process, per the Cures Act, poses a threat to patient safety.

E. A Step Back in Time?

Each of the three sections of the Cures Act provide for significant changes in the drug approval process. While each individually poses benefits, these benefits do not outweigh the risks associated with relying on less rigorous data for drug approval. Benefits, such as cost-saving and efficiency are noteworthy. However, where public health disasters are at stake, these benefits cannot supersede the FDA's duty to protect public health by approving only those drugs that have been adequately and rigorously tested and are based on rigorous data.

As the drug and device provisions indicate, quick delivery as a goal seems to be gaining traction among the FDA's review processes. While the randomized clinical trial is here to stay, it remains questionable how much significance the FDA wields given that new forms of review tools, like real-world evidence and a greater reliance on surrogate endpoints and patient experience, with less stringent standards are now available for the FDA's use. These provisions of the Cures Act, indeed, may represent a step backwards for the FDA. Given the agency's past history, this may present itself to be a dangerous step.

V: BROADER IMPLICATIONS AND NECESSARY REFORMS FOR A LESS THAN IDEAL SYSTEM OF DRUG APPROVALS AND RECALLS

The Cures Act will redefine the game when it comes to getting drugs on the market. However, the Cures Act is also wrought with real implications, many of which will be harmful to the future of safe and effective drugs. There are concerns about how patients

¹⁴³ Aaron S. Kesselheim & Jerry Avorn, *New "21st Century Cures" Legislation: Speed and Ease vs. Science*, 317 JAMA 581, 582 (2017).

will fare under the Cures Act, with the potential that they will now be exposed to treatments and devices that have not been adequately tested and whose risks and safety concerns are not completely known. There are concerns that the intrusion of less rigorous data, such as patient experience data into the review process will erode trust in the FDA's approval process.

One of the biggest issues with the Cures Act's provisions on evidentiary standards for drug approvals, however, can be viewed through the lens of the current framework for drug recalls and through an analysis of the FDA's effectiveness and diligence in adequately monitoring post-market approval studies. The stand-alone drug provisions in the Cures Act by themselves are controversial, but coupled with a slow and lengthy drug recall process, and inadequate post-market approval studies by the FDA, the problem is magnified. Provisions like the ones in the Cures Act that speed up drug approvals demand urgent mechanisms for addressing the ramifications that can result from approvals based on less reliable data. Currently, the FDA's mechanisms for addressing drugs that pose risks after approval are inadequate.¹⁴⁴ If a drug that has been approved based on using the methods in the Cures Act presents danger, the "back-end" procedures must be in alignment with the "front-end" procedures, ensuring that the drug can be removed quickly, or that the manufacture can remedy the problem before it causes more harm.¹⁴⁵

For low-income patients, the Cures Act will even pose more of a risk.¹⁴⁶ Physicians, who are given samples by drug companies, often give low-income patients these samples for free.¹⁴⁷ While this seems at first glance a controversial practice, it is also a means by which low-income patients can access drugs that may help them that would otherwise be unavailable to them.¹⁴⁸ However, the main dilemma is that the free samples tend to be drugs that have been

¹⁴⁴ Kesselheim et al., *supra* note 62, at 5.

¹⁴⁵ *See id.*

¹⁴⁶ Katie McDonough, *This Health Care Bill Congress Is about to Pass Seems Too Good to Be True. That's Because It Is.*, FUSION (Dec. 1, 2016, 4:45 PM), <http://fusion.net/story/373229/21st-century-cures-act-fda-danger/>.

¹⁴⁷ *Id.*

¹⁴⁸ *Id.*

newly approved.¹⁴⁹ According to Dr. Reshman Ramachandran, an assistant scientist at the Johns Hopkins Bloomberg Institute of Public Health,

The concern [I have], especially for underserved populations, is that the things we have in our back pocket—through sample closets or discount cards—would be approved based on a lower standard,” she said. “It’s a bad mix—giving our underserved populations access to potentially unsafe and ineffective drugs.¹⁵⁰

Approvals under the Cures Act will put an already disadvantaged population in harm’s way, posing both safety and ethical implications.

Beyond safety and efficacy concerns, the bill also raises other dilemmas, including financial waste. If treatments are not adequate and rigorously tested and lack strong scientific support, insurers may potentially dole out resources for treatments that may prove later to be medically ineffective.¹⁵¹ Relatedly, many proponents of relaxed regulatory burdens on drugs entering the market argue that doing so will actually bring down the alarmingly high costs of prescription drugs.¹⁵² Their argument follows that introducing multiple drugs into the market that treat the same condition will create competition and decrease prices.¹⁵³ However, this has not

¹⁴⁹ *Id.*

¹⁵⁰ *Id.*

¹⁵¹ Alan M. Garber, *Evidence-Based Coverage Policy*, 20 HEALTH AFFAIRS 62, 66–67 (2001).

¹⁵² Maura A. Calsyn & Thomas Huelskoetter, *The FDA is Not the Problem: Why Undermining the Drug Approval Process is Not the Answer to High Drug Prices*, CTR. FOR AM. PROGRESS (Mar. 9, 2016, 2:38 PM), <https://www.americanprogress.org/issues/healthcare/reports/2016/03/09/132850/fda-is-not-the-problem/> (“Even if there were no concerns that these reforms increase risks to patients, there is little reason to believe that pushing new branded drugs to market would guarantee meaningful price reductions in the absence of generic competition. Newly approved drugs enjoy patent and marketing exclusivity that limit competition, and manufacturers continue to set prices based on what they think the market will bear, not the drug’s value to patients.”).

¹⁵³ *Id.*

been the case.¹⁵⁴ On a similar note, expedited drug approval and development also will result in financial waste of government resources.¹⁵⁵

The Cures Act may also present opportunity for product liability suits when persons are harmed by taking a drug that has been approved based on less rigorous data. This problem is particularly amplified in light of the public's general misconception regarding FDA approval to begin with.¹⁵⁶ Many patients do not fully understand what the FDA's "seal of approval" means.¹⁵⁷ According to a study by researchers regarding the meaning of FDA approval, patients had several misconceptions about FDA approval, including, (1) that the FDA approves only those drugs that are extremely effective, (2) that the FDA does not approve drugs with serious side effects, and (3) that the FDA only allows those drugs that are 'extremely effective' to be advertised.¹⁵⁸ The general problem seems to be that FDA approval is demonstrative of efficacy level certification.¹⁵⁹ The public's trust in "FDA approval" may be sorely misplaced when FDA approval processes under the Cures Act accept less rigorous data, a fact which consumers may be unaware of.

Finally, another concern surrounds the question of what the Cures Act means for the direction of regulation moving forward and the legitimacy of the FDA. In an era in which the current administration has already taken a strong approach towards deregulation,¹⁶⁰ the safety and effectiveness of drugs remains an

¹⁵⁴ *Id.* at 9 ("For instance, although 11 major drug alternatives to treat multiple sclerosis have entered the market over the past two decades, all of them are priced in roughly the same high-cost range. These manufacturers have not attempted to undercut each other's prices in order to gain market share").

¹⁵⁵ Kesselheim et al., *supra* note 62, at 5.

¹⁵⁶ Jonathan J. Darrow, *Pharmaceutical Gatekeepers*, 47 IND. L. REV. 363, 387 (2014).

¹⁵⁷ *Id.*

¹⁵⁸ *Id.*

¹⁵⁹ *Id.* at 388.

¹⁶⁰ Katie Thomas, *Trump's FDA Pick Could Undo Decades of Drug Safeguards*, N.Y. TIMES (Feb. 5, 2017), https://www.nytimes.com/2017/02/05/health/with-fda-vacancy-trump-sees-chance-to-speed-drugs-to-the-market.html?_r=0.

issue. The Trump Administration's executive order, promulgating that for every new government regulation, the government must get rid of two existing regulations, also presents significant uncertainty about the implementation of the Cures Act, particularly as to how much its implementation will be delayed.¹⁶¹ The Cures Act's representation of a continued trend towards lax regulation may very well undermine the objective of the FDA: to promote and protect public health.

On the other hand, the FDA's management of the clinical trial process has also been imperfect and demands the agency's attention.¹⁶² In a 2015 study, researchers found that the FDA was not transparent in communicating findings to the scientific community about deviations from "good clinical practice and research misconduct" the FDA discovered from inspecting clinical sites doing research on human participants, resulting in reliance on data from faulty clinical trials.¹⁶³

VI: CONCLUSION

While the FDA drug approval process could benefit from reforms that might bring therapies to the market quicker, the provisions in the Cures Act may run counter to their very intent: to give patients access to *effective* drugs and therapies and to

¹⁶¹ Sheila Kaplan, *Trump Order on Regulations Could Create Hurdles for FDA, Cures Act*, STAT (Jan. 30, 2017), <https://www.statnews.com/2017/01/30/fda-regulations-executive-order-trump/>.

¹⁶² Charles Seife, *Research Misconduct Identified by the US Food and Drug Administration*, JAMA 637 (2014).

¹⁶³ *Id.* ("Fifty-seven published clinical trials were identified for which an FDA inspection of a trial site had found significant evidence of 1 or more of the following problems: falsification or submission of false information, 22 trials (39%); problems with adverse events reporting, 14 trials (25%); protocol violations, 42 trials (74%); inadequate or inaccurate recordkeeping, 35 trials (61%); failure to protect the safety of patients and/or issues with oversight or informed consent, 30 trials (53%); and violations not otherwise categorized, 20 trials (35%). Only 3 of the 78 publications (4%) that resulted from trials in which the FDA found significant violations mentioned the objectionable conditions or practices found during the inspection. No corrections, retractions, expressions of concern, or other comments acknowledging the key issues identified by the inspection were subsequently published.").

encourage innovation. Drugs that have not undergone the rigors of the usual FDA process characterized by the controlled clinical trial present significant safety risks to the patients the agency is tasked with protecting. Further, allowing drugs to be approved based on less rigorous standards delays the development of other drugs that *have* undergone the rigors of a controlled clinical trial and are more likely to pose less safety and efficacy issues for patients.

Real-world evidence, drug development tools like biomarkers, and patient experience data have presented benefits that the clinical trial itself cannot achieve, including flexibility, ease in generating data, and cost-cutting results. However, none of these can serve as substitutes for controlled clinical trials, even with their imperfections.

Until the current system of drug recalls is improved and post-marketing approval studies are better monitored and conducted, further loosening of drug approvals standards will not solve the problem of stifled drug development and innovation. If the trend to reduce burdens upon drug sponsors when initially approving a drug continues, then removal procedures must be proportional in order to ensure that potentially unsafe and ineffective drugs can be removed from the market. Additionally, reducing evidentiary burdens for drug approvals presents a host of other issues, not limited to privacy, ethical, financial, and reimbursement-related concerns.

The FDA must balance two competing interests: (1) ensuring that patients—especially those who are in dire situations—can access effective drugs and treatments, where other therapies or alternatives might not exist, and (2) at the same time, ensuring that the safety and effectiveness of drugs are not being compromised simply for speed. In the end, the FDA is presented with the quality versus quantity and access dilemma and must remember to stay true to its objectives.