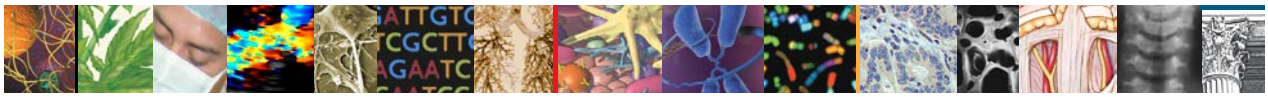

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Perspective

The 21st Century Cures Act — Will It Take Us Back in Time?

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In May 2015, the 21st Century Cures Act was introduced in the U.S. House of Representatives, with the goal of promoting the development and speeding the approval of new drugs and devices.[1] Championed by the pharmaceutical, biotechnology, and device industries, the bill was approved unanimously (51 to 0) in committee and continues to be debated. If enacted into law, some of its provisions could have a profound effect on what is known about the safety and efficacy of medical products, as well as which ones become available for use.

Some aspects of the bill could indeed enhance the development of and access to new drugs. The legislation calls for annual increases in the stagnating budget for the National Institutes of Health (NIH) amounting to about 3% per year for 3 years when adjusted for inflation. It would also provide an additional $2 billion per year for 5 years to create an "NIH Innovation Fund." Together, this support would help counteract the effects of sequestration and budget cuts that have reduced the purchasing power of the NIH to its lowest level in years. Given the crucial role that NIH-funded research plays in generating the findings on which so many new drugs are based,[2] this boost would be a welcome development. Another useful provision could make deidentified data from NIH-funded clinical trials more available to researchers.

Other proposed changes could lead to less salutary outcomes for patients and the health care system. An underlying premise of the bill is the need to accelerate approval for new products, but this process is already quite efficient. A third of new drugs are currently approved on the basis of a single pivotal trial; the median size for all pivotal trials is just 760 patients. More than two thirds of new drugs are approved on the basis of studies lasting 6 months or less[3] — a potential problem for medications designed to be taken for a lifetime. Once the Food and Drug Administration (FDA) starts its review, it approves new medications about as quickly as any regulatory agency in the world, evaluating nearly all new drug applications within 6 to 10 months, an impressive turnaround for such complex assessments.

Nonetheless, as introduced, the 21st Century Cures Act instructs the FDA to consider nontraditional

study designs and methods of data analysis to further speed approvals. Adaptive trial designs and the use of Bayesian methods hold promise in some kinds of evaluations, particularly in oncology. However, more problematic proposals include encouraging the use of "shorter or smaller clinical trials" for devices and the request that the FDA develop criteria for relying on "evidence from clinical experience," including "observational studies, registries, and therapeutic use" instead of randomized, controlled trials for approving new uses for existing drugs. Although such data can provide important information about drug utilization and safety once a medication is in use, there is considerable evidence that these approaches are not as rigorous or valid as randomized trials in assessing efficacy.

The bill would also encourage the FDA to rely more on biomarkers and other surrogate measures rather than actual clinical end points in assessing the efficacy of both drugs and devices. The FDA already uses surrogate end points in about half of new drug approvals.[3] Some biomarkers are accurate predictors of disease risk and can be useful measures of the efficacy of a new drug (such as low-density lipoprotein cholesterol for statins). But though a drug's effect on a biomarker can make approval quicker and less costly, especially if the comparator is placebo, it may not always predict the drug's capacity to improve patient outcomes. Bevacizumab (Avastin) delayed tumor progression in advanced breast cancer but was shown not to benefit patients. Similarly, rosiglitazone (Avandia) lowered glycated hemoglobin levels in patients with diabetes even as it increased their risk of myocardial infarction. In 2013, patients began to receive a new drug for tuberculosis approved on the basis of a randomized trial relying on a surrogate measure of bacterial counts in the sputum — even though patients given the drug in that trial had a death rate four times that in the comparison group, mostly from tuberculosis.[4] These provisions in the legislation would not immediately change FDA approval standards, but they would give the agency greater discretion, backed by congressional support, to approve drugs on the basis of less rigorous data.

The proposed legislation would make immediate changes with respect to new antibiotics and antifungals by enabling their approval without conventional clinical trials, if needed to treat a "serious or life-threatening infection" in patients with an "unmet medical need." In place of proof that the antimicrobial actually decreases morbidity or mortality, the FDA would be empowered to accept nontraditional efficacy measures drawn from small studies as well as "preclinical, pharmacologic, or pathophysiologic evidence; nonclinical susceptibility and pharmacokinetic data, data from phase 2 clinical trials; and such other confirmatory evidence as the secretary [of health and human services] determines appropriate to approve the drug." Antimicrobials approved in this manner would carry disclaimers on their labeling, but there is no evidence that such a precaution would restrict prescribing to only the most appropriate patients. If passed in its current form, the bill would also provide hospitals with a financial bonus for administering costly new but unproven antibiotics, which could encourage their more widespread use. The bill gives the secretary of health and human services the authority to expand this nontraditional approval pathway to other drug categories as well, if "the public health would benefit from expansion."

The 21st Century Cures Act goes still further in altering the requirements for approving medical devices — an area long criticized for lack of rigor as compared with drug evaluations,[5] though regulatory oversight has improved in recent years. As proposed, the new law would redefine the evidence on which high-risk devices can be approved to include case studies, registries, and articles in the medical literature, rather than more rigorous clinical trials. Another section would allow device makers to pay a third-party organization to determine whether the manufacturer can be relied on to assess the safety and effectiveness of changes it makes to its devices, in place of submitting an application to the FDA. Thus certified by the external company, a device maker would be authorized to continue to assess its own products on an ongoing basis.

Informed consent by patients in drug trials has traditionally been sacrosanct, with exceptions made only when consent is impossible to obtain or contrary to a patient's best interests. But another clause in the proposed law adds a new kind of exception: studies in which "the proposed clinical testing poses no more than minimal risk" — a major departure from current human subject protections. It is not clear who gets to determine whether a given trial of a new drug poses "minimal risk."

Embedded in the language of the 21st Century Cures Act are some good ideas that could streamline the development and evaluation of new drugs and devices; its call for increased NIH funding may prove to be its most useful component. But political forces have also introduced other provisions that could lead to the approval of drugs and devices that are less safe or effective than existing criteria would permit.

Over the past 80 years, this country's regulatory approach has embraced steadily improving criteria for accurately assessing therapeutic efficacy and risk. Patients and physicians would not benefit from legislation that instead of catapulting us into the future, could actually bring back some of the problems we thought we had left behind in the 20th century.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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The 21st Century Cures Act

TO THE EDITOR: In their Perspective article (June 25 issue),[1] Avorn and Kesselheim argue that the 21st Century Cures Act, which is currently being debated in Congress, would lower the regulatory standards of the Food and Drug Administration (FDA) by giving it greater discretion to approve drugs on the basis of less rigorous data. In particular, the authors argue that the legislation would authorize the FDA to "rely" on observational analyses, which are less rigorous than random-

ized controlled trials (RCTs). But the Cures Act does not diminish the FDA's standards for requiring that new medical products are safe and effective. Rather, it recognizes that recent developments in genomics, systems biology, electronic data systems, and other fields can provide additional tools and resources to support better premarketing and postmarketing regulation and more efficient development of drugs and medical devices.

The authors note that the FDA now relies on evidence beyond RCTs. Patients with coexisting conditions or rare diseases are not studied much in traditional RCTs; further progress in precision medicine is likely to make RCTs even more difficult. The Cures Act facilitates the use of new types of evidence, enabling a more comprehensive understanding of risks and benefits for particular patients. The authors argue that such uses of adaptive trials, Bayesian statistics, biomarkers and surrogate end points, and data from postmarketing registries and surveillance systems will adversely affect the FDA's ability to approve safe and effective drugs. However, as the authors state, such tools have been valuable in many situations. For example, progress in therapies for the human immunodeficiency virus and the hepatitis C virus reflects the use of validated biomarkers. The point of the legislation on biomarkers is to develop better evidence on other markers that could be valuable for evaluating treatments for currently unmet needs. Similarly, the point of developing better evidence on patient-reported outcomes, and better systems for studying clinical experience, is to better assess the disease experience of particular groups of patients.

As such, the legislation's provisions can increase the feasibility, efficiency, and influence of RCTs by enabling them to be better targeted and more effectively designed — and perhaps to be carried out in more routine clinical practice. The law empowers the FDA to use its expertise to guide the development of better science for the regulation of medical products.

Better evidence and up-to-date regulatory science are the best foundation for regulatory decisions and meaningful progress in biomedical innovation. They are also the best way to avoid turning back the clock on new opportunities to develop safe and effective treatments for unmet medical needs.

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Dr. McClellan reports serving on the board of directors of Johnson & Johnson. No other potential conflict of interest relevant to this letter was reported.

1. Avorn J, Kesselheim AS. The 21st Century Cures Act — will it take us back in time? N Engl J Med 2015;372:2473-5.

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TO THE EDITOR: Avorn and Kesselheim raise concerns about the 21st Century Cures Act, a bipartisan piece of legislation with provisions for billions in additional funding for the National Institutes of Health (NIH), as well as a section on the use of biomarkers as surrogate end points. It is important to note that the FDA's standards are not altered by the bill. Rather, the bill will create a solid scientific framework for the use of biomarkers for drug development.

Biomarkers can be precise and accurate measures of disease and efficacy. Phenylalanine, for example, is strongly associated with a decline in IQ in patients with phenylketonuria. But IQ as an end point can take years to observe and can be difficult to measure. Without the biomarker end point, phenylketonuria treatments based on IQ would not be developed.[1]

The use of qualified biomarkers as surrogate end points is crucial for quickly bringing therapies to patients with rare diseases.[2] The 21st Century Cures Act provides hope to millions of patients who for too long have surrendered their lives to devastating rare diseases.

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TO THE EDITOR: We agree with Avorn and Kesselheim that increased funding for the NIH in the 21st Century Cures initiative is a highly needed step. However, we disagree with their opposition to the Limited Population Antibacterial Drug (LPAD) approval pathway, also in the legislation, which facilitates the evaluation of new antibiotics for serious infections for which current therapies are inadequate. Every year, at least 2 million Americans contract antibiotic-resistant infections, and 23,000 die.[1] For many of these infections, the limited number of patients and lack of appropriate comparator therapies make standard clinical trials impractical. The LPAD pathway was recommended by the President's Council of Advisors on Science and Technology.[2] This pathway is also supported by the Infectious Diseases Society of America (IDSA), representing more than 10,000 physicians and scientists.[3] Antibiotics studied as proposed in the Cures bill would be approved only for that specific, limited population, similar to drugs for orphan diseases. Concerns expressed about approving potentially riskier drugs must be balanced against the greater risk of not being able to provide the antibiotics desperately needed by patients.

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Dr. Calderwood reports serving as the current president of the IDSA, having served on the scientific advisory boards of Pulmatrix and PharmAthene and holding stock in Pulmatrix and stock options in PharmAthene. Dr. Murray reports serving as the immediate past president of the IDSA, receiving consulting fees from Rib-X Pharmaceuticals, GlaxoSmithKline, Theravance, and the Innovative Medicines Initiative, and serving as a coinvestigator on research funding provided to her institution by Astellas Pharma, Cubist Pharmaceuticals, Forest Laboratories, and Theravance. Dr. Chambers reports serving as the chair of the Antimicrobial Resistance Committee of the IDSA, receiving consulting fees from Cubist Pharmaceuticals, AstraZeneca, Theravance, and Pfizer, holding stock from Merck, and serving as an investigator in research funded by Cubist Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: McClellan and Sigal contend that 21st Century Cures "does not diminish the FDA's standards," but that is not true. Several provisions codify lower approval standards: section 2062 instructs the FDA to develop a process to approve new uses for existing drugs on the basis of lower-quality evidence than that provided by clinical trials, including "experience," "observational studies," and "registries"; section 2222 permits approval of high-risk devices on the basis of case studies of patients or poorly conducted studies, as long as they are published in a journal; and section 2121 appears to encourage the approval of antimicrobials and antifungals on the basis of effects observed in laboratory tests or preliminary studies involving small numbers of patients.[1] Section 2121 also permits the secretary of health and human services to apply this bypass track to other drug categories if "public health would benefit," language open to abuse by future administrations inclined to further reduce FDA authority. Of course regulatory flexibility is warranted to address urgent unmet needs, but the FDA already has this authority[2] and uses it frequently.[3] Once Congress starts providing detailed instructions for altering the FDA processes used to scientifically evaluate products (an odd proposition at best), such guidance could become standard practice beyond the uncommon instances in which these approaches' benefits may outweigh their risks.

We agree with Kakkis and Bronstein that high-quality biomarkers can be essential for approving new drugs, particularly for rare diseases. However, the FDA can already approve new drugs on this basis, as it approved sapropterin (Kuvan) for phenylketonuria on the basis of its effect on blood phenylalanine levels. What's needed is research to discover and validate more such biomarkers, a prospect the bill advances only marginally, with its modest proposed increase in NIH funding. By contrast, pushing the FDA to approve drugs

on the basis of biomarkers that are not rigorously linked to patient outcomes, as other provisions do, can hurt patients by exposing them to ineffective or unsafe treatments,[4] wasting resources, and giving false hope.

Calderwood et al. do not adequately consider the likelihood of substantial off-label use of antibiotics approved through the proposed "limited population" pathway, already common practice with certain drugs approved only for limited populations.[5] Few clinical situations warrant authorizing physicians to prescribe antibiotics not known to improve clinical outcomes. Such a policy for antibiotics would be particularly self-defeating, since it would induce resistance to those drugs and to other, related drugs. A better solution would be to encourage the enrollment of patients with serious infections in trials of investigational antibiotics to offer the chance of treatment even as we advance the understanding of the medications.

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Since publication of their article, the authors report no further potential conflict of interest.

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