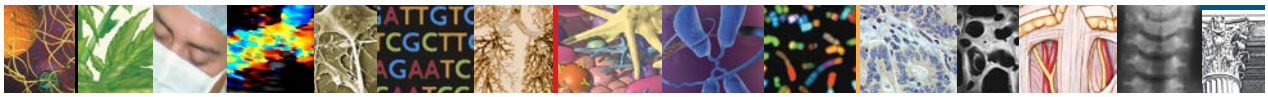

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JUNE 25, 2015

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.

An audio interview with Dr. Avorn is available at NEJM.org

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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This article was published on June 3, 2015, at NEJM.org.

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DOI: 10.1056/NEJMp1506964

Medical Facts versus Value Judgments — Toward Preference-Sensitive Guidelines

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The radiation oncologists apologetically informed us that they would not be able to offer my wife Paula a sixth week of treatment — a "boost" therapy aimed at the place where her breast cancer had resided before she received her lumpectomy. This tumor bed was no longer localizable, because Paula had received immediate reconstruction that had obscured its location. I was aghast. Although Paula would receive 5 weeks of whole-breast irradiation, she would not receive the benefits of that final week of treatment, the boost therapy that, according to National Comprehensive Cancer Network (NCCN) guidelines, is "recommended" for women like Paula, whose breast cancer is diagnosed before they are 50 years of age and who have axillary involvement.[1]

After the radiation oncology appointment, I obtained the main clinical trial that had established the value of boost therapy[2] and looked for the survival curves that corresponded to the size and location of Paula's tumor. I could see how much boost therapy would have reduced her chance of local recurrence. But I could also see the downside of this treatment, which increased the risk of breast fibrosis. It made me wonder: how did the NCCN come to so definitively recommend boost therapy for women like my wife?

A couple of years later, I stood in front of an audience of radiation oncologists, presenting a lecture on shared decision making. I asked them to imagine that they faced a choice between two types of radiation therapy for early-stage breast cancer. The first treatment would leave them with a 15% chance of local recurrence and a 10% chance of moderate or severe breast fibrosis. The second treatment would leave them with only an 8% chance of local recurrence but a 30% chance of moderate or severe fibrosis. The radiation oncologists raised their hands in almost equal numbers for the two treatments. Some believed the higher risk of fibrosis was unacceptable, given the treatability of most local recurrences, whereas others believed the trauma of recurrence outweighed the discomfort of fibrosis.

This division of opinion was not completely surprising. Often medical facts — such as data on rates of cancer recurrence versus rates of fibrosis — don't point toward an objectively superior