To: Collaboration for Research Integrity and Transparency at Yale  
From: Collaboration for Research Integrity and Transparency at Yale  
Date: October 31, 2016  
Re: The House 21st Century Cures Act and the Senate Medical Innovation Bills

The Collaboration for Research Integrity and Transparency (CRIT) is a joint initiative of Yale Law School, Yale School of Public Health, and Yale School of Medicine. Our mission is to promote health by improving the integrity and transparency of biomedical and clinical research. We are dedicated to ensuring that the evidence base for medical products is complete, accurate, and available for scientific and public health inquiry.

The House’s 21st Century Cures bill attempts to overhaul the FDA’s regulation of medical products with the underlying objective of accelerating approval for drugs and devices. We prepared this memorandum for Eric Anthony at Senator Chris Murphy’s office to identify provisions in the 21st Century Cures bill (and any companion provisions in the Senate bills) that would weaken the FDA’s regulation of drugs and devices and could lead to less safe and effective medical products on the market.

21st Century Cures weakens the FDA’s regulation of medical devices

1. Priority review for “breakthrough” devices

   Section 2201 expands the expedited pathways program for “breakthrough” devices, which would permit the FDA to approve more devices through a less stringent review process. The provision broadens the definition for “breakthrough” and encourages the FDA to rely on “shorter or smaller clinical trials” and “surrogate endpoints.” The Senate’s Advancing Breakthrough Medical Devices for Patients Act (S. 1077) is the companion bill for this provision. The Senate’s bill has a vague definition for “breakthrough” and raises similar concerns of allowing more devices to qualify for expedited review.[1] Research shows that drugs billed as “breakthrough” have often not been clinically effective, and it is critical that a breakthrough designation for medical devices is reserved for those devices that are truly transformative and beneficial technologies.[2]

2. Weaker scientific standards for the approval of high-risk devices

   Section 2222 permits the FDA to approve high-risk devices on the basis of less rigorous evidence, such as case studies (i.e. anecdotal evidence), registries, and medical journal articles. While it is impossible to discover all safety concerns before a device is marketed, conducting controlled clinical trials helps to ensure that there is adequate evidence of safety and effectiveness. Pressuring the FDA to rely on uncontrolled studies or journal articles could...
prevent the FDA from learning and assessing important safety risks.[3] The potential harm to patients is greater when taking into account that many high-risk devices are permanently implanted and their removal can be difficult and possibly dangerous. There is no companion provision in the Senate bills.

3. Third-party assessment for device changes

Section 2221 allows devices makers to select and pay a nongovernmental third-party to certify that changes to devices are safe and effective, in lieu of submitting an application to the FDA. Such a system creates a conflict of interest and makes it difficult for physicians and patients to trust the safety or effectiveness of modified devices.[3] Device makers could make changes to even the highest risk medical devices (such as artificial heart valves) without first notifying the FDA or demonstrating to the FDA that the modified device remains safe and effective.[4] According to an FDA report from 2012, the use of third-party review for medical devices in Europe has resulted in unsafe devices on the market that were not approved for distribution in the U.S.[5] There is no companion provision in the Senate bills.

21st Century Cures encourages the use of less rigorous evidence to approve new drugs and new uses for drugs

1. “Patient experience data”

Section 2001 requires the FDA to establish a process for using “patient experience data” in the risk-benefit assessment for new drug approvals. The provision sets forth a broad definition for “patient experience data” – essentially any information on the impact of a disease or therapy on patients’ lives. While patient experience is valuable for contextualizing the risks and benefits of a drug, it should not be a substitute for well-designed and controlled clinical studies.[6,7] The FDA’s recent approval of Sarepta’s Duchenne Muscular Dystrophy drug Eteplirsen provides an example of the controversies arising from approving a costly new drug due to external pressures from patient groups despite the lack of strong clinical evidence.[8] The Senate’s Patient-Focused Impact Assessment Act of 2016 (S. 1597) is the companion bill for this provision.

2. “Evidence from clinical experience”

Section 2062 requires the FDA to develop criteria for relying on “evidence from clinical experience” for the approval of new uses or satisfying post-market study requirements. The provision describes clinical experience evidence as data about a drug derived from sources other than randomized clinical trials, such as “observational studies, registries, and therapeutic use.” Although evidence from clinical settings provides valuable information and can guide the design of more rigorous trials, research shows that these approaches are not as valid as randomized controlled trials for assessing the safety and effectiveness of a drug’s specific use.[6] There is no companion provision in Senate bills.

3. Biomarkers and surrogate measures
Section 2021 and Section 2022 encourage the FDA to rely more on biomarkers and other surrogate measures, rather than actual clinical end points, in assessing the efficacy of drugs and devices, even those that are not for serious or life-threatening conditions. While some biomarkers are accurate indicators of disease risk and useful for assessing the efficacy of drugs, they do not always predict patient outcomes.[6,7]

21st Century Cures weakens the FDA’s approval standards for antibiotics while increasing financial incentives for hospitals to use costly new antibiotics

Section 2121 permits the FDA to approve antibiotics and antifungals without conventional clinical trials, if they are intended to treat “serious or life-threatening infection[s]” in patients for which there is “unmet medical need.” Rather than requiring clinical evidence that the antibiotic decreases morbidity or mortality, the FDA would be able rely on “alternate endpoints” and grant approval on the basis of preclinical data or data from phase 2 clinical trials (which generally consist of only a few hundred participants). While an antibiotic approved through this “limited population pathway” must contain a disclaimer in its labeling, there is the risk that the drug could be prescribed and marketed for a wider population.[6,7] Furthermore, the provision grants the FDA the authority to expand the “limited population pathway” to other categories of drugs intended to treat serious or life-threatening conditions. Such a provision encourages the approval of new drugs where the risks are not fully understood and where the benefits are not proven by reliable evidence.

Section 2123 provides a financial bonus to hospitals for administering costly new antibiotics. Antibiotic resistance, largely driven by an overuse of antibiotics, has been recognized as a global threat to public health.[9] Approving new antibiotics and antifungals through a less stringent expedited pathway and then encouraging their widespread use would drive up healthcare costs and accelerate the rise of antibiotic-resistant infections.[4,7]

The Senate’s Promise for Antibiotics and Therapeutics for Health Act (S.185 §§3-4) contains the companion provision for Section 2121 (“limited population pathway”), but there is no companion provision in the Senate bills for Section 2123 (financial incentives for hospitals to use new antibiotics).
Sources:


