May 19, 2015

Dear Members of the United States House of Representatives:

The undersigned organizations represent healthcare providers, clinical researchers, public health experts, and consumer advocates. We thank you for this opportunity to comment on the 21st Century Cures draft legislation. Acknowledging the need for increased discovery, development, and distribution of new treatments for a variety of diseases, **we are concerned that the proposed legislation as written fails to ensure a comprehensive and scientifically based approach that supports patients' access to affordable treatments**. Instead, the draft legislation would allow for unsafe and ineffective drugs and medical devices to enter the market while further limiting access to effective medicines for patients.

Although we strongly support increases in funding for the National Institutes of Health (NIH), this positive component of the draft legislation comes at the expense of too many provisions that we cannot support. Moreover, the authorization of NIH funding increases does not guarantee the appropriation of such funds.

Rather than addressing the true scientific bottleneck in drug and device development, the bill includes unnecessary, costly, and potentially harmful regulatory changes and financial incentives for pharmaceutical and medical device companies that would put patient safety at risk and undermine public health. **We therefore are unable to support the current version of the 21st Century Cures Draft legislation.**

Our specific concerns regarding the 21st Century Cures draft legislation are as follows:

1. **21st Century Cures would further undermine the FDA's ability to ensure the safety and efficacy of medical devices (Sections 2222 and 2221).**

   Section 2222 would allow for new high-risk medical devices to be approved by the FDA based on case studies or medical journal articles alone. High-risk devices should not be approved on the basis of uncontrolled case studies of just one, two, or even a series of patients (in essence, clinical anecdotes). Medical journal articles often leave out critical information because of space limitations or because concerns that admitting shortcomings in study design or conduct will make it difficult to get the article published. A recent study found that out of 78 clinical trials for which FDA inspectors identified significant research misconduct (including involving submission of false information), the associated journal article reported the misconduct in only three cases.[1] Journal editors and peer reviewers rely on the accuracy and integrity of the authors; they do not examine raw data or inspect clinical trial sites. Given this lack of oversight, it is not surprising that a disturbing number of articles

[1] Seife C, Research misconduct identified by the US Food and Drug Administration: Out of sight, out of mind, out of the peer-reviewed literature. *JAMA Intern Med.* doi:10.1001/jamainternmed.2014.7774. Published online February 9, 2015.

are later found to be inaccurate, misleading, or fraudulent.[2] FDA reliance on journal articles as the sole basis for device approvals, as permitted under Section 2222, could prevent the FDA from learning of important problems with clinical testing, which could lead to serious patient harm.

In addition, Section 2221 would allow companies to make changes to even the highest-risk devices (like artificial heart valves) without first notifying the FDA or documenting that the modified device remains safe and effective. Instead, device manufacturers would pay third-party contractors to certify that the manufacturer had an adequate "quality system," after which the manufacturer would be authorized to determine for itself whether each device remained safe and effective following important changes. Changes to high-risk devices can be dangerous, as illustrated by recent cases of massive bone and tissue damage caused by changes to the materials used in certain "metal on metal" hip implants.[3] These changes should not be exempted from FDA oversight.

2. 21st Century Cures would allow for antibiotics and antifungals to be approved based on lower FDA standards, putting patients at risk of being treated with unsafe and ineffective drugs (Section 2121).

Included in the legislation is the ***Antibiotic Development to Advance Patient Treatment (ADAPT) Act*** (Section 2121), which presents a fast-track pathway for FDA drug approval based on surrogate clinical endpoints and data from animals, test tubes, mathematical modeling, and small, early-stage clinical trials in humans with diseases, rather than larger, later-stage trials. Results from clinical trials based on surrogate clinical endpoints must be confirmed with phase III trial data. Data from non-clinical trials or early, small-scale clinical trials can offer misleading evidence of efficacy or miss important safety risks. Approving antibiotics based solely on this evidence violates the FDA's mission to protect public health by ensuring the safety and efficacy of these drugs. The provision could also allow the FDA to approve drugs based on preclinical data that actually show the drugs to be inferior to existing drugs. Drugs approved by the FDA should improve efficacy and/or decrease harm to patients, and/or otherwise meaningfully improve therapy.

FDA regulations already give the agency the authority to expedite drug approval for limited, well-defined sets of patients. Studies have shown that more than half of all newly approved novel drugs already receive the benefit of at least one special expedited development or review designation, making another pathway unnecessary.[4] In fact, compared to other drug classes, antibiotics already have a higher rate and speed of approval.[5] In addition, the agency has just issued a new draft guidance to expedite the "compassionate use" of investigational drugs for individual patients. Physicians can make requests far more readily than in the past

---

[2] Many of these issues, including inaccuracies, misleading information, and fraud, have been documented by bloggers Adam Marcus and Ivan Oransky on the blog: Retractionwatch.com.

[3] Meier B, Concerns over "metal on metal" hip implants. New York Times. March 3, 2010. http://www.nytimes.com/2010/03/04/health/04metalhip.html. Accessed May 19, 2015.

[4] Kesselheim, A. S., & Darrow, J. J. (2015). FDA Designations for Therapeutics and Their Impact on Drug Development and Regulatory Review Outcomes. *Clinical Pharmacology & Therapeutics*, *97*(1), 29-36.

[5] DiMasi, J.A., Success rates for new drugs entering clinical testing in the United States. Clin Pharmacol Ther, 1995. 58(1): p. 1-14.

for individual patients with unmet medical needs who are willing to take an informed risk while the drugs are still being studied for the wider public. Patients can obtain access quickly through these expanded access pathways while waiting for appropriate clinical trials data to be obtained. This mechanism protects the broader public.

As ADAPT would fail to truly address antibiotic resistance and would lower FDA standards for approving antibiotics and antifungals, resulting in harm to patients, we strongly urge you to withhold your support for this legislation. Instead, we urge you to consider a broader, more effective approach such as that in the newly-released House bill, the ***Helping Effective Antibiotics Last*** **(HEAL) Act**, sponsored by Representatives DeLauro, Slaughter, and Meng.

3. 21st Century Cures could introduce serious conflicts of interest into the process for defining when bacteria are considered to be antibiotic-resistant, promoting overuse and misuse of new antibiotics and accelerating development of resistance to new antibiotics (Section 2122).

ADAPT also would allow susceptibility testing of breakpoints for antibiotic resistance to be determined by a "nationally or internationally recognized standard development organization" which may include members that have disclosed potential financial conflicts of interest or ties to the pharmaceutical industry. The statute requires only that the standard development organization establish and maintain "procedures to address potential conflicts of interest and ensure transparent decision-making," but does not bar conflicted members. Since many conflict of interest policies merely require disclosure of conflicts, but do not bar conflicted members from serving, this language could allow key decisions to be made by a committee for which the majority of members have disclosed potential financial conflicts of interest. For example, currently, 11 of the 14 members of the Subcommittee on Antimicrobial Susceptibility Testing at the Clinical and Laboratory Standards Institute (CLSI), an organization likely to be selected under the proposed new provision, have reported financial conflict of interest. In fact, four out of the 14 members of the subcommittee are pharmaceutical industry employees. This organization has been criticized for adopting antimicrobial susceptibility criteria that expand the definition of "antibiotic resistance" to dramatically increase the use of newer, broader-spectrum antibiotics while offering no improvement in clinical outcomes.[6]

Shifting the goalposts of defining antibiotic resistance in this way would lead paradoxically to greater resistance, by encouraging the unnecessary, increased use of these broader-spectrum antibiotics that should instead be reserved for infections against which they are truly needed. Rather than delegate this work to a committee mainly comprised of conflicted members, the legislation should require that the process for determining antimicrobial susceptibility criteria be transparent, independent of financial conflict of interest, and based on patient-centered outcomes from clinical studies.

---

[6] Tamma PD, Wu H, Gerber JS, Hsu AJ, Tekle T, Carroll KC, Cosgrove SE. "Outcomes of Children with Enterobacteriaceae Bacteremia with Reduced Susceptibility to Ceftriaxone: Do the Revised Breakpoints Translate to Improved Patient Outcomes?" Pediatr Infect Dis J 32, no. 9 (2013): 965-9. http://www.ncbi.nlm.nih.gov/pubmed/23470679. Accessed May 19, 2015.

4. **21st Century Cures would weaken the reporting requirements under the Physician Payment Sunshine Act, allowing for secret influence from pharmaceutical and medical device companies on the practice of medicine and medical education (Section 3041).**

   Section 3041 of the bill would create an exemption under the Physician Payment Sunshine Act for drug and medical device manufacturers, allowing them to not report speaker fees or gifts to doctors that are intended for "continuing medical education" (CME) purposes, regardless of cost. Speaking fees can be a lucrative source of income for physicians, and gifts intended for medical education may include lavish items, such as admission to an expensive conference at a fancy resort, as long as the gifts are represented as intended for medical education. An additional provision would exempt expensive medical textbooks and journals from reporting by classifying them as "educational materials that directly benefit patients." These valuable gifts should be reported under the Physician Payment Sunshine Act.

   The Center for Medicare and Medicaid Services (CMS) has already provided flexibility to drug and medical device manufacturers in its clarification of the Final Rule.[7] Here, CMS has allowed for a reporting exemption where a manufacturer provides funding for a CME provider and does not select or pay the speaker directly. Arguably, this exemption already raises troubling opportunities for potential abuse. Certainly it is not necessary for the 21st Century Cures proposal to expand this exemption, which would further weaken the already accommodating reporting requirements under the Physician Payment Sunshine Act. Such additional exemptions for CME and educational materials would allow for the secret influence of industry on physician prescribing behavior and medical education, undermining the intent of the Physician Payment Sunshine Act to reveal, and therefore discourage, potential industry influence over physician behavior.

5. **21st Century Cures would hasten the rise of resistant superbugs by incentivizing hospitals to use new antibiotics rather than conserving them for appropriate use (Section 2123).**

   Section 2123 of the bill would give hospitals a reimbursement incentive to use new antibiotics. Such a provision would encourage the overuse of antibiotics by giving hospitals a financial bonus each time these drugs are prescribed, rather than encouraging hospitals to use older, effective antibiotics before using new ones that may not be medically necessary. This practice will only speed the rise of antibiotic resistant infections, as bacteria will increasingly become resistant to these new drugs as they are used more often. This provision, coupled with the financial conflict of interest in the selection of breakpoints for antibiotic resistance would further exacerbate antibiotic resistance and further limit the number of drugs available to treat patients. These changes would directly undermine recent efforts by the President and the Centers for Disease Control to slow the emergence of resistant bacteria through judicious

---

[7] Policy and Medicine. Physician Payments Sunshine Act: CMS Proposes Removing CME Exemption, Some Speaker Pay May Still Fall Under "Indirect Payment" Exclusion. July 7, 2014. http://www.policymed.com/2014/07/physician-payments-sunshine-act-cms-proposes-removing-cme-exemption-some-speaker-pay-may-still-fall-under-indirect-payment.html. Accessed May 19, 2015.

use of antibiotics in health care and other settings.[8] Rather than encourage this type of use, the bill should be re-drafted with incentives for good stewardship to encourage hospitals to preserve these drugs.

6. 21st Century Cures 21st Century Cures will bar generic entry of medicines for a longer period and will deny patients access to affordable, life-saving medicines (Section 2151)

Under Section 2151, the bill provides an additional 6 months exclusivity on top of a drug's existing exclusivity period if a new "orphan" indication is approved that involves treatment of a rare disease. This provision will extend the exclusivity period for all of the drug's indications, not just the orphan indication, increasing healthcare costs and limiting patient access to new drugs for a potentially broad range of diseases. The impact of monopoly pricing on patient access was illustrated by a recently published study, which found that in the year after marketing exclusivity was awarded to a common treatment for gout, a highly prevalent chronic condition in the United States, patients were less likely to receive a prescription, and that healthcare costs rose significantly for this population during this same time period.[9] These provisions would only further bar generic entry for an extended period, restricting patient access to affordable life-saving medicines they need.

In summary, the 21st Century Cures draft legislation as written would allow for the increased barriers for patients' access to care as well as for approval of unsafe and ineffective treatments**. We urge you to withhold support for this legislation, as it carries real and serious dangers for public health.**

Sincerely,

National Physicians Alliance
Public Citizen
American Medical Student Association
Treatment Action Group
Consumers Union
AIDS United
Knowledge Ecology International
Young Professionals Chronic Disease Network

cc: Members, Committee on Health, Education, Labor and Pensions, United States Senate

---

[8] Burwell SM, Vilsack T, Carter A, Our plan to combat and prevent antibiotic-resistant bacteria. The White House Blog. March 27, 2015. https://www.whitehouse.gov/blog/2015/03/27/our-plan-combat-and-prevent-antibiotic-resistant-bacteria. Accessed May 19, 2015.

[9] Kesselheim, A. S., Franklin, J. M., Kim, S. C., Seeger, J. D., & Solomon, D. H. (2015). Reductions in Use of Colchicine after FDA Enforcement of Market Exclusivity in a Commercially Insured Population. *Journal of general internal medicine*, 1-6.