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ADAPT Act: Problems and Solutions

The CDC estimates that over two million Americans are infected with antibiotic-resistant bacteria each year and at least 23,000 die as a direct result.[1] New antibiotics that improve patient outcomes are needed, but the key bottlenecks to antibiotic R&D may not be regulatory, but, in fact, scientific. ADAPT places patient safety at risk by weakening FDA drug approval standards that are already low and does not follow scientific best practices. A study commissioned by the U.S. Department of Health and Human Services (HHS) has shown that efforts to shorten antibiotic clinical trial, as proposed by ADAPT, will not change the economic incentives to bring effective antibiotics to market.

1. ADAPT does nothing to address the scientific bottlenecks to antibiotic drug discovery.

- The key bottlenecks to antibiotic R&D are scientific. Even major drug companies have had very low yields when screening for promising antibiotic drug compounds. In fact, screening for promising antibiotics has resulted in less than one tenth of the yield as compared to all other therapeutic areas.[2]

2. ADAPT will not change the economic incentives by which drug firms bring antibiotics to market.

- Modeling economic incentives for HHS, the Eastern Research Group found that shortening clinical trials would not make a difference for drug companies, unless their trial lengths could be cut by 75%--an impossible goal without compromising patient safety.[3]

3. ADAPT places patient safety at risk by compromising the FDA drug approval process.

- Another expedited approval pathway for limited populations is not needed. The FDA already has expedited drug approval pathways. Antimicrobials, in fact, already have a higher rate and speed of approval than other drugs.[4,5] A Harvard study showed that drugs approved in the two months before PDUFA target deadlines were almost four times more likely to be withdrawn for safety reasons and over five times more likely to receive a black box warning.[6,7]
- Approval of new antibiotics already relies on studies with too few patients in clinical trials. This results in FDA approval of new antibiotics, like Tigecycline, which has been later shown to cause more deaths in patients who already have existing effective and safe therapies. Since its approval in 2005, Tigecycline has received two black-box warnings from FDA.[8]
- Dalbavancin, an antibiotic approved by the FDA in May 2014 for treatment of acute bacterial skin and skin structure infections, did not qualify for the Center for Medicare and Medicaid Service's (CMS) new technology add-on payments (NTAP). CMS stated that "We do not believe there is sufficient objective clinical evidence to determine that Dalbavancin significantly improves clinical outcomes for Medicare beneficiaries… the NTAP application process and approval requires a demonstration of a substantial clinical improvement, which is not inherent in the FDA's regulatory process…. and we do not believe that the technology meets the substantial improvement criterion."[9]

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[1] Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States, 2013. Atlanta, GA: CDC, 2013.
[2] Payne DJ, et al. "Drugs for Bad Bugs: Confronting the Challenges of Antibacterial Discovery." *Nat Rev Drug Discov* 6, no. 1 (2007): 29-40.
[3] Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V and Outterson K. "Analytical Framework for Examining the Value of Antibacterial Products." *Eastern Research Group.* April 2014.
[4] DiMasi, J.A., Success rates for new drugs entering clinical testing in the United States. *Clin Pharmacol Ther*, 1995. **58**(1): p. 1-14.
[5] Evans R, Hinds S, Hammock D. Portfolio analysis and R&D decision making. *Nat Rev Drug Discov* 2009; 8: 189-90.
[6] Darrow JJ., Avorn J, Kesselheim AS. "New FDA Breakthrough-Drug Category — Implications for Patients." *New England Journal of Medicine* 370, no. 13 (2014): 1252-1258.
[7] Carpenter D ,Zucker EJ and Avorn J. "Drug-Review Deadlines and Safety Problems." *New England Journal of Medicine* 358, no. 13 (2008): 1354-1361.
[8] Prasad P, Sun J, Danner RL, Natanson C. "Excess Deaths Associated with Tigecycline After Approval Based on Noninferiority Trials," *Clinical Infectious Diseases* 2012; 54(12): 1699-709.
[9] Center for Medicare & Medicaid Services. 79 FR 163 (August 22, 2014), p 49931.

- Regulatory mistakes and subsequent litigation, as was the case with Ketek, an antibiotic approved by the FDA based on unreliable patient safety data, could have a chilling effect on drug R&D.

4. ADAPT risks placing FDA standard setting of antimicrobial susceptibility criteria in the hands of private groups that may be exposed to undue industry influence.

- Breakpoints for classifying antibiotics as effective or not could be determined by a committee, on which only two out of twelve members, not counting the Chair and Vice Chair, have reported no potential financial conflict of interest and ties to the pharmaceutical industry.[10]
- A study from Johns Hopkins shows that adopting the antimicrobial susceptibility criteria for one key antibiotic would have resulted in a 300% increase in the number of cases classified as drug-resistant, prompting healthcare providers to switch to more expensive, broader-spectrum antibiotics, yet not making any difference in saving the lives of the children treated.[11]

5. ADAPT has no safeguards on conserving novel antibiotics for use in these limited populations.

- CDC estimates that up to 50% of all antibiotics prescribed for people are not needed or not optimally effective as prescribed, yet no safeguards are put in place to limit expansion of use from a limited to a general population under ADAPT. [12]
- ADAPT does nothing to support the development of diagnostics needed to limit and conserve the use of the novel antibiotics that might be approved under a limited approval pathway.
- ADAPT fails to mandate the disclosure of data that would actually improve innovation of new antibiotics as well as their effective stewardship.

Solutions

ADAPT severely compromises patient safety and effectiveness of antibiotics and should not be passed. Combating antibiotic resistance in the 21st century requires targeted incentives that spur the development of truly novel antibiotics with improved effectiveness. These initiatives should address the real bottlenecks in R&D rather than dismantle clinical trial safety. Legislation built on the strategy outlined in the Executive Order signed by President Obama such as strengthening clinical trial infrastructure, implementing antibiotic stewardship programs and encouraging development of novel antibiotics and diagnostics, will enable us to tackle effectively antibiotic resistance. Legislation should:

1. **Target the scientific bottleneck** faced in antibiotic innovation by bolstering National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), National Center for Advancing Translational Sciences (NCATS) and Biomedical Advance Research and Development Authority's (BARDA) efforts to support development of novel antibiotics and diagnostics.
2. **Strengthen rather than undermine the FDA approval process** by designing clinical trials that reflect clinical benefits for patients based on endpoints such as mortality.
3. Provide **proper incentives for antibiotics that address unmet medical needs**, that are studied in the patients with these unmet medical needs, and that **demonstrate added benefits for these patients.**
4. **Ensure antibiotic stewardship** through measures that might include limiting prescribing to trained providers or certified institutions, like what is already done for drugs whose use needs to be better controlled under the FDA's Risk Evaluation and Mitigation Strategy.
5. **Remove conflict of interest** in standard setting of antimicrobial susceptibility testing of drugs and ensure that the standards are based on patient-centered outcomes from clinical studies.
6. **Foster data transparency** of clinical trial data as well as of use and sales of antibiotics to ensure greater knowledge sharing for scientific innovation and for improving the rational use of antibiotics.

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[10] Clinical and Laboratory Standards Institute, Subcommittee on Antimicrobial Susceptibility Testing—Disclosure Summary, 5/27/14. Available at: http://clsi.org/wp-content/uploads/sites/14/2013/07/Disclosure-of-Interest_June-2014.pdf

[11] Tamma, P. et al. Outcomes of children with Enterobacteriaceae bacteremia with reduced susceptibility to ceftriaxone: do the revised breakpoints translate to improved patient outcomes?.*The Pediatric infectious disease journal*, *32* no. 9 (2013): 965-969

[12] Centers for Disease Control and Prevention (CDC). *Antibiotic Resistance Threats in the United States, 2013*. Atlanta, GA: CDC, 2013.