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Why The Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013 Fails to Address The Real Problems of Antibiotic Resistance

Antibiotic Resistance threatens public health

In the United States, the CDC estimates that over two million people are infected with antibiotic resistant bacteria each year, and at least 23,000 people die as a direct result.[1]

The economic burden of antibiotic resistance is estimated at $20 billion in direct healthcare costs and more than $35 billion in lost wages, extended hospital stays, and premature deaths.[2]

New Antibiotics are Needed, but the bottleneck is not regulatory

The real bottleneck is the scientific challenge in discovering new drugs and a broken economic model for how drug sales are linked to reimbursement, exacerbating resistance. No new classes of antibiotics with novel mechanisms of action have been discovered since 1987.[3] Worse yet, an EMA-ECDC-ReAct study found that of the antibiotics in the R&D pipeline targeting Gram-negative infections, none had a novel mechanism of action.[4]

Going back to 1964, antimicrobials have had the highest rates of regulatory agency approval of any therapeutic class (28%).[5] A more recent analysis among drug R&D projects of various therapeutic indications shows that for drug candidates in Phase 1 clinical trials, nearly half of anti-infective agents make it through to market approval in contrast to 44% for musculoskeletal and 24% for anticancer agents. And among 17 therapeutic areas, the time in clinical development for anti-infectives (87 months) is among the shortest of all, considerably speedier than, say, anti-cancer agents (108 months).[6]

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[1] Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States, 2013. Atlanta, GA: CDC, 2013. Available at http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

[2] Ibid.

[3] World Economic Forum. Global Risks 2013. 8 ed. Geneva, Switzerland: World Economic Forum, 2013. Available at http://www.weforum.org/reports/global-risks-2013-eighth-edition.

[4] Freire-Moran, Laura, Bo Aronsson, Chris Manz, Inge C. Gyssens, Anthony D. So, Dominique L. Monnet and Otto Cars. "Critical Shortage of New Antibiotics in Development against Multidrug-Resistant Bacteria—Time to React Is Now." Drug Resistance Updates 14, no. 2 (2011): 118-124. Available at http://www.sciencedirect.com/science/article/pii/S1368764611000197

[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.

[6] Evans R, Hinds S, Hammock D. Portfolio analysis and R&D decision making. *Nat Rev Drug Discov* 2009; 8: 189-90.

ADAPT is not the answer

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

- **The bottlenecks to antibiotic R&D are scientific, not regulatory.** Most striking is data from the pharmaceutical industry that shows only a 7% yield from screening promising antibiotic drug compounds, less than one tenth of the yield for finding promising drugs in all other therapeutic areas.[7] This bottleneck is well BEFORE the point of testing promising drugs in clinical trials.
- **Shortening clinical trials will not stimulate antibiotic innovation.** Modeling economic incentives for the U.S. Department of Health and Human Services, 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.[8]

Issue 2: ADAPT places patient safety at risk by compromising the FDA drug approval process.

The ADAPT bill would create an expedited FDA approval pathway for antibacterial and antifungal drugs intended to treat limited patient populations. Approval could be based on "smaller" datasets with alternative endpoints, from findings in test tubes, laboratory animals or mathematical models rather than outcomes that really matter to patients, like decreasing deaths.

- **Another expedited approval pathway for limited populations is not needed.** The FDA already has expedited approval pathways to decrease the duration of FDA review. More effective drugs need smaller numbers of patients to show they save lives. However speed may sacrifice safety. The Prescription Drug User Fee Act (PDUFA) imposed formal deadlines for the completion of FDA reviews. To comply, this has resulted in more approval decisions being made in the weeks shortly before the PDUFA deadlines. However, a Harvard University study showed that drugs approved in the two months before these 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.[9,10]

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[7] Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. "Drugs for Bad Bugs: Confronting the Challenges of Antibacterial Discovery." *Nat Rev Drug Discov* 6, no. 1 (2007): 29-40.
Available at http://www.nature.com/nrd/journal/v6/n1/full/nrd2201.html

[8] 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.
Available at: http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm#_Toc382830308

[9] 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. Available at http://www.nejm.org/doi/full/10.1056/NEJMhle1311493

[10] Carpenter D ,Zucker EJ and Avorn J. "Drug-Review Deadlines and Safety Problems." *New England Journal of Medicine* 358, no. 13 (2008): 1354-1361. Available at http://www.nejm.org/doi/full/10.1056/NEJMsa0706341#t=articleResults

- **Approval standards for registering new antibiotics are already low.** Lowering clinical trial standards by allowing approval based on alternative endpoints and smaller data sets puts at risk patient safety. In the case of Sirturo (bedaquiline), the drug was approved in 2012 to treat multi-drug resistant TB based on alternative endpoints (that is, TB bacteria no longer appear in the sputum of patients) rather than the patient outcomes that matter like death. In the single trial with about 80 patients that formed the basis for the drug's approval, there was a 5-fold increase in deaths in those treated with bedaquiline compared to those patients who already have options and were given standard TB treatment.[11]

  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). Dalbavancin was the first drug to receive Qualified Infectious Disease Product (QIDP) designation established by the GAIN Act. 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."[12]

- **Approval of new antibiotics already use too few patients in clinical trials, resulting in FDA approval of new drugs actually causing more deaths in patients than existing therapy.** For example, Tigecycline--a new glycylcyline antibiotic--received expedited FDA approval in 2005. By 2010, the FDA warned that its use was associated with an increased risk of death. An NIH study pooling the results of ten published and three unpublished studies evaluating tigecycline against comparator treatments confirmed an increased risk of death and non-cure for indications for which the drug was approved. This study concluded that "Tigecycline cannot be relied on in serious infections."[13] In 2013, the FDA added yet a further new black boxed warning noting that "an additional analysis shows an increased risk of death when intravenous (IV) Tygacil (tigecycline) is used for FDA-approved uses as well as for non-approved used."[14] Tragically, the number of patients studied in the clinical trials that led to Tigecycline's expedited FDA approval were inadequate to show that patients did better on existing treatments without this new drug.

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[11] Laessig K. NDA 204-384 Deputy Division Director Summary Review. Silver Spring, MD: U.S. Food and Drug Administration, 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204384Orig1s000SumR.pdf.

[12] Center for Medicare & Medicaid Services. 79 FR 163 (August 22, 2014), p 49931. Available at: http://www.gpo.gov/fdsys/pkg/FR-2014-08-22/html/2014-18545.htm

[13] 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. Available at: http://cid.oxfordjournals.org/content/54/12/1699.short

[14] "FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning," available at: http://www.fda.gov/drugs/drugsafety/ucm369580.htm

- **Such regulatory mistakes could have a chilling effect on drug R&D.** The drug Ketek (telithromycin), an antibiotic developed by Sanofi-Aventis to treat community-acquired respiratory tract infections was reviewed three times by the FDA and approved in 2004 despite lack of evidence of added benefit compared to older drugs. A previous FDA investigation had uncovered clinical trial fraud and unreliable patient safety data, but the advisory committee, unaware of these problems, approved the drug.[15] The public and governmental scrutiny of the FDA following the approval of drugs with unaddressed safety and efficacy issues may actually set back rather than make more efficient the FDA approval process.

Issue 3: ADAPT risks placing FDA standard setting of antimicrobial susceptibility criteria in the hands of private groups that may be exposed to undue industry influence.

Under ADAPT, the Secretary would perform quarterly evaluations of susceptibility test interpretive criteria including those from private entities and change these criteria based on "preclinical and clinical data, Bayesian and pharmacometric methodologies, and other confirmatory evidence." These methods are not "confirmatory," but are useful only in developing hypotheses that need to be tested by evaluating patient outcomes.

- **Breakpoints for antibiotic resistance could be determined by a committee where majority of members have disclosed potential financial conflicts of interest or ties to the pharmaceutical industry.**
  Only three out of the fourteen members of the Subcommittee on Antimicrobial Susceptibility Testing at the Clinical and Laboratory Standards Institute (CLSI) reported no financial conflict of interest. In fact, four out of the fourteen members of the subcommittee are pharmaceutical industry employees.[16]

- **Adopting antimicrobial susceptibility criteria from such a group could lead to the use of broader-spectrum antibiotics at greater expense, but with no benefit to patients.**
  For example, in 2010, the CLSI lowered antibiotic resistance breakpoints for ceftriaxone, which would have resulted in a 300% increase in the number of antibiotic resistant infections classified as antibiotic resistant.[17] Such a chance would have prompted clinicians to prescribe newer, broad-spectrum antibiotics for these cases. But this study from Johns Hopkins University showed that such a shift in prescription practices would have offered no improvement in clinical outcomes. Shifting the goalposts of antibiotic resistance could lead

[15] Ross, DB. "The FDA and the Case of Ketek." *New England Journal of Medicine* 356, no. 16 (2007): 1601-1604. Available at http://www.nejm.org/doi/full/10.1056/NEJMp078032
[16] 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
[17] 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/23470679

paradoxically to greater resistance from the unnecessary, increased use of these broader-spectrum antibiotics that should otherwise be reserved for infections against which they are effective.

Issue 4: ADAPT has no safeguards on conserving novel antibiotics for use in these limited populations

Antibiotic use is the most important factor that leads to antibiotic resistance. A recent CDC report estimates that up to 50% of all antibiotics prescribed for people are not needed or not optimally effective as prescribed.[18]

- **No safeguards are put in place to limit expansion of use from a limited to a general population under ADAPT.** Though antibiotics may have favorable results in small populations of critically-ill patients, the lack of additional testing before they are released for the general population may lead to inappropriate usage based on incomplete safety and efficacy data.

- **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.** Absent appropriate diagnostics, it is not possible to limit effectively the use of an approved antibiotic to patients who might benefit as opposed to prescribing the drug to patients that may already have proven, effective and safe alternative options.

- **Failure to restrict the prescribing of antibiotics may lead to more widespread antibiotic resistance.** The final section of ADAPT states that "nothing in the bill shall restrict the prescribing of antibiotics or other products by healthcare providers," including those that are approved for use in limited populations. This statement may be interpreted to imply that although antibiotics may only be approved for use in limited populations, providers may prescribe them for any patient. This unregulated use may again lead to treatment based on incomplete clinical data and the earlier development of resistance to new antibiotics. This provision also removes any incentive for companies to perform further studies.

Issue 5: ADAPT fails to mandate the disclosure of data that would actually improve innovation of new antibiotics as well as their effective stewardship

ADAPT focuses its monitoring efforts after the fact—on the healthcare delivery system's use and the resulting resistance patterns. It does nothing to mandate disclosure of drug company sales or promotion of these drugs, some approved only for limited populations. Nor does it require the release of clinical trial data of shelved products, of those receiving five more years of data exclusivity (or extended monopoly pricing) under the GAIN Act as qualifying infectious disease products, or of drug trials conducted after approval for this limited population use.

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[18] Centers for Disease Control and Prevention (CDC). *Antibiotic Resistance Threats in the Unted States, 2013*. Atlanta, GA: CDC, 2013. Available at http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

The Way Forward

Combating antibiotic resistance in the 21st century will require targeted incentives that spur the development of truly novel antibiotics. These initiatives should address the real bottlenecks in R&D rather than simply undermining clinical trial requirements.

What we need is legislation that addresses this important public health challenge by:

1. **Targeting the real bottlenecks faced in antibiotic innovation.** The scientific bottleneck to antibiotic innovation is significant. One cannot have a regulatory bottleneck if promising novel antibiotics are never discovered and brought to clinical trial. A coordinated federal government-wide approach would involve bolstering NIH's efforts, from the National Institute of Allergy and Infectious Diseases' research program to study antibiotic drug resistance mechanisms to the National Center for Advancing Translational Sciences' programs that support help drug firms and academic groups to bring new drugs forward for testing in humans. Beyond work on counter-terrorism agents, BARDA could be encouraged to deepen its support of antibiotic drugs and diagnostic testing. Support for diagnostics R&D, including a Grand Challenge prize fund, could help develop tools that might not only target use of novel antibiotics better, but also lower the costs of clinical trial recruitment—a better approach than just undermining clinical trial requirements.

2. **Providing incentives only 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.** These drugs should improve efficacy (superiority, not just non-inferiority) and/or decrease harm to patients. ADAPT fails to target incentives towards the development of truly novel antibiotics as opposed to me-too products. Financial incentives like the Generating Antibiotic Incentives Now (GAIN) Act continue to extend monopoly protections (five extra years of data exclusivity) for a broad range of antibiotic drug candidates, none of which need to show any added value over existing treatments. Lowering the standards for clinical trial testing will only exacerbate this problem and increase therapeutic competition. The withdrawal rate of antibiotics from the market (43%) is already more than three times higher than non-antibiotics (13%).[19] Many of these withdrawn drugs appear just not to be effective enough to compete with existing regimens.

   Increasing therapeutic competition decreases the financial incentive to produce new antibiotics. Promoting the development of me-too antibiotics--that is, modified versions of existing drugs--instead of novel antibiotics decreases the return on investment for truly novel antibiotics. This therapeutic competition actually diminishes the incentive to produce new antibiotics by making it more difficult for these new products to gain market share.[20] Without

[19] Outterson K, Powers JH, Seoane-Vazquez E, Rodriguez-Monguio R, Kesselheim AS. "Approval and Withdrawal of New Antibiotics and Other Antiinfectives in the U.S., 1980-2009." *J Law Med Ethics* 2013; 41(3): 688-96. Available at http://onlinelibrary.wiley.com/doi/10.1111/jlme.12079/pdf

[20] Keener, A. B. (2014). First QIDP drug approved, but designation may fail urgent needs. Nature Medicine, 20(7), 690-691. http://www.nature.com/nm/journal/v20/n7/full/nm0714-690.html

targeted incentives for therapies with added benefits for antibiotic R&D, ADAPT may, in fact, hinder rather than increase innovation by increasing therapeutic competition.

3. **Strengthening, not undermining, the FDA approval process:** Clinical trial design should reflect the clinical benefit on an unmet medical need (e.g., if the unmet need is patient death, the endpoint should be mortality, not an alternative endpoint). Clinical trials can have fewer numbers of patients when the drug is more effective. Increased harm to patients occurs when less effective drugs are studied in smaller numbers of patients as already seen with drugs like tigecycline. The NIH could support a clinical trials network to help facilitate more rapid recruitment of patients for clinical trials on promising drugs that treat the unmet need of serious, resistant bacterial infections. Establishing a system for sharing historical control data from such trials could also support clinical testing efforts of new drugs.

4. **Ensuring Antibiotic Stewardship:** With FDA expedited approval of novel antibiotics, there should come responsibilities for ensuring antibiotic stewardship. For other drugs where their use might result in harming the patient, FDA has required a Risk Evaluation and Mitigation Strategy (REMS) that can take various measures to ensure appropriate use. These measures might include limiting prescribing and dispensing to certain trained providers or certified institutions, requiring administration in specific healthcare settings, or enrolling treated patients in a registry for monitoring follow-up outcomes. Furthermore, extended data exclusivity awarded by the FDA should be made contingent upon demonstrating improved outcomes (e.g. fewer deaths) in humans, not the test tube.

5. **Removing conflict of interest in standard setting of antimicrobial susceptibility testing of drugs:** The FDA should insist 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. In relying on outside entities for inputs into its standard setting process, the FDA should demand no less.

6. **Ensure data transparency to ensure greater innovation and better antibiotic stewardship:** Beyond monitoring the use of antibiotics, clinical trial data, with appropriate protections for patient confidentiality, should be released publicly, so that treatment decisions are based on the most complete clinical data and other drug developers can avoid placing patients through unnecessary risks.