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Testimony before the Committee on Energy & Commerce, Subcommittee on Health
United States House of Representatives

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Chairman Pitts, Ranking Member Pallone, and members of the subcommittee, thank you for holding this hearing on the need for broad action to combat antibiotic resistance and for the opportunity to provide testimony. My name is Allan Coukell and I direct drug, medical device and food programs for The Pew Charitable Trusts. Pew is an independent, nonpartisan research and policy organization that has focused for several years on the urgent need for new antibiotics and on the widespread inappropriate use of antibiotics in animal agriculture. My comments today will focus on the need for strong policies to encourage the innovation of antibiotics for patients with unmet medical needs.

The public health need

The threat of antibiotic resistance is real and growing, particularly among at-risk populations including children, seniors, people who are immunocompromised, for example those undergoing cancer treatment, and people with other underlying conditions such as cystic fibrosis. There is also a growing threat to another population, the men and women in serving in the military who are surviving battle wounds but then succumbing to drug resistant infections. I would like to tell you about one such person: Lance Corporal Jonathan Gadsden, a U.S. marine whose story reflects the growing need for new antibiotics to treat infections increasingly resistant to our front-line therapies.

On August 21, 2004, Cpl. Gadsden was seriously wounded after a homemade bomb exploded under his Humvee in Anbar Province, Iraq. He was treated on the scene by combat medics and then underwent surgery at a nearby military hospital before being brought home to the National Naval Medical Center in Maryland. By September, Cpl. Gadsden appeared to be on the road to recovery, and his mother was told that her son might soon return home. However, in early October, Cpl. Gadsden began to exhibit symptoms of infection. Doctors administered powerful antibiotics, but they proved insufficient. He died on October 22, 2004.

Unfortunately, this is not an unusual story. More than a third of U.S. service members injured in Iraq and Afghanistan developed infections as a result of their wounds.[1] Among the broader population, a 2013 threat assessment released by the Centers for Disease Control and Prevention (CDC) estimated that at least two million people in the United States are sickened by resistant bacteria each year, and 23,000 die as a result. The CDC acknowledged that these numbers surely underestimate the true burden of resistant infections. Among the most critical threats are infections caused by resistant Gram-negative bacteria, such as carbapenem-resistant Enterobacteriaceae, or CRE. Resistant to all, or nearly all, current drugs, CRE has caused infections and outbreaks in 47 states.

In its threat assessment, CDC identified the four pillars of a strategy to comprehensively address the spread of resistant bacteria: prevention and infection control; surveillance; antibiotic stewardship; and the development of new drugs and diagnostic tests.

The drug pipeline and the need for action

Pew maintains a continually updated antibiotic pipeline analysis that clearly shows too few drugs in development to meet current and anticipated patient needs (see Appendix A).[2] We find 38 antibiotics in phase 1 through 3 clinical trials, including five in advanced development with the potential to address Gram-negative pathogens, the most pressing medical need. This analysis is somewhat encouraging until one considers that the general rule for drug development is that 80 percent of products that enter clinical testing will fail for reasons of toxicity or inadequate efficacy. What's more, few of the drugs now in development represent new classes that might significantly delay resistance.

Infectious disease is certainly not the only therapeutic area where new drugs are needed, but there are some things that make antibiotics a special case. First, almost every one of us will need an antibiotic at some point in our lives, and most of us will know someone with a resistant infection. Second, the future of resistance is hard to predict, and the sudden emergence of some new resistant strain could render all or most existing drug ineffective. Unlike other therapeutic areas, the inevitable emergence of resistance means that to stand still is to go backwards. It is important to recognize how much of modern medical care—from cancer chemotherapy to intensive care medicine to organ transplantation—would be impossible without effective antibiotics. Finally, let us recognize that this is a solvable problem. We have done it before: the discovery of penicillin and the heyday of other drugs that followed effectively conquered the threat of bacterial illness for a time. We must commit, and ensure that we get there again.

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[1] Patricia Kime, "DoD takes lead on finding drugs to fight superbugs," *Air Force Times*, Aug. 31, 2014, http://www.airforcetimes.com/article/20140831/NEWS/308310021/DoD-takes-lead-finding-drugs-fight-superbugs

[2] The Pew Charitable Trusts "Tracking the Pipeline of Antibiotics in Development." http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development. Accessed September 16, 2014

Spurring antibiotic innovation will require decisive action. This Committee has already taken a leadership role, taking up and passing the Generating Antibiotic Incentives Now (GAIN) Act in 2012 – a bill championed by Representatives Gingrey, Degette and Green, as well as other House and Senate champions. Pew was proud to support that effort, which was enacted as part of the Food and Drug Administration Safety and Innovation Act. GAIN increases the potential profits from new antibiotics by giving companies more time to recoup their investment costs by selling their drugs without generic competition. As of September 2014, at least 23 novel antibiotics in development have been designated as qualified infectious disease products (QIDP) under GAIN. Of these, three have recently received FDA approval, with a fourth decision expected by the end of this year.

GAIN was an important first step towards incentivizing the development of antibiotics and demonstrated a bipartisan commitment from Congress to address this growing threat to the public's health. However, further work is needed, particularly for drugs that treat resistant infections. Studying these drugs is challenging, because only a small number of patients with a given infection (pneumonia, say) will have the resistant pathogen.

A limited-population pathway would speed drugs to market

To help address these challenges, the President's Council of Advisors on Science and Technology (PCAST), in its 2012 report,[3] recommended an approval pathway for drugs for use in a limited population of patients with few or no other treatment options. This approach, when applied to antibiotics, is referred to as a limited population antibacterial drug – or LPAD – pathway. It would permit the FDA to approve new antibiotics for specific, limited populations of patients with unmet medical needs, such as those with highly resistant infections. The risk-benefit assessments for these individuals with limited treatment options would be different than for patients with susceptible infections, and the drugs may be approved for use based on smaller data sets. However, it is essential that this pathway be accompanied by strong labelling provisions to ensure healthcare providers are aware of the limitations of the data underlying the products' approval.

Early last year, Pew held a one day LPAD conference, bringing together infectious disease physicians, hospital stewardship personnel, antibiotic developers, health insurers and the FDA to examine how the pathway could work. Out of this event, Pew, along with the Infectious Diseases Society of America (IDSA), issued a core set of principles to guide the establishment of an LPAD pathway, including the need for effective labeling to foster appropriate use of LPAD products. A number of other organizations, representing industry, professional societies, and public health, have since signed on.[4]

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[3] President's Council of Advisors on Science and Technology, "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation," Sept. 2012, http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

[4] The Pew Charitable Trusts and Infectious Diseases Society of America", Core Principles for a Limited Population Antibacterial Drug (LPAD) Pathway," http://www.pewtrusts.org/en/about/news-room/news/2013/09/12/core-principles-for-a-limited-population-antibacterial-drug-lpad-pathway. Accessed Sept. 16, 2014

Part of what we considered is the potential for an LPAD approval to support premium pricing of antibiotics. In other words, could a drug approved for an infection with no other treatment be reimbursed at a level that is higher than existing antibiotics? We provided two hypothetical drug models with effectiveness against specific organisms and priced at $15,000 to $30,000 per course. Panelists at the conference generally agreed that the narrow market established by a limited population pathway would set the stage for such pricing. They also emphasized the importance of economic and clinical outcomes data to support such pricing and of systems to monitor use of the drugs.

The ADAPT Act

In December 2013, Representatives Phil Gingrey and Gene Green, champions of GAIN, introduced the bipartisan Antibiotic Development to Advance Patient Treatment (ADAPT) Act, which would create an LPAD approval pathway for antibiotics filling an unmet medical need. In addition, ADAPT would give FDA the authority to review promotional materials before a drug developer could use them for marketing, and would mandate retrospective evaluation to assess whether drugs approved through this pathway were prescribed as intended. Pew, IDSA, the American Medical Association, Trust for America's Health, a number of antibiotics manufacturers, and others, have expressed support of this bipartisan legislation and have urged the bill sponsors to strengthen labeling language to ensure a safe and effective limited population pathway.

ADAPT would allow drug developers to bring drugs through the approval process for very narrow indications. By allowing drug developers to rely on smaller datasets, and clarifying FDA's authority to tolerate a higher level of uncertainty for these drugs when making a risk/benefit calculation, ADAPT would make the clinical trials more feasible than the larger clinical trials that companies now have to conduct in order to get a broader indication.

Let's take two different hypothetical approvals as concrete examples. Drug A is approved for bacterial pneumonia. Some of these pneumonias are treatable by other drugs and others are almost untreatable. When FDA approves that drug, the agency needs to consider the universe of people who may be taking this drug—some of whom may have other options and may not be willing to tolerate a higher potential for serious side effects, and some of whom will clearly die without this drug and would be willing to accept the chance that the drug could cause serious problems.

Drug B is approved to treat only life-threatening pneumonias for which there are no other drugs. If the patient doesn't take drug B, the patient has a high chance of dying. Those are the people for whom Drug B is indicated and FDA needs to make a benefit/risk calculation for only those patients. Patients with no other options will willingly accept more uncertainty than those who have alternatives.

Once the drug reached market, FDA would pre-review the promotional materials for the drug and the Department of Health and Human Services would monitor how the drug is

used, in order to understand whether the limited population designation is working as intended.

For this pathway to work properly—that is to foster the development of drugs for patients with few or no other options—the prescriber has to know that the drug has been approved under the pathway and that it is meant for this limited population. Pew, IDSA, Trust for America's Health, and a number of other provider and public health groups, are asking that the labeling language be strengthened in order to achieve the goal of the legislation.

The Energy & Commerce committee has long understood the threat of antibiotic resistance and has done great work to bring this issue to the national stage. The need for new antibiotics and the potential an LPAD pathway has to bring therapies to critically-ill patients has been highlighted at a number of hearings and roundtables the committee has held as part of the 21st Century Cures initiative. We appreciate your leadership and continued commitment to this issue.

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Summary
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Pew is an independent, nonpartisan research and policy organization that has focused for several years on the urgent need for new antibiotics and on the widespread inappropriate use of antibiotics in animal agriculture. We support strong policies to encourage the innovation of antibiotics for patients with unmet medical needs.

The public health need: The threat of antibiotic resistance is real and growing. The Centers for Disease Control and Prevention (CDC) estimates that at least two million people in the United States are sickened by resistant bacteria each year, and 23,000 die as a result.

The drug pipeline and the need for action: Pew's analysis of the antibiotic pipeline clearly shows too few drugs in development to meet current and anticipated patient needs. We were proud to support the 2012 Generating Antibiotic Incentives Now (GAIN) Act, which was an important first step towards incentivizing the development of antibiotics. However, further work is needed, particularly for drugs that treat resistant infections.

A limited-population pathway would speed drugs to market: A limited population antibacterial drug – or LPAD – pathway would permit the FDA to approve new antibiotics for specific, limited populations of patients with unmet medical needs, such as those with highly resistant infections. The risk-benefit assessments for these individuals with limited treatment options would be different than for patients with susceptible infections, and the drugs may be approved for use based on smaller data sets. However, it is essential that this pathway be accompanied by strong labelling provisions to ensure healthcare providers are aware of the limitations of the data underlying the products' approval.

The ADAPT Act: The Antibiotic Development to Advance Patient Treatment (ADAPT) Act, introduced in December 2013 by Representatives Phil Gingrey and Gene Green, would create an LPAD approval pathway for antibiotics filling an unmet medical need. In addition, ADAPT would give FDA the authority to review promotional materials before a drug developer could use them for marketing, and would mandate retrospective evaluation to assess whether drugs approved through this pathway were prescribed as intended. Pew, IDSA, the American Medical Association, Trust for America's Health, a number of antibiotics manufacturers, and others, have expressed support of this bipartisan legislation and have urged the bill sponsors to strengthen labeling language to ensure a safe and effective limited population pathway.

The Energy & Commerce committee has long understood the threat of antibiotic resistance and has done great work to bring this issue to the national stage. We appreciate your leadership and continued commitment to this issue.