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Energy & Commerce Committee

Re: 21st Century Cures Input

Dear Chairman Upton and Representative Degette,

Thank you for the opportunity to comment on the "21st Century Cures" initiative. We applaud your efforts and believe that it is important to address the challenges in drug and device discovery and development.

Attached please find our comments.

Sincerely,

Allan Coukell
The Pew Charitable Trusts

Spurring Antibiotic Innovation

Thank you for the opportunity to submit comments to the 21st Century Cures initiative. These comments are being submitted by the Antibiotics and Innovation group at the Pew Charitable Trusts. Pew is an independent, nonpartisan research and policy organization that has made a multi-year commitment to advancing public policies to spur the development of new antibacterial drugs. As the Committee considers the challenges to medical product discovery and development, we urge that one focus be the obstacles to developing new antibiotic drugs because of the public health importance of these critical therapies.

Antibiotics are one of the greatest success stories in modern medicine. Without them, women would be more likely to die in childbirth, surgeries would be more dangerous, and cancer treatments would expose patients to untreatable infections. Evolving resistance continually chips away at our antibiotic supply, making a robust pipeline essential. However, because antibiotic infections are opportunistic and often secondary to another illness, there is no cohesive patient advocacy coalition calling for better cross-sector cooperation or pushing for antibiotic drug discovery. There will be no organized marches on Capitol Hill seeking to compel members of Congress to make antibiotic drug discovery a national priority, so it is important that Congress recognize and address this urgent public health need.

The history of antibiotics is a race between innovation and resistance – as innovative science furnishes novel drugs, bacterial evolution can quickly render them ineffective. And, in fact, the problem of antibiotic resistance is real and growing. Drug-resistant bacteria are spreading in our hospitals and our communities. According to a 2013 report by the Centers for Disease Control and Prevention (CDC), more than 2 million people a year are sickened by drug-resistant infections, and more than 23,000 die as a result.[i] In the past few years, pathogens resistant to multiple antibiotics, so-called "superbugs", have emerged as an even greater public health concern. Doctors already face patients with untreatable infections, and threats such as carbapenem-resistant Enterobacteriaceae (CRE) – which CDC calls a "nightmare bacteria" – hint at the potential of worse to come. CRE has spread rapidly across the nation, from one medical facility in one state in 2001 to medical facilities in 47 states and counting as of February 2014.[ii] Nearly half of hospital patients who contract bloodstream infections from CRE will die from this infection.

The pipeline of new antibiotics is running dry. The World Health Organization recently concluded that we may be entering the very real possibility of a "post-antibiotic" era in the 21st century. Drug makers developed 13 new classes of antibiotics between 1935 and 1968, but only three new classes since that time. Pew analysis found 45 new antibiotics currently in clinical development. However, on average, only one in five to one in ten drugs that make it to the initial phase of clinical trials receive Food and Drug Administration (FDA) approval. Given this failure rate, it is clear that there are too few drugs in development to meet current and anticipated patient needs.

Three principal challenges present obstacles to antibiotic drug development:

- The first is economic: Antibiotic drug development is a poor return on investment compared to "blockbuster" drugs such as those for high blood pressure or cholesterol.

- The second hurdle is regulatory: Existing approval pathways are not well tailored to meeting our most pressing needs for new antibiotics – those to treat serious or life threatening infections for which few or no treatment options currently exist.

- The third challenge is scientific: Fundamental scientific challenges and a need for a more robust clinical trial insfrastructure hinder the development of new antibiotic drugs.

Economic Solutions

Members of Congress have taken the threat of antibiotic resistance seriously. In 2012, Congress passed the Generating Antibiotic Incentives Now (GAIN) Act, as part of the Food and Drug Administration Safety and Innovation Act. This bipartisan legislation extends by five years the exclusivity period during which antibiotics that treat serious or life-threatening infections can be sold without generic competition. This increases the potential for profits from new antibiotics by giving innovative companies more time to recoup their investment costs. As of June 2014, at least 18 novel antibiotics in development have been designated as qualified infectious disease products (QIDP) under GAIN and one product has reached market. While the GAIN incentives are an important first step, the antibiotic pipeline is not nearly robust enough and more work is needed.

Regulatory Solutions

Regulatory approval for drugs to treat highly resistant bacterial infections is especially challenging because only a small number of patients contract such infections and meet the requirements to participate in traditional clinical trials. These are daunting odds for any company, but especially challenging for small companies.

In order to address some of the regulatory barriers to antibiotic development, Representatives Phil Gingrey and Gene Green have introduced the bipartisan Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742. This legislation would help streamline the regulatory pathway for antibiotics that could address CRE and other dangerous pathogens. It directs the FDA to approve new antibiotics for specific, limited populations of patients with life-threatening infections where few or no treatment options currently exist.

This pathway was endorsed by the President's Council of Advisors on Science and Technology in its 2012 report. While the PCAST recommendation was broader than antibiotics, the report specifically called out antibiotics as appropriate for this pathway. Specifically, PCAST said:

> Currently, FDA may not grant approval without extensive clinical trials in the larger population due to concerns about safety risks resulting from possible off-label use in broader groups. It would be desirable to have a pathway under which such drugs could rapidly reach high-need patients while reducing the risks from wider use of the drug. In the case of antibiotics, there would also be clear public health benefits to limiting the use of new antibiotics effective against drug-resistant bacteria, to stave off the emergence of drug-resistant strains.

ADAPT would implement this recommendation by directing the FDA to create this pathway, allowing FDA to approve antibiotics for use in limited populations.

PCAST recommended that the approval pathway be accompanied by a designation that would "send a clear and effective signal to patient, physicians, payors and malpractice insurers that the drug should be reserved for use in the specific subgroup of patients. The …designation would not forbid off-label use, but would be intended to affect the likely usage by shifting responsibility to educated prescribers and payors. In doing so, it would shift the overall benefit-risk balance and allow the FDA to responsibly approve drugs intended for patients with the serious manifestation."

As PCAST points out, the intent of the designation is not to prohibit off-label use, and the ADAPT legislation appropriately includes language that makes it clear that this legislation would not limit the practice of medicine. While ADAPT does have a labeling provision, the language should be strengthened in order to fully achieve the goals laid out by PCAST. Specifically, antibiotics approved under this pathway should be clearly labeled with a visual element or other branding so that prescribers and dispensers can immediately know that the risk/benefit calculation FDA made in approving the LPAD drugs was specific to the patient with no other options and that the drug may not be appropriate for patients who have other treatment options.

Pew, the Infectious Diseases Society of America, and a number of other prominent provider and public health groups are advocating that ADAPT be amended to allow for this kind of designation so that the legislation will fully implement the intent of the pathway. With this one alteration, ADAPT would help to fill an urgent public health need by providing a pathway for the most essential new antibiotics to reach the patients who need them.

Because the threat of antibiotic resistance is pressing and increasing, we urge the committee to consider moving ADAPT as an immediate first step in this important new initiative.

Scientific Solutions

Addressing the economic and regulatory barriers to antibiotic drug development are critical steps, but ensuring that new therapies continue to become available will also require attention to

the basic science that primes the antibiotic drug pipeline. Without innovative antibiotic research, we cannot hope to stay ahead of drug resistance.

Current research is not addressing fundamental scientific questions that are long-standing obstacles to antibiotic drug discovery. For example, we do not fully understand how to get drugs into, and prevent them from being expelled from, the formidable Gram-negative bacteria that include many of the most dangerous pathogens.

NIH has begun to address the gap between basic research and commercial products through unprecedented federal funding for translational science. While this work is critical for addressing antibiotic resistance, it is not enough.

In order to best leverage public and private investment, we need new, creative partnerships to tackle fundamental scientific problems that slow antibiotic discovery and development. Other countries have already begun to foster better communication and collaboration between academia and industry – the Innovative Medicines Initiative (IMI), for example, is a partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations that supports research and development projects between industry and academic researchers. The PCAST 2012 report recommended the creation of a similar broad-based partnership to promote innovation and improvement in the discovery, development, and evaluation of new medicines for important public health needs.

Federal investments can also make clinical trials more feasible, bringing down the costs of drug development and potentially speeding up development time. Clinical trials for antibiotics pose particular challenges for both enrollment and outcomes assessment: the need to start treatment urgently complicates trial enrollment, and treatment often begins prior to the availability of culture and sensitivity results, posing challenges for subject selection. A clinical trials network that could be used by industry as well as academics would facilitate drug development, particularly for small companies.

Antibiotic resistance is a societal issue that requires partnership and collaboration across government agencies, including NIH, CDC, and FDA, and between academia and industry partners. We are depending on leaders in Congress to help ensure that federally funded antibiotic research is coordinated and supports promising ideas and innovation by tackling long-standing obstacles to antibiotic drug discovery and exploring new areas of science to develop innovative approaches to address growing antibiotic resistance.

Conclusion

Antibiotics not only treat acute infections, but also underpin much of health care – interventions ranging from routine surgical procedures to organ transplants and cancer treatment rely on the availability of effective antibiotics. As the Committee considers how to move medical innovation forward, the availability of effective antibiotics will be important to ensuring the viability of a wide range of other therapies. By moving the ADAPT Act in the near term, and

focusing long-term attention on research and clinical trials, the 21st Century Cures initiative could have a lasting impact on the antibiotic drug pipeline, and help ensure the continued availability of the wide range of medical treatments that are only possible because of the availability of the antibiotics they depend on.

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Big data can accelerate patient access to new medical products

The following comments are submitted on behalf of the Medical Device group at the Pew Charitable Trusts. The device project works to foster innovation that will benefit patients and to improve medical device safety, in particular through improved postmarket surveillance.

As Congress considers the challenges to medical product innovation, it will be important to consider whether there are ways to facilitate the clinical trials that are so important to get the data about whether a product is safe and effective. This data is critical to regulators, payers, clinicians and patients so they can make informed decisions. The development of new drugs and medical devices for patients can take more than a decade and cost more than a billion dollars. The clinical trials needed to obtain data to assess the safety and effectiveness of new products are the primary contributor to the length and cost of product development. The answer to this conundrum is not to do away with this vital scientific tool, but rather to develop more efficient methods and trial infrastructure.

The expansion of health information technology and increased adoption of electronic health records (EHRs) have the potential to dramatically decrease the costs and time of products to market without sacrificing data on safety and effectiveness. These new tools can aggregate large amounts of information—known as big data—to support drug and medical device innovation.

A recent clinical trial conducted in Europe demonstrated the ability of these electronic tools to quickly collect large amounts of data without breaking the bank. Researchers used established registries—databases that contain information on patient outcomes—to evaluate whether a specific procedure helped patients with heart attacks. By using these data, they conducted a "registry-based randomized clinical trial" involving more than 7,000 patients that lost no one during the follow-up period. This unprecedented study only cost $300,000, roughly $50 per patient. Conducting such a study outside of a registry in the United States would cost hundreds of millions of dollars, if not more. The study—known as the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial—demonstrates the value of registries to efficiently—and cost-effectively—conduct large clinical studies.

What are registries?

Put simply, registries are large databases that collect information on a group of patients treated for a particular medical condition so that their outcomes can be assessed over time. Medical product registries focus on patients who have used a certain drug or medical device in order to understand how well it has worked.

Typically, medical product registries in the United States have been used to conduct postmarketing surveillance by tracking the experience of a broader patient population for a longer period of time than was studied in premarket clinical trials. Hip implants, for example, are expected to last 15-20 years but typically require only two years of clinical data for FDA

approval. Registries can be a cost-effective way to study devices such as these for longer periods of time.

An example of a high-performing registry is the Australian Orthopaedic Association National Joint Replacement Registry, which was implemented in 2002 to improve quality of care for patients receiving implanted prosthetics. In 2007, the registry showed that metal-on-metal hips—introduced in 2003 for younger patients needing hip replacements—failed at a rate more than two times higher than conventional hips, leading to a worldwide recall of the problematic hips.

The United States also has large registries, such as the American College of Cardiology's National Cardiovascular Data Registry which collects data to improve the quality of cardiovascular care through a suite of hospital-based and outpatient registries. FDA has used data from this registry to investigate potential safety problems with cardiac devices. This registry, though, does not routinely conduct analyses on medical products.

Registries have the potential to become a pillar of the data collection infrastructure in the United States and to provide patients, clinicians, payers, manufacturers and regulators with information on the safety and effectiveness of products used in care.

Registries' role in expediting patient access to new products

Registries can also play a critical part in efforts to accelerate patient access to new products by efficiently collecting robust information on safety and effectiveness. They can promote innovation in a number of ways.

First, registries can serve as platforms for more efficient premarket clinical trials. As demonstrated by the TASTE trial, registries can collect data on outcomes from thousands of patients at low cost over extended periods of time. In another example, FDA approved an expanded indication for an innovative heart valve based on the use of an existing registry.

Dr. Jeff Shuren, director of FDA's Center for Devices and Radiological Health, mentioned this example at the Energy and Commerce Committee's roundtable last month. He stated, "We very recently actually allowed for expansion of the labeling indication on the device, where the company and two health care professionals societies were going to do a clinical trial and we told them don't do it, don't waste your time. We looked at the registry data and we said we think it is good enough."

Robust postmarket data on patient outcomes can also provide manufacturers with more information to inform the next generation of product development. Registries can efficiently collect data on large numbers of patients, making it easier understand how the product works in various patient subpopulations. As health care embraces personalized medicine, discerning differences in how patient subgroups respond to treatments will become increasingly essential to the next generation of cures.

With this information, manufacturers can refine their product or update labeling to address concerns raised by the data, develop new tests to better identify patients for whom the product would work best, and utilize the data to develop new products for patient subpopulations. This infrastructure creates a feedback loop to continuously inform product development and accelerate treatments for patients in need.

Finally, sophisticated tools—like registries—to collect robust postmarket data on patient outcomes can support recent efforts by Congress and FDA to speed access to drugs and devices. FDA may be reluctant to approve products more quickly if the agency is not confident that safety problems will be detected in the postmarket setting. To mitigate risks, FDA must have strong postmarket data collection tools, such as registries, to collect needed data on the safety and effectiveness of the products.

Challenges to registry adoption

Despite the proven value of registries to facilitate innovation, there are a number of challenges that must be overcome to enhance their adoption.

First, despite the dramatic uptake of EHRs and other electronic health information sources, these systems cannot easily transmit data among one another. This lack of interoperability, for example, prevents data transmission across EHR systems developed by different manufacturers.

It also hinders the ability for registries to extract clinical and outcomes data from EHRs. Instead, registries must develop the ability to extract information from the EHR systems at each facility, or require manual entry from providers. The Office of the National Coordinator for Health Information Technology (ONC), under the leadership of Dr. Karen DeSalvo, has made interoperability a top priority. ONC last week released a policy paper outlining its 10-year vision for health information technology interoperability, including both short- and long-term goals. We urge the Committee to lend its full support to interoperability efforts.

There are also potential advances in clarifying when registries must obtain patient consent, and what level of federal privacy protections apply. There are two policies that regulate patient consent and privacy protections: (1) the Common Rule, which requires that human research participants give fully informed consent, and (2) the Health Insurance Portability and Accountability Act (HIPAA), which provides federal protections for individually identifiable health information and security standards for transmitting health information. The differing—and sometimes conflicting—requirements in the Common Rule and HIPAA create a barrier for collecting patient data for registries. Registries have sought clarity on the level of patient consent that is needed, given their use of data that is collected as part of usual clinical care.

While individual privacy is of paramount importance, but progress in healthcare and medical product innovation depends on improving our ability to collect and use aggregate data efficiently and effectively. Identifying the appropriate balance requires additional conversations among stakeholders, including Congress.

The Pew Charitable Trusts—in conjunction with the Blue Cross and Blue Shield Association and the Medical Device Epidemiology Network Infrastructure Center at Weill Cornell Medical College—convened a series of meetings with stakeholders to begin addressing some of the issues facing registries. We will release a report based on our findings within the next few weeks.

Conclusion

Given the proven value of electronic health information and registries – and the much greater potential yet to be realized, Congress should explore whether statutory changes are required to maximize the potential of these data sources to expedite patient access to safe and effective medical products. Tthrough its oversight capabilities, Congress can also ensure that the Administration is aggressively supporting efforts to harness the power of big data to improve the lives of patients.

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[i] Centers for Disease Control and Prevention, Antibiotic Resistance Threats to the United States, 2013, http://www.cdc.gov/drugresistance/threat-report-2013/index.html.

[ii] "Tracking CRE", Centers for Disease Control and Prevention, last modified February 10, 2014. http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html.