

21ST CENTURY CURES: EXAMINING WAYS TO COMBAT ANTIBIOTIC RESISTANCE AND FOSTER NEW DRUG DEVELOPMENT

HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED THIRTEENTH CONGRESS SECOND SESSION

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21ST CENTURY CURES: EXAMINING WAYS TO COMBAT ANTIBIOTIC RESISTANCE AND FOSTER NEW DRUG DEVELOPMENT

FRIDAY, SEPTEMBER 19, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 9:00 a.m., in room 2123, Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Present: Representatives Pitts, Burgess, Shimkus, Gingrey, Lance, Bilirakis, Ellmers, Pallone, Green, and Waxman (ex officio).

Also Present: Representative DeGette.

Staff Present: Clay Alspach, Counsel, Health; Gary Andres, Staff Director; Sean Bonyun, Communications Director; Leighton Brown, Press Assistant; Noelle Clemente, Press Secretary; Paul Edattel, Professional Staff Member, Health; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Tim Pataki, Professional Staff Member; Chris Sarley, Policy Coordinator, Environment and Economy; Heidi Stirrup, Health Policy Coordinator; Ziky Ababiya, Minority Staff Assistant; Eric Flamm, Minority FDA Detailee; Karen Nelson, Minority Deputy Committee Staff Director For Health; Rachel Sher, Minority Senior Counsel.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. The subcommittee will come to order. The chair will recognize himself for an opening statement.

According to the World Health Organization's Antimicrobial Resistance, Global Report on Surveillance 2014, antimicrobial resistance, AMR, is an increasingly serious threat to global public health. British Prime Minister David Cameron warned in July that if we do not confront the threat of antibiotic resistance, we could be "cast back into the dark ages of medicine where treatable infections and injuries will kill once again."

And just yesterday, the President announced an executive order focused on efforts his administration plans to take with regards to the antibiotic resistance issue. In 2012, this committee sought to help combat this global threat by passing the GAIN Act as part of the Food and Drug Administration Safety and Innovation Act of

2012. The GAIN Act was an important first step in the fight against antibiotic resistance and a great example of how bipartisan collaboration on this committee can save lives. And I want to commend the bipartisan authors that made GAIN possible, including Representatives Gingrey, Green, Shimkus, DeGette, Whitfield, and Eshoo for their leadership.

I also want to commend the FDA for its role in making GAIN a success since its passage. But what is clear to many in this room is that GAIN did not fully fix the problem, and much more is needed if we are to incentivize the type of drug development needed to combat this global threat.

And to that end, Congressmen Gingrey and Green have introduced another piece of legislation, the ADAPT Act, which would seek to address problems related to the FDA approval process of antibiotic drugs. It is one of a series of proposals that warrants serious consideration by this committee as part of our 21st Century Cures, and I want to thank them for their continued efforts in this space.

I would like to thank all of our witnesses for being here today and yield the remainder of my time to the vice chair of the subcommittee, Dr. Burgess.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

The Subcommittee will come to order.

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I would like to thank all of our witnesses for being here today, and I yield the remainder of my time to Rep. _____.

Mr. BURGESS. Thank you, Mr. Chairman, and I certainly appreciate the fact we are having this hearing today. It is necessary as we proceed with the Cures initiative to talk about some of the things that are most important, some of the things that are relied

upon and familiar in our front line of our ability to fight infections and those are antibiotics. Antibiotic resistance, specifically resistant strains, is a growing problem. Equally troubling, despite widespread support, is the lack of a pipeline of new drugs that can improve on previous generations or fight drug resistance strains. A lot of facets to this issue, and there is no single silver bullet solution.

But here is the deal, our drug arsenal is our drug arsenal. Today the committee continues to probe the various market reasons why we are not producing new antibiotics, and if the proper market incentives and regulatory pathways exist to encourage the development of new drugs. Very important strides that have been made in the FDA Safety and Innovation Act, most notably through the GAIN Act, but they were just the first steps. Part of the deal is once nature adapts, it is hard to force nature to unadapt. These resistant strains are out there, and they aren't going away. Once this evolutionary leap has taken place, we are not going back, and that is why we need a continuous pipeline of new drugs.

I would also just point out on a historical note, since the election in Scotland was yesterday, and Scotland is going to remain part of the British empire, and of course, it was a famous Scotsman, Sir Alexander Fleming who developed, or is credited with the discovery of penicillin, but Sir Alexander Fleming couldn't produce a lot of penicillin, and it was Andrew Moyer from Indiana, who actually developed the deep fermentation process that allowed the penicillin to be mass produced and really made a significant difference in the lives of our soldiers returning—or the saving of lives of our soldiers returning from World War II, and parenthetically dropped the cost of a course of penicillin from \$20, at that time was a significant amount of money, to less than 50 cents.

So we know we can do this and we know we should do this, that is, we have done it before, so the forefront of innovation, and that is what the Cures Initiative is all about, and I think that is an important part of our discussion. I will submit this article on Andrew Boyer for the record.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. Without objection, it will be entered into the record. The chair thanks the gentleman and now recognize the ranking member of the subcommittee, Mr. Pallone, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts. In 2006, in my State of New Jersey, a 17-year-old honor student named Rebecca Lohsen went to the hospital and within days died from a resistant strain of MRSA. Though her doctors were able to identify the infection and treat it with the available antibiotics, it failed to respond to treatment, advancing rapidly and cutting her life short. And stories like Rebecca's are all too common and all the more frustrating given the remarkable advances in American medicine.

The threat posed by antibiotic resistant bacteria or "super bugs" is growing, yet the supply of new antibiotic drugs is dwindling due to drug manufacturers' declining interest and ability to produce

new drugs to meet this threat. In a CDC report released last year, they find that 2 million Americans are infected with antibiotic resistant bacteria each year, and unfortunately, 23,000 will eventually die as a consequence of their infections. Additionally, 5 to 10 percent of patients in American hospitals will acquire an infection during the course of their treatment. And, though the majority of these infections can be treated, this complicates the recovery process and ultimately imposes greater costs on patients and the healthcare system.

Due to the current state of the market, manufacturers are incentivized to focus their efforts elsewhere, at the expense of the research and development with new antibiotics to combat these rapidly evolving strains of bacteria. This reason is why Congress included many of the provisions of the GAIN Act in the FDASIA legislation, which was signed into law in 2012. The GAIN Act was an important step toward solving this problem. Through GAIN, we are supporting manufacturers in the development and introduction of new drugs largely through the use of marketing exclusivities. So far we have seen meaningful progress.

Because of GAIN, FDA has approved a number of new drugs through the Qualified Infectious Disease Product designation. With priority review, these drugs are able to combat an imminent infectious disease threat and reach patients at an accelerated pace.

However, we should also remember why other laws such as the Hatch-Waxman Act, are so successful. If Congress decides to intervene in the market, using the carrot of marketing and regulatory exclusivities, we should be sure that it achieves the necessary impact on the pipeline of new drugs to safeguard the public health.

In pursuit of the greater good, government struck a balance between the interests of private industry in the public, and society reaped the benefits. And so that is why I have concerns about ideas such as transferable exclusivity, the practice of giving a specified period of exclusivity to a company to use on any product it wishes as a reward for developing a new antibiotic. This is a recipe for higher cost drugs with no direct connection to the cost to developing new antibiotics.

Yet, there are some ideas that are worth further examination, such as the ADAPT Act introduced by Congressmen Green and Gingrey. That bill would establish a limited population approval pathway that would permit FDA to approve drugs based on smaller clinical trials. So Mr. Chairman, there are a number of angles the government and private industry can take to meet this problem head on. I think we all agree this is an issue which warrants further action, and I welcome the opportunity to hear from our witnesses today. A special welcome to Adrian Thomas from Johnson & Johnson, which is headquartered in my district. I am always pleased to see you represented in front of our committee.

So I would like to yield the remainder of my time to Mr. Green.

Mr. GREEN. Thank you, Ranking Member, for yielding. Few issues in the public health today are as grave and urgent as combating the growing threat antibiotic resistance. I am pleased to learn that yesterday the White House announced the President's Executive order on the national Combating Antibiotic Resistance

Bacteria, CARB strategy. We need to control bacteria and carbs, I guess.

Recently, both the World Health Organization and the United Kingdom joined the United States in recognizing antibiotic resistance as a global threat. Fighting antibiotic resistance is both a public health and a national security priority. It is a threat that I take seriously and believe Congress has a strong role in answering. The FDA has played a central role in this important effort, and I thank the agency for their work. We must all work together to ensure that we have effective antibiotics for the future.

In 1929, Alexander Fleming invented the process for the first antibiotic wonder drug, penicillin. Such discoveries for the 21st century can happen as well if we encourage greater investment in the development of novel antibiotic drugs. Antibiotics have saved millions of lives by treating infections caused by bacteria and made through therapies like surgery, chemotherapy, and care for neonatal infants possible. By nature, bacteria evolve and become resistant over time. In addition, misuse and inadequate diagnosis have contributed to antibiotic resistance, and most antibiotics are now less effective or ineffective against infections.

The consequences of antibiotic resistance must not be underestimated. With each day, many more patients will have few or no therapeutic options because of the resistance to available therapies. I thank the chair and ranking member for this hearing today. Antibiotic resistance and development must be a high priority for this committee and central to the way we treat and cure disease in the 21st century. I look forward to the hearing, and again, I want to thank my colleague, Congressman Gingrey, for partnering both on the GAIN Act last Congress and also on the ADAPT Act this Congress, and I yield back my time. Thank you.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Georgia, Dr. Gingrey, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Mr. Chairman, I want to thank you. I want to thank you for calling today's hearing within the 21st Century Cures Initiative entitled, "Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development." Let me first commend Chairman Upton and our colleague from Colorado, Ms. DeGette, for spearheading this bipartisan endeavor that really looks at ways we can address emerging challenges in the healthcare industry.

I have participated in a number of the hearings and roundtable discussions and have found each to be very beneficial to all the members of this subcommittee. Mr. Chairman, we all understand that antibiotic resistant pathogens are a growing concern not only across the country, but across the globe. According to the CDC in Atlanta, each year more than 2 million Americans get infections that are resistant to antibiotics, resulting in the deaths of some 23,000 people and costing our healthcare system nearly \$20 billion in direct cost, probably \$35 billion more in indirect cost, lost time from work, et cetera.

This year alone, both the World Health Organization and the U.K. have acknowledged this looming threat. Just yesterday, the Obama administration took action on antibiotic resistance as well. Through the signed Executive order, the national strategy on Combating Antibiotic Resistant Bacteria and the President's Council of Advisors on Science and Technology, referred to as PCAST, will be issuing a report, this is an issue that is now receiving global attention. Unfortunately, though, according to the FDA, new antibiotic approval has decreased by 70 percent since the mid 1980s.

A combination of barriers, including, of course, the high cost of drug development and the small profit margins have helped to drive companies out of the anti-infectious space to markets where the return on investment is much higher. You think of your favorite drug, whether it is for arthritis or whatever, they simply can make a lot more money and there is a lot bigger market. These few incentives for companies to produce new antibiotics have yielded a stagnant research and development pipeline for antibiotics, and it is ill-equipped to keep up with the evolving bacterium.

Mr. Chairman, I am glad that Congress has been a true leader in this arena. With the partnership of my colleague from Texas, Gene Green, as the other lead author/sponsor of the GAIN Act, we were able to find a path for this legislation to be signed into law, and it was, in July of 2012. As many of the witnesses' testimonies state, the GAIN Act has been an important step to encourage new development of antibiotics by focusing on economic incentives to keep companies in the game, in the market. However, despite these advances, there is still more work that needs to be done. That is precisely why Mr. Green and I authored H.R. 3742, the ADAPT Act during this Congress.

This legislation, a logical next step to the GAIN Act, develops a new pathway at the FDA for antibiotics aimed at treating merging threats in limited and high-need populations when they have no available option at their disposal. The ADAPT Act will also streamline the process by which the FDA updates break points information so doctors and medical researchers have the most up-to-date information in which to expedite the decisions in the drug approval process.

Mr. Chairman, the model of the 21st Century Cures Initiative work on the GAIN Act and the ADAPT Act has been a true bipartisan product, and I commend Mr. Green for his continued efforts with me on both pieces of legislation. Earlier this morning, both of us spent an hour on Washington Journal discussing our efforts addressing drug resistant bacteria with a sense of comity befitting our committee, and I think Mr. Green and the moderator and hopefully all the viewers and listeners would agree with that. And with that in mind, I look forward to hearing from all of our witnesses today, the first and second panel.

I had the pleasure yesterday of meeting with Dr. Barbara Murray, who will be on the second panel, the President of the Infectious Disease Society of America, and after hearing some of her anecdotal accounts of life-threatening infections with her own patients, I am even more motivated to continue the fight against drug resistant bacteria.

I will give a real quick anecdote, Mr. Chairman. I know I am running out of time, but my brother is 1 year older than me, and in 1941, he was sick as a gourd, home with pneumonia, and the family doctor came to the house and told my parents that he was going to die unless he gave him a shot of this new antibiotic called penicillin. And my brother James got that shot of penicillin and fortunately he lived. Now, there have been some days since then that I wish he hadn't. He beat me up every day since then and still does, but that is my own little anecdote, Dr. Murray.

Mr. Chairman, as we continue with the 21st Century Cures Initiative, we must work in a bipartisan manner to address this growing problem across our country. Ultimately, I believe that the ADAPT Act is the next step in the fight. It is my hope that we will mark up this legislation during the lame duck session later next month. Until then, I welcome the testimony that we will be hearing today to further educate members of the subcommittee on this critically important issue.

Make no mistake, the cost of inaction in the fight against life threatening infections is grave, and the CDC has already provided us with the statistics to prove that. Today's hearing will serve as a great way to raise awareness on this important issue.

Mr. Chairman, thank you for allowing me the time normally reserved for Chairman Upton, and I look forward to continuing to work with all of my colleagues as this process moves forward. Thank you for the extra time and being a little soft on the gavel, Mr. Chairman, as I yield back.

Mr. PITTS. The chair thanks the gentleman and thanks him for his leadership on this issue.

Now recognizes the ranking member of the full committee, Mr. Waxman, for 5 minutes for opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman. We held hearings in this committee in 2010 on the problem of antibiotic resistance and the fact that it is a growing and dangerous threat to public health. It is certainly an issue that deserves the full and complete attention of this committee, so I am pleased you are holding this hearing. Our overarching goal should be to ensure that people continue to benefit from these life-saving treatments, both here and in the United States and around the globe.

This is an inherently difficult goal to achieve. After all, when we use these antibiotics, it leads to the development of pathogens that can no longer be treated by those antibiotics. Rather than use it or lose it with antibiotics, it is use it and lose it.

So we are at great risk of losing much of the progress that has been made in fighting infection and subsequent disease. Many Americans die or are infected each year from antibiotic resistant microbes. We pay a high price in other ways as well, additional hospital stays, hospital readmissions, increased doctor visits, all add unnecessarily to the Nation's annual healthcare bill. It will take a multi-pronged approach to overcome this very serious problem. There is no question that our arsenal of effective antibiotics

is dangerously low today as a result of antibiotic resistance, so we need to replace ineffective antibiotics with new ones.

In the 2012 FDA user fee legislation, we enacted a law designed to create incentives for companies to replace those antibiotics and develop new ones. That legislation included provisions from the what was called the Generating Antibiotic Incentives Now Act called the GAIN Act, and that granted a 5-year period of exclusive marketing for new antibiotics for serious and life-threatening diseases.

I look forward to hearing today from our witnesses about what impact that legislation is having on investments in these drugs. Exclusivity rewards drug companies by allowing them to charge higher prices. As a result, it also imposes a significant burden on patients and on the healthcare system overall, so we need to approach this particular form of incentive with great caution.

One bad idea, in my opinion, is the concept of transferable market exclusivity which is sometimes called the wildcard exclusivity. This form of exclusivity would give a company that developed a new antibiotic the ability to transfer a term of exclusivity to another drug, any other drug that they have, and this is a hugely costly idea that leads to unfair cross subsidies. If AstraZeneca were to develop a specified antibiotic, it could earn a term of exclusivity that it could transfer to Nexium, a treatment for heartburn which is the second highest grossing drug last year and earns over \$6 billion. Even if the term of exclusivity were just 6 months, that would result in a reward of almost \$3 billion. That means Nexium patients pay higher prices for longer even though they may never actually take the antibiotic itself.

As we tackle the problem of antibiotic resistance, we need to ensure that whatever form the incentive takes, it bears some reasonable relationship to the amount of the investment the company is making. I hope we will discuss today another approach to getting new antibiotics on the market. That is what has been referred to as the ADAPT Act, or the Antibiotic Development to Advance Patient Treatment. That bill would establish a limited population approval pathway that would permit FDA to approve drugs based on smaller clinical trials. This is an idea worth examining.

If we do create such a pathway, any drugs approved as a result would need to be clearly marked with a prominent symbol to alert providers and patients that the safety and effectiveness of these drugs has only been assessed on a limited population. Requiring a designation is integral to the idea of a limited population approval pathway because providers have to know that these drugs are to be used only when absolutely necessary. Otherwise, they will not only put patients at risk but will contribute to the more rapid development of antimicrobial resistance to the drugs.

In addition to incentives for developing new antibiotics, we ought to find ways to cut back on the overuse and misuse of these drugs. Patients cannot expect to get them every time they come down with a cold, and physicians should only prescribe them when they are truly necessary. Perhaps most important, the indiscriminate administration of these drugs in animal agricultural operations needs to stop. We should mandate an end to this practice, but if we cannot take that step, we should at least have better data about

how and where antibiotics that are important for humans are being used in food animals. We know practically nothing about this situation.

As a recent Reuters article points out, the data exists in the hands of major corporations producing these animals. I would like, Mr. Chairman, another 30 seconds.

Mr. PITTS. Go ahead.

Mr. WAXMAN. Like Perdue and Tysons, and I have a bill that would finally give the public access to this information, H.R. 820, the DATA Act. I hope this commonsense bill can be included in the 21st Century Cures legislation.

I thank the witnesses for being here today and for their testimony. And Mr. Chairman, I would like to ask unanimous consent that a statement prepared by Congresswoman Louise Slaughter be included in the record. She is talking in her statement about ways to combat antibiotic resistance and foster new drug development.

Mr. PITTS. Without objection, so ordered.

Mr. WAXMAN. Thank you, Mr. Chairman.

[The prepared statement of Ms. Slaughter follows:]

PREPARED STATEMENT OF HON. LOUISE M. SLAUGHTER

Mr. Chairman, thank you for the opportunity to submit remarks for the record this morning. I appreciate the attention being paid to the crisis of antibiotic resistance and the immediate need to address it. While I appreciate that the focus of today's hearing is on the development of new antibiotics, I cannot let the opportunity pass to discuss the overuse of antibiotics in agriculture and the connection to the development of superbugs resistant even to some of our last line of defense antibiotics.

Almost 70 years ago, Alexander Fleming first warned about the possibility of a post-antibiotic era, warning that—quote—“the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

I'm not sure Dr. Fleming could have envisioned that the biggest threat to antibiotics in the future would come from factory farms—where 80 percent of the antibiotics in this country are used in animals that eventually end up on our dinner plate. His warning rings true today: the daily distribution of antibiotics in feed and water at sub-therapeutic levels is creating resistant superbugs, and destroying the effectiveness of these miracle drugs.

According to a recent report from the World Health Organization, “Antibiotic resistance is now a bigger crisis than the AIDS epidemic,” and if we do not curb our antibiotic overuse, “a post-antibiotic era in which common infections and minor injuries can kill far from being an apocalyptic fantasy, is instead a very real possibility for the twenty-first century.” This would redefine modern medicine. Routine infections like strep throat could be fatal. A skinned knee that became infected could become fatal. Life-saving surgeries like open-heart surgery or organ transplants that require antibiotics to stave off infection would become too dangerous for doctors to consider. All of these medical advances would be thrown away because we are wasting these critical antibiotics on the farm.

There are those who say there is not a connection between overuse of antibiotics on the farm and resistant diseases in humans. I struggle to understand their decision-making process when the National Antimicrobial Resistance Monitoring System (NARMS) reports that antibiotic resistant bacteria exist in 81% of ground turkey, 69% of pork chops, 55% of ground beef, and 39% of chicken breasts, wings and thighs found in grocery stores. More than 27% of bacterial isolates found on retail chicken are resistant to more than five classes of antibiotics.

Just this week, the top scientific minds in this country who make up the President's Council of Advisors on Science and Technology released their report on antimicrobial resistance and confirmed what I and over 450 of the leading medical, scientific and consumer groups in the country who support my legislation have been shouting from the rooftops for years. Allow me to quote that report:

“Substantial evidence demonstrates that use of antibiotics in animal agriculture promotes the development of antibiotic-resistant microbes in animals and that retail

meat can be a source of microbes, including antibiotic-resistant microbes. Moreover, antibiotic resistance can spread between microbes (through the transfer of DNA elements, such as plasmids, between species) and antibiotic-resistant microbes can spread from animals to people who come into contact or close proximity with them. For example, poultry workers in Maryland and Virginia have been reported to be much more likely to be colonized by gentamicin-resistant *E. coli* and are at a higher risk of infection by multi-drug resistant *E. coli* than residents of the community surrounding the poultry operation. A survey of over 900 adults in Wisconsin and Minnesota found that drug-resistant *E. coli* bacteria isolates present in humans were similar to those in poultry meat, whereas drug-susceptible *E. coli* bacteria isolates were not. A study of veterans in rural Iowa reported that the frequency of resistant *Staphylococcus aureus* was 88% higher among veterans living within one mile of a high-density swine-feeding operation.”

Despite the substantial evidence and despite the nightmare scenario of a post-antibiotic era, both our federal regulatory agencies and the Congress are still refusing to acknowledge the devastating role that antibiotic use in agriculture is having on the future of medicine in the United States. I am imploring you today, as you consider the future of antibiotic development in this country, that you also consider that the routine overuse of future antibiotics would result in the same conditions we face today. We must preserve those antibiotics critical to human health for use in treating disease—not for growth promotion or disease prevention. Antibiotics are for treatment of illness—period.

My legislation—the Preservation of Antibiotics for Medical Treatment Act—would save eight critical classes of antibiotics for human use while still allowing the treatment of sick animals. I’ve carried this bill for seven years now, and I’m not going to rest until it becomes law. There are too many lives at stake to give up. We can and must preserve antibiotics—the future of modern medicine depends upon it.

Thank you.

Mr. PITTS. And I have a unanimous consent request. I would like to submit the following for today’s hearing record. First, a letter from the Flag and General Officers’ Network, an official 501(c)(19) War Veterans Organization representing three-quarters of all living U.S. Armed Forces Flag and General Officers. Secondly, a statement from Cubist Pharmaceuticals, a global pharmaceutical company headquartered in Lexington, Massachusetts. And thirdly, a statement from the California Healthcare Institute, CHI, their statewide public policy organization representing California’s leading biomedical innovators, over 275 research universities in private, non-profit institutes, venture capital firms, and medical device diagnostic biotechnology and pharmaceutical companies. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. All members’ written opening statements will be made a part of the record. At this point, we have two panels to present testimony. On the first panel today, we have again Dr. Janet Woodcock, the director of the Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Thank you very much, Dr. Woodcock, for coming. Your written testimony will be made a part of the record, and you will be given 5 minutes to summarize your testimony before questions. So at this point you are recognized for 5 minutes for your opening statement.

STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

Dr. WOODCOCK. Thank you, Mr. Chairman, and members of the committee for holding this hearing on this really important issue. There is broad agreement that antimicrobial resistance is a worldwide crisis that is going to require major efforts to combat. In 2012,

the Congress took a significant step in passing GAIN Act which we have been implementing. In Europe, the Innovative Medicines Initiative, which is a public/private partnership launched a major research effort on antimicrobial resistance. Yesterday, the Administration released a national strategy for combating antimicrobial resistance. A high level task force was established by Executive order to carry out and develop an action plan to carry out the goals.

The strategy is a multi-sector effort to attack this problem in all its diverse forms by bolstering basic research, enhancing product development, improving the surveillance, which has already been alluded to, of resistance and use of antimicrobials, modifying the use of antibiotics in food animals, and strengthening international collaboration.

PCAST, which is the President's Council of Advisors on Science and Technology also released a scientific report and scientific recommendations yesterday.

Over the past year, the Center for Drugs at FDA has been very busy on this issue. We have issued many new or revised guidances on antimicrobial drug development. We approved three drugs designated under the GAIN Act. We recently cosponsored a workshop on this topic with the National Institutes of Health. Of course, our fellow center, the Center for Biologics has been working on vaccines, another way of addressing this problem, and the Device Center working on testing methods.

Despite all this progress, we must recognize that a robust pipeline of new investigational antimicrobials does not currently exist, nor is there a large number of drug discovery laboratories out there working to bring forth the next generation of candidate drugs. So, we don't have a robust pipeline. The reason for this, apparently, is primarily the absence of commercial incentives to antimicrobial development. This problem must be solved one way or another if we are going to prevail in our fight against the ever-changing microbes.

We don't just need new treatments for resistant organisms, although we need those urgently, we need to keep introducing additional treatments against common conditions as well, since our existing armamentarium is inevitably going to weaken over time. We don't just need to respond to the current crisis, we need a robust pipeline going forward.

Because this is such a multidimensional problem, we all must work together to prevent the loss of these critical weapons against disease, so I am very happy to answer any questions.

Mr. PITTS. The chair thanks the gentlelady.

[The prepared statement of Dr. Woodcock follows:]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

**STATEMENT
OF
JANET WOODCOCK, M.D.
DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH**

**FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**BEFORE THE
SUBCOMMITTEE ON HEALTH
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES**

**"21ST CENTURY CURES: EXAMINING WAYS TO COMBAT ANTIBIOTIC
RESISTANCE AND FOSTER NEW DRUG DEVELOPMENT"**

SEPTEMBER 19, 2014

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman, Ranking Member Pallone, and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the current state of antibiotic resistance and the need for new solutions to the current crisis.

The decline in antibacterial drug research and development (R&D) in the private sector, at a time when serious antibiotic resistant infections are on the rise, is a tremendous public health problem, resulting in a very serious unmet medical need. The impact of antimicrobial-resistant infections on affected patients and families is significant and tragic. According to the Centers for Disease Control and Prevention (CDC), each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. Many more people die from other conditions that are complicated by an antibiotic resistant infection. As the Infectious Diseases Society of America (IDSA) reports, "The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating. Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays."

Antibacterial drugs first became available during the 1930s and 1940s, offering a tremendous advance in medicine, and were soon adopted as the standard of care in the treatment of a variety of infectious diseases. Many infections that were previously fatal, or left individuals with severe disabilities, became treatable or preventable. Today, antibacterial drugs are critically important across medicine, including in the care of premature infants and for use in surgery, chemotherapy, and organ transplantation. However, bacteria are adept at becoming resistant to antibacterial drugs so it is essential to use these drugs judiciously to delay the development of resistance. Moreover, new antibacterial drugs are needed to provide treatment options in cases where resistance has eroded the effectiveness of existing drugs.

Many factors contribute to the spread of antimicrobial resistance. Any use of an antibacterial drug can encourage the development of drug-resistant bacteria. So it is important that we use antibacterial drugs only when their benefits outweigh their risks. In some cases, doctors prescribe antibiotics either too frequently or for infections that do not warrant an antibiotic, such as infections caused by a virus such as influenza. Sometimes patients do not take their antibiotic regimen as prescribed, making it more likely that microbes will develop resistance. The use of subpotent or counterfeit antibiotics also can contribute to resistance; counterfeit antibiotics are a problem encountered particularly in the developing world. The injudicious use of important antibiotics in animal agriculture is also of particular concern. Through international trade and travel, resistant microbes can spread quickly worldwide. As of today, antimicrobial-resistance mechanisms have been reported for all known antibacterial drugs that are currently available for clinical use in human and veterinary medicine. FDA has partnered with CDC's antibiotic

stewardship programs, including the Get Smart Campaign—which seeks to ensure that all patients get the right antibiotic at the right dose for the right amount of time—to improve consumer and provider education around appropriate use. Antibiotic stewardship programs and education will always serve a critical role in preserving the effectiveness of antibiotic treatment, be it for penicillin or our newest antibiotic therapies.

In some cases, bacterial strains that are resistant to multiple antibacterial drugs have been isolated. Such multi-drug-resistant (MDR) pathogens represent a substantial public health threat. The lack of available antibacterial drugs to treat infections caused by MDR organisms—particularly MDR Gram-negative bacteria¹—that have spread widely through the U.S. health system, have created an area of urgent unmet medical need. Unfortunately, there are very few antibacterial drugs in the R&D pipeline with the capacity to treat these infections.

The Challenges Impacting Antibacterial Drug Development

There are significant scientific and economic challenges impeding the development of new antibiotics. From a scientific standpoint, many patients with bacterial infections are often very sick and need to begin antibiotic therapy immediately. But enrolling a very sick patient in a clinical trial at the same time can be very difficult.

¹ Gram-negative bacteria are a type of bacteria defined by their staining characteristics on microscopic examination.

From an economic standpoint, antibiotics are generally viewed as less profitable by companies and venture capitalists, because of their relatively low price and because they are generally taken only for a short period of time and often only for one course of treatment, by any given patient. Compare this to the long, dependable income stream from a diabetes medicine or a blood pressure medicine that patients take indefinitely, often for the rest of their lives, or the relatively high price associated with cancer and some antiviral drugs. These economic realities can make it challenging for a company to justify large expenditures for the development of drugs in this area, as a recent Eastern Research Group (ERG) report, funded jointly by HHS and FDA, affirms.²

Common medical practices that accelerate the development of antibiotic resistance, such as the inappropriate use of antibacterial drugs, are at odds with the public health goals of preserving the long-term effectiveness of these drugs. The ability of drug resistance to be transferred from one microorganism to another and spread among a population of patients is a phenomenon unique to infectious diseases. Judicious use of antibacterial drugs is essential.

However, the judicious use of antibacterial drugs is at odds with the traditional business models and marketing practices used by the pharmaceutical industry for other drug categories, and serves as just one more disincentive to investment in antibiotics. To address this phenomenon as well as to incentivize antibacterial R&D in general, various thought-leaders in the United States

² http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm.

and Europe have discussed new business models for antibacterial development that delink the sales of these drugs from companies' returns on investments (e.g., an insurance-type model, defense contractor model, antibiotic corporate bond/patent extension certificate financial model, and price for service model, rather than existing price for product model).³ Should such models be adopted in the future, they likely would include new ways of risk-sharing in antibiotic R&D, such as establishing public-private partnerships or new reimbursement models to pay for these essential medicines post-approval.

What FDA is Doing to Address the Current Challenges

Provisions in a law passed a little over two years ago, commonly known as the Generating Antibiotics Incentives Now Act, or the GAIN Act, are helping to stimulate the development of new antibiotics. Under GAIN, certain antibacterial or antifungal drugs intended to treat serious or life-threatening infections can be designated as "Qualified Infectious Disease Products" (QIDPs). As part of its QIDP designation, a drug receives priority review⁴ and is eligible for fast-track designation.⁵ At the time of approval, a product with QIDP designation may be

³ These delinking-type models were discussed at the September 1, 2014, Big Innovation Centre/Chatham House Workshop: "New Commercial Business Models for Antibiotics—What Can Be Learnt From Other Industries?" held in London, United Kingdom.

⁴ Priority-review designation directs overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions or for drugs that have a QIDP designation. Priority-review designation does not affect the length of the clinical trial period. FDA informs the applicant of a priority-review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement.

⁵ Fast-track designation is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Once a drug receives fast-track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process.

eligible for an additional five years of marketing exclusivity, in addition to certain existing exclusivity periods under the Federal Food, Drug, and Cosmetic Act. To date, FDA has granted 59 QIDP designations for 39 different unique molecules. In the past few months, FDA has approved three new antibacterial drugs with this beneficial QIDP designation. The three drugs, Dalvance (dalbavancin), Orbactiv (oritavancin), and Sivextro (tedizolid phosphate), are intended to treat acute bacterial skin and skin-structure infections (ABSSSI) caused by methicillin-resistant *Staphylococcus aureus* and certain other types of bacteria. It is wonderful to have so many QIDP designations and to have drugs approved that are benefitting from the designation. However, we also have to keep in mind that not all products in development ultimately make it to approval; more will be needed to meet patient needs.

FDA is working hard to streamline requirements for clinical trials for studying new antibacterial drugs, and the provisions of the GAIN Act are being actively implemented. But more is needed. There are still significant economic and scientific challenges in the development of new antibacterial drugs that need to be addressed. Additional financial incentives, as well as new approaches to reducing the costs of studying antibacterial drugs, such as common clinical trial protocols, could provide other important means to stimulate antibacterial drug development. We also need cutting-edge science to move forward the development of new and innovative antibacterial drugs, as well as alternative therapeutics to combat bacterial infections. To help drive this effort, CDER has assembled an Antibacterial Drug Development Task Force (Task Force), a group of expert scientists and clinicians from within FDA, to consider opportunities to help facilitate antibacterial drug development. FDA also has an Agency-wide Task Force on

Antimicrobial Resistance, which assures coordination of FDA activities across multiple product areas.

The Task Force is working with many leaders, including those drawn from academia, regulated industry, professional societies, patient advocacy groups, and government agencies. For example, FDA has contributed to the efforts of the Biomarkers Consortium of the Foundation for the National Institutes of Health (NIH) to develop new endpoints for studying antibacterial drugs. FDA also works closely with the Clinical Trials Transformation Initiative (CTTI), a key group of dedicated scientists focused on streamlining and advancing clinical trials for more efficient drug development. As a result, FDA and CTTI have partnered to help convene a variety of important scientific meetings and initiate activities on vital topics related to efficient design and conduct of clinical trials for testing new antibiotics. Our Task Force has also helped FDA team up with colleagues at the Brookings Institution's Engelberg Center for Health Care Reform to galvanize the scientific community's efforts in new antibiotic drug development. The first Brookings Council for Antibacterial Drug Development (BCADD) meeting was held in August 2012, and the Brookings Institution has continued to convene meetings focused on a range of antibacterial drug development issues.

FDA and our Task Force members also have been busy on our own. In February 2013, we held a public meeting focused on creating an alternative approval pathway for certain drugs, such as antibacterial drugs, that are intended to address unmet medical needs. We also have asked

stakeholders for input; in May 2013, we issued a *Federal Register* Notice,⁶ seeking input from the public on a wide range of topics related to antibacterial drug development. Since the GAIN Act, FDA has generated 11 guidance documents for industry⁷ in draft and final form, which describe FDA's scientific thinking with regard to developing new antibacterial drugs.

As part of our Task Force's collaborative efforts, FDA is working closely with NIH to further advance the development of new antibacterial drugs. In July 2014, we jointly hosted a two-day Public Workshop to identify strategies for promoting clinical trials for antibacterial drugs and encouraging partnerships to accelerate their development. The Eastern Research Group (ERG) report was presented at the workshop and other specific issues were discussed, including:

- Priorities and strategic approaches to conducting clinical trials for antibacterial drugs
- Regulatory pathways, including streamlined development programs for antibacterial drugs for patients with limited or no treatment options
- Clinical trial design issues, such as the development of common clinical protocols; using common control groups; statistical analysis issues; sharing data across trials (and data standards); appropriate clinical trial endpoints; and lessons learned from other therapeutic areas

⁶ <https://www.federalregister.gov/articles/2013/05/31/2013-12925/new-approaches-to-antibacterial-drug-development-request-for-comments>.

⁷ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm406769.htm>.

- The role of public-private partnerships in advancing the scientific and clinical trials enterprises.

The implementation of the GAIN Act and the work of the FDA Task Force have provided good first steps toward strengthening the antibacterial drug pipeline, and recent reports suggest that the pipeline is beginning to open up. But, we must do more. Additional attention to financial incentives, new approaches for studying antibacterial drugs (such as the creation of common clinical trial protocols), and streamlined development pathways will likely be needed to improve the climate.

Encouraging the Development of New Antibacterial Drugs

FDA recognizes its role in fostering the translation of scientific advances into the development of drugs that can treat disease and in considering novel approaches that might facilitate development of drugs that can treat unmet needs. Traditional drug development programs are designed to evaluate the benefits and risks of treatment with a high degree of precision for the full range of manifestations of a disease or condition. Often this will involve studies that expose a large number of patients to the drug. In some cases, such as when safety issues have arisen with prior drugs in a class or are noted in early clinical trials, additional trials are needed to help characterize potential serious, but infrequent, risks. Typically, these studies are needed when there is an expectation that the drug will be used broadly in patients with less severe manifestations of the condition.

Existing processes to expedite drug development and review of important new therapies have worked effectively in many circumstances, such as under the accelerated approval pathway, which permits drugs that are intended to treat serious or life-threatening diseases or conditions to be approved based on surrogate or intermediate endpoints. In addition, FDA's long-standing commitment to regulatory flexibility regarding the evidence required to support approval has effectively facilitated development of drugs for patient populations with serious unmet medical needs.

However, we can do more. Given the public health threat posed by antimicrobial resistance, FDA believes it is necessary to consider new mechanisms for encouraging the development of new antibacterial drugs to address unmet medical needs in the treatment of serious and life-threatening bacterial infections. We look forward to ongoing engagement with consumers, clinical experts, researchers, industry, and others to achieve this goal.

As the Committee knows, one option that has been proposed is the establishment of a new Limited Population Antibacterial Drug (LPAD) program. It is our understanding that, as a general matter, drugs approved using an LPAD pathway would be based on more streamlined development programs that establish that the drug is safe and effective in a limited population of patients with serious or life-threatening infections and unmet medical needs.

Importantly, because under this proposal, as we understand it, LPAD drugs would be approved based on streamlined development programs, there would be more uncertainty about potential risks posed by the product. This may result in a positive benefit-risk profile in a limited population of patients with serious or life-threatening infections and unmet medical needs. However, the benefit-risk assessment would be different for a broader, more heterogeneous patient population with less serious manifestations of the infection and which has other treatment options. A clear branding mechanism would convey accurately to physicians using the product the limitations of the data supporting approval, including the uncertainty and the unique benefit-risk profile associated with the drug. Such labeling is particularly important in the context of antibiotic drugs, where historical overuse has led to increased antimicrobial resistance.

Expedited Updating of Susceptibility Test Interpretive Criteria (Breakpoints) To Maximize the Effective Use of Existing Antimicrobial Products

Enabling physicians to select appropriate antibacterial drugs is critical to individual health, as well as the public health, as we continue to combat antimicrobial resistance. Generally, physicians rely on antimicrobial susceptibility test (AST) devices, which provide information about whether a bacterium is either susceptible or resistant to an antibacterial drug. The criteria used to determine susceptibility are commonly referred to as “breakpoints.” This information helps physicians choose appropriate antibacterial drugs for treatment. As a general matter, a key part of the information that physicians use to select an antibacterial drug is whether the patient’s infecting bacteria is categorized as susceptible.

Outdated breakpoints can result in selecting a drug that may not effectively treat a patient's infection, and in serious or life-threatening situations, the patient could succumb to the infection or its complications. Outdated breakpoints can also interfere with the implementation of appropriate infection control procedures. Hospitals need up-to-date breakpoint information in order to determine whether an infection is caused by a resistant pathogen, and to put appropriate infection control procedures in place for those antibiotic-resistant bacteria.

AST device manufacturers need to be able to incorporate up-to-date breakpoint information into their devices quickly. However, currently, it can take several years to do so.

Under the current regulatory framework, each antibacterial drug manufacturer updates its drug labeling with new breakpoint information and only then does each device manufacturer update its device algorithms and labeling. Reviewing breakpoint labeling supplements for each individual drug product (even when it shares the same active ingredient(s), and thus, generally has the same breakpoints) is no small task. There are approximately 200 reference-listed antibacterial drug products and more than 400 generic copies of those products. Moreover, the process begins with the submission of labeling supplements from the drug manufacturers. This protracted process of manufacturers updating the product labeling for each antimicrobial drug product adversely affects the public health by preventing AST device manufacturers from being able to promptly update the breakpoint information in their devices, and it utilizes both industry

and Agency resources that could otherwise be used for antibacterial and antifungal drug development or reviews that could confer greater benefits for patients.

Recognizing the significant challenges involved in updating breakpoints, in 2007, as part of the Food and Drug Administrative Amendments Act of 2007 (FDAAA), Congress directed FDA to prioritize breakpoint labeling updates, and FDA has done so. Approximately 150 of 207 product labels for reference-listed drugs have been updated over the past seven years. However, bacteria evolve and develop new resistance mechanisms, so breakpoints can shift periodically over time. Accordingly, the process of updating breakpoint information in drug labeling is never-ending. So, even as we finish updating the initial 207 product labels, we will be re-updating product labels for some drugs that were updated in the last seven years.

Moreover, while health care providers will always encounter infections caused by a wider range of bacteria than those identified in clinical trials, currently, AST devices are generally only labeled for reporting information on the susceptibility of bacteria identified in clinical trials conducted for the approved indication(s). We need a better, more modern and streamlined administrative process to help AST device manufacturers incorporate up-to-date and comprehensive breakpoint information in their devices more quickly, in order to get this information to health care providers sooner for the care of patients.

Solution for Updating Breakpoint Information Faster

In order to address the problems with the current scheme for updating breakpoints, FDA needs to take breakpoints out of the drug product label and utilize more rapid, electronic means of communicating this information. Posting breakpoint information on FDA's Internet website could enable us to update breakpoint information more efficiently. As mentioned, many antibacterial drugs have the same active ingredient(s), and thus the same breakpoints. Accordingly, as a general matter, breakpoints are neither proprietary, nor specific to a particular drug product. Therefore, if FDA posted appropriate breakpoints for penicillin or amoxicillin products on the Internet, then FDA could take one single action to update the breakpoints for multiple drug products simultaneously.

To help FDA ensure that it can update breakpoint information accurately and expeditiously, the Agency could leverage the work being done by standards-development organizations to develop breakpoints, and recognize them, when FDA agrees that they are appropriate. FDA would retain full authority to accept a standard in whole or in part, or to establish alternative breakpoints. In addition, companies could submit data to support alternative breakpoints, if they disagree with the recognized standard.

CONCLUSION

It is virtually undisputed that we are facing a tremendous public health crisis because of the rise of serious antibacterial infections and the simultaneous decline in R&D in this area. FDA is using the tools we have to begin to strengthen the antibiotic drug pipeline. However, more work is needed to improve the current climate, and FDA is looking forward to continuing to work with stakeholders to address this public health crisis.

I am happy to answer any questions you may have.

Mr. PITTS. I will begin the questioning and recognize myself 5 minutes for that purpose.

Dr. Woodcock, yesterday FDA Commissioner Hamburg posted a blog post titled, "FDA's Take on the Executive Order and National Strategy to Combat Antibiotic Resistance Bacteria" where she wrote "Few issues in public health today are as critical and time urgent as combating the growing threat of antibiotic resistance. It is a high priority for FDA to work with our partners to find solutions for this serious public health problem."

Would you explain the urgency of this situation for public health and national security?

Dr. WOODCOCK. Well, as many of the members have already stated—

Mr. PITTS. Press your—

Dr. WOODCOCK. Sorry. As many of the members have already stated, for public health, we are already seeing excess deaths, and we are seeing people who in fact cannot be treated with any existing therapy that we have, and I think the threat here to public health is that we can have emerging epidemics of these organisms that they will spread. Right now they are fairly limited and sporadic, but will spread, and we will be in a situation where we literally can't treat an infection that is unfolding in a wider sense.

In addition, each year we are seeing greater and greater resistance problems for ordinary microorganisms, and so doctors are having to turn to what we would call second or third line antimicrobial agents, agents we use to reserve for very selected situations. And as that occurs, more resistance to those will evolve, and so eventually we are going to be empty handed.

Mr. PITTS. OK. In the case of antibiotics, even slight variations in the bacteria's genetic makeup can be the difference between a drug working or not working. Understanding that bacterial resistance compounds this problem many times over, why is it important for our antibiotic drug pipeline that we have multiple drug options for the same class or family of drugs?

Dr. WOODCOCK. Yes. Well, what we know is when we develop an antimicrobial it evolves over time after that antimicrobial is used, and after time, it may be that it can be effective against certain forms of an organism and not against other more resistant forms, and the mechanism of resistance is different. There are many different mechanisms of drug resistance. That is why having a large number of drugs in a class or even improvements in a class can be extremely helpful in this situation because you can match the antimicrobial to the organism you are trying to treat.

Mr. PITTS. Do we have the type of drug redundancy highlighted above that we need to effectively combat this problem right now?

Dr. WOODCOCK. We do not because that is sort of the cutoff line. The antimicrobials that are no longer useful against many infections is getting higher and higher every year, especially for certain types of bugs.

Mr. PITTS. Do you believe that we need to further incentivize new drug and diagnostic development if we are to appropriately address the issue of antibiotic resistance, and if so, what would you recommend?

Dr. WOODCOCK. I do believe we must incentivize it because the current situation shows that the incentives have not been enough to stimulate development in this area. So for drug development, apparently, developing antimicrobials is still not attractive enough. It still doesn't appear that it might not be a loss to business, that there isn't an attractive enough business model to build those robust programs that are needed to both discover and then develop new classes of antimicrobials.

For diagnostics, I will tell you that Louis Pasteur and Alexander Fleming would recognize the methods we use today because they invented them, and so there is a lot of room at the top for improvement. We are using genetic sequencing of human genome, which is huge compared to the microbial genome, but using clinical practice of advanced methods is not the norm, and that, improving diagnostics would tremendously simplify clinical trials and also treatment.

Mr. PITTS. Now, we are talking about incentives here. Do you believe that such incentives could be used in other unmet need areas beyond just antibiotics?

Dr. WOODCOCK. Well, of course, I believe that that is possible. However, as I think Mr. Waxman said, there are tradeoffs you have to balance. There are always tradeoffs in putting these incentives in place, and I, being a physician and a scientist, am not the most qualified person to make those tradeoffs. I think Congress really has to weigh those.

I can tell you that the public health urgency for this problem is severe and will continue, and I think you'll hear that from other experts as well. We are not over the hump here. We have not succeeded in developing a system that will continue to generate effective new antimicrobials. We don't have that. We have sort of heroic efforts here and there.

Mr. PITTS. Thank you, Dr. Woodcock. My time is expired. The chair recognizes the ranking member, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman. Both the Executive order issued yesterday and the report of the President's Council of Advisors on Science and Technology emphasize the danger of antibiotic use in the agriculture industry.

While it is clear we should do more to encourage greater research in development of new drugs, it also makes sense that we should be investing in efforts to limit the further spread of drug resistant bacteria strains and make the best use of existing drugs so they can remain effective for longer periods.

So Dr. Woodcock, in your testimony, you point to FDA's cooperative effort with CDC to promote greater stewardship, including the "Get Smart" campaign. I would like you to elaborate on this partnership, and on FDA's role in the initiatives laid out in yesterday's Executive order.

Dr. WOODCOCK. Well, obviously there needs to be better stewardship both in human and agricultural uses of antimicrobials, as has already been said. About half, CDC estimates, of antimicrobial outpatient prescriptions are not necessary, given the condition the patient has, and that leads, especially if people only take the drugs for a little bit, can lead to big problems, and also in the animal

world. Now, in the human area, FDA is collaborating with CDC on these efforts, but CDC is primarily the lead on improving better use in health care, and that is a multi-faceted effort.

In the animal health space, FDA had put out a guidance to the Center for Veterinary Medicine calling on manufacturers to cease use of important human antimicrobials for growth promotion in food animals, and they have secured the cooperation of all the manufacturers who are engaged in that space, to my understanding, and then there will be a process whereby those indications are withdrawn. And then use in food animals would be required under the supervision of a veterinarian for a health condition in the animal, so that would be a great improvement.

Also, as was discussed in the report yesterday, though, we need better surveillance and data to understand the link between antimicrobial use in animals, or humans, in the development of resistance. That is still rather poorly understood.

Mr. PALLONE. All right. Thanks. I wanted to get FDA's views on certain aspects of the ADAPT Act. As I understand the purpose of the bill, its goal is to facilitate FDA's ability to approve new antibiotics that have been tested only in a limited population, and for which the need for the drug is critical. I know you already do approve drugs tested in limited populations, for example, drugs for rare diseases, so I would like you to explain if and why the existing accelerated approval mechanisms aren't meeting the current need. I would also like you to address whether you believe the ADAPT Act as currently drafted provides the FDA with sufficient authority to ensure that ADAPT antimicrobials would be labeled in a way that clearly distinguishes them as different from other antimicrobials.

It seems that if we are considering allowing drugs on the market tested only in very limited clinical trials, we need to be confident that providers and patients understand the care with which these drugs must be used.

Dr. WOODCOCK. Yes. Well, we think the ADAPT Act has elements that we have been discussing for a long time. Let me explain some of the situation. We approve drugs for limited population all the time, orphan drugs, rare subsets, but generally speaking, the clinical community is not tempted to use those for somebody with a cold, right. It is for some rare enzyme deficiency or some cancer, rare cancer or whatever. With antimicrobials, the big problem is really the use outside of where it would really clinically be indicated, and one of the barriers for these highly resistant organisms is that their occurrence is sporadic.

We are very lucky that there are not widespread outbreaks, right, but because there are not widespread outbreaks, it means the testing of the drugs in broad populations is difficult. Actually, that is good news because otherwise we would really be in trouble, all right, if there were large numbers of people suffering like this.

So that means, by definition, if you are going to get these drugs on the market for these small populations of resistant organisms, you are going to have to have small trials, and you will have more uncertainty about the effects. So more uncertainty about the effects, and worries that the drug will be used in conditions where

it is not warranted, those are the two issues we are trying to address.

In orphan conditions, yes, there is uncertainty about the effects, but the orphan community that uses these drugs, usually those are sub-specialists who are treating a very rare disease, and they have a very good understanding of what studies were done on the drug and so forth. It often may be the only drug ever studied for that condition.

So our thoughts, and the Administration has not taken a position on this, but we have thought about this, that to offer very small development programs is a big incentive, but the quid pro quo really is to send a signal to the clinical community, some kind of signal, some kind of message that this is special. That there is more uncertainty and also use good stewardship with this particular product because using it in a lot of conditions where it is not warranted would also more rapidly increase the development of resistance.

Mr. PALLONE. Thank you.

Mr. PITTS. The chair now recognizes the gentleman from Georgia, Dr. Gingrey, 5 minutes for questions.

Mr. GINGREY. Mr. Chairman, thank you for recognizing me. I know that the vice chairman of the subcommittee, my colleague, Dr. Burgess, was scheduled to go next, and Mike, thank you for letting me ask my questions now.

Dr. Woodcock, thank you, too. As a witness, we have had you before our committee many times since I have been on the committee, and you are just always so straightforward and you explain things in a very clear way, and I mean that sincerely. You do a great job, and we appreciate that very much.

I want to continue in the line of questioning that Mr. Pallone started, and again, I have limited time, so let me get right into that. Congressman Green and I had been working on this ADAPT Act, as you know, and it is legislation that supports the FDA's flexibility to consider all forms of evidence in addition to data from clinical trials when considering novel antibiotics.

How important do you believe adaptive and unique trial designs can play in encouraging new antibiotic drug development? And before you answer that part, and I am sure everybody in the hearing probably knows this, but in your typical phase 3 trials before a drug can get to market, you are going to have to have a population of 1,000 or more people that you are treating, and there are also other requirements that they can't have had an antibiotic within 24 hours of the start of the trial, or at one point it was 3 days, I think, and then we got it down to 24 hours.

But you are going to have a limited population of people that have these diseases, and when they get to the hospital sick as heck, the first thing the doctor is going to do, the emergency room physician is going to hang some antibiotic, even if it is wrong, they are going to start treating them, and then, all of a sudden they are not eligible, and you have a limited number of people. If you wait till you get 1,000, it is too late. So if you will kind of take that a step further and discuss that for us.

Dr. WOODCOCK. Thank you. And thank you, and Mr. Green, for your leadership on this. I think it is very important.

Yes, there is a range, and I think that is what people have to recognize. There is a range of development programs that are needed. For common conditions, outpatient pneumonia, we have a lot of drugs out there that still work. If we introduce new drugs, we want them to be just as good as the other drugs, and they are going to need larger development programs, and that is true for many. But for these very rare, fortunately, resistant organisms that are multi-drug resistant, there is almost nothing to treat them. These cases are occurring sporadically here and there or in outbreaks in ICUs or something like that, and we have to think of different ways of evaluating new treatments. We can't just set up a trial and wait for all this to happen and expect we will be able to enroll thousands of people. And it is true, in fact, if we enrolled thousands of people, it will have been too late, this would be a terrible thing.

So it is true that all antimicrobial drug development is very difficult. In addition to the economic problems, there is this huge difficulty in doing trials, especially in people who are really sick. You can't use a placebo, obviously. You don't know, because of the problem with diagnostics, you may not know for a few days what organism they are infected with. So there are all these technical problems that make it very difficult to do antimicrobial drug development.

So because we have a tremendous unmet medical need for people—where there is no treatment available, typically what we do in that case is we accept more uncertainty, and that means novel trials that we might do.

Mr. GINGREY. Dr. Woodcock, speaking of that uncertainty, I think that is probably why, and I commend the President for this in his executive order of just yesterday, the \$20 million award for the development of these point-of-care diagnostics so someone could take a pill or a piece of tape or something and put it inside their mouth. If it turns a certain color, you know what you are dealing with right there, and you don't have to just shotgun approach.

Dr. WOODCOCK. That is right.

Mr. GINGREY. You can immediately go right to what you need, so I think it is a great thing.

Dr. WOODCOCK. I agree. I mean, if we could bring diagnosis of infectious disease into the 21st century, we would have made a huge advance and really accelerated the development of therapy, so that is a good thing.

Mr. GINGREY. Thank you very much, Mr. Chairman. I yield back, and thank you for your courtesy.

Mr. PITTS. The chair thanks the gentleman. Now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for questions.

Mr. WAXMAN. Thank you, Mr. Chairman. I also want to say to you, Dr. Woodcock, this may be the last hearing where you and I will have the opportunity to publicly talk like this, but you have done a wonderful job at the FDA, and your responses to questions from both sides of the aisle have been very, very thoughtful, and I want to commend you for the work you have been doing and thank you for it.

I want to echo the comments by Mr. Pallone about the importance of strong labeling statement or logo in the context of the

ADAPT Act. I think it is essential that the drug bear a prominent statement describing the abbreviated pathway by which it came to market. Without this requirement, I am not sure that the whole thing would work. It would be much less likely to achieve its purpose of fostering and facilitating the development of critical new antibiotics for life-threatening resistant pathogens. And additionally, inappropriate or injudicious use of a drug developed through this pathway could result both in patient harm and in more rapid loss of the drug to antibiotic resistance, so I just wanted to underscore that point.

I want to ask you about a concept that you mention in your testimony designed to spur development of new antibiotics. That is delinkage. As I understand it, under this model, the sale of antibiotics would be delinked from the returns on investment. After all, we don't want to say that we want more antibiotics sold. We want to make sure that the antibiotics that are sold and used are antibiotics that are going to stay effective for as long as possible.

So some other funding mechanism would be created besides the traditional way of selling more drugs to ensure that a company was able to make a profit from developing an antibiotic. As others have noted, the usual pharmaceutical business model doesn't fit very well in the case of antibiotics.

We need to, however, recognize companies need to be able to recoup their investment and make a reasonable profit. Others have raised the notion of a wild card exclusivity. I mention in my opening statement I think it is a very dangerous idea. We don't want to force patients taking one type of drug to fund development of another, so ensuring that antibiotic developers still can make a profit without linking that profit to how much antibiotic is actually sold seems like a brilliant way to approach this problem. Could you elaborate on this, tell us more about what ideas you have along these lines?

Dr. WOODCOCK. Well, yes, because right now we have incentives that actually weigh against our objectives. Our objectives are that we have the most judicious use of new antimicrobials possible, and yet the incentive, if you have spent \$500 million developing the drug, you need to recoup that amount of money and a fair profit to stay in business and develop the next generation. And so these incentives are sideways to each other and countervailing, and so that is one idea that has been raised that we mentioned to delink the need to have a large volume of the antibiotic used which would then lead to faster development of resistance. So if that were delinked from the—

Mr. WAXMAN. Do you have ideas on how to do that?

Dr. WOODCOCK. I, as I said, I am really not good at financial matters, and so I am sorry.

Mr. WAXMAN. We could count on you for everything, economic advice as well as pharmaceutical and food and other things that FDA does.

Well, let me talk to you about another issue and that is in stewardship, using antibiotics judiciously. It seems to me this is a critical component of any effort to address the antibiotic resistance problem. The just released report on Combating antibiotic resistance from the President's Council of Advisors in Science and Tech-

nology, or the PCAST, stresses the importance of increasing the longevity of current antibiotics by improving the appropriate use of existing antibiotics and it discusses the need to look at both human use and animal use of existing antibiotics.

We know there is a lot of inappropriate use of antibiotics, both on the human side and I believe on the animal side. The PCAST report describes the important role that diagnostics can play in reducing this type of inappropriate use. Do you agree that diagnostics are important for stewardship efforts? And you alluded to this earlier, but can you describe how the widespread adoption of diagnostic tests would help preserve existing antibiotics, and is FDA taking any actions to foster the development in the use of these tests?

Dr. WOODCOCK. Well, I believe diagnosis should be the foundation of therapy, and unfortunately, in the infectious disease space, often you are treating well before you know or before you ever know what the person has, and this is a fundamental problem. Like I believe the advent of rapid strep testing has really reduced the use of drugs for presumptive strep that often is colds or something, upper respiratory infections of one sort or another.

So if we could get more certainty into the diagnosis early, be able to reassure the doctor and the patient or family that, no, this is not a dreaded bacterial infection that needs an antimicrobial, we could go a long way, I think, to lowering this inappropriate use. So diagnostics are the key. It is just we are far away from that right now and need to stimulate that.

Mr. WAXMAN. Give more incentives for that?

Dr. WOODCOCK. I believe so, uh-huh.

Mr. WAXMAN. Thank you. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman. Now recognizes the vice chair of the subcommittee, Dr. Burgess 5 minutes for questions.

Mr. BURGESS. Thank you, Mr. Chairman. And Dr. Woodcock, again, welcome to our humble little subcommittee. Your last statement, diagnostics are the key, now, this is not part of this discussion today, but we have had discussions on diagnostics, and I realize it is not your part of FDA that is talking about increasing the regulation of testing, particularly laboratory diagnostic tests, or laboratory developed tests, rather, but that that factors into the equation. I mean, yes, we are talking about the length of drugs, of time it takes drugs to get through the pipeline, but if it also takes the testing longer to get through the pipeline, we are actually making things harder on ourselves, are we not?

Dr. WOODCOCK. Yes. Well, recently, for example, we have had a workshop with Brookings on this issue of the co-development and the technical issues. On the final guidance that we put out recently on co-development and companion diagnostics said for life-threatening disease, we are going to go ahead and approve the drug even if the test isn't fully baked yet.

There are technical problems in getting these tests developed right now, and I think all of us believe that for many of the genomic tests, that next generation sequencing is really going to be a key and really rapidly improve this situation. So I have great hope that that will be coming soon because we are facing it now.

Every disease—say cystic fibrosis, for example, there are 150 different mutations in that gene, each of which may translate to a slightly different phenotype in prognosis, and that goes with cancer and many other diseases. We really need to rapidly get to a point where we have a true standard that we can all agree upon so that we know what we are dealing with, and that, yes, that will rapidly improve development of drugs for these serious conditions.

Mr. BURGESS. Well, I share your enthusiasm for genomic testing. I am somewhat more pessimistic because it seems like I can remember Dr. Elias Zerhouni in my first term on this committee, which was many, many years ago talking about some of these same things and where it is sort of the Jetson's flying car. We are still waiting for that to happen.

On the issue, and at HHS, you did your study on antibiotic initiatives, the incentives for development of new drugs, vaccines, and rapid diagnostics for bacterial disease, and then talked about moving the needle in monetary terms for companies by a reduction of the time for clinical trials, correct?

Dr. WOODCOCK. Yes.

Mr. BURGESS. Is it really possible to move the needle on that?

Dr. WOODCOCK. Well, I believe for the limited population antibiotic development use that is possible. That is only one factor, but if you have a very high bar to getting on the market, then you are going to need much stronger incentives. I believe for those very rare, right now, resistant organisms, we could have very small development programs and that there be a societal agreement that having a treatment available for those is better than having nothing. And so we could have very small development programs.

We simply would like to have a signal then to say to the clinical community, "No, that this is different, OK. No, this didn't have a huge development program. We are offering you a tool, but you ought to be aware and provide good stewardship of this tool." So we do believe in most cases it is possible, and even for common diseases, we have worked with new guidances to try to lower the cost of a development program so that the pipeline can be, you know, more robust.

Mr. BURGESS. On the issue of judicious use and stewardship, and I hear the birds that are set on that, but when you talk about using things outside their area of indication, we tend to think of the world in which we live, but I am from Texas, and just a little bit south of Texas there is a different world where there is not a prescription required and people can simply go to the farmacia and say I need this—

Dr. WOODCOCK. Right.

Mr. BURGESS [continuing]. And the pharmacist may direct them to a particular drug or they may just simply come in with a recommendation from a family member and make that purchase. So it is obviously harder to control that within the jurisdiction of the United States when it is happening right outside; is that not correct?

Dr. WOODCOCK. I totally agree. Everywhere is right outside with modern air travel, and so we are getting soldiers back from combat who have acquired very dire resistant infections. We have travelers who are coming back in the United States who have been in—there

are many countries where antimicrobials are used very freely and may be available to consumers without intermediaries.

Mr. BURGESS. And it concerns me that we want to put the onus on the doctor treating the patient in an emergency room with a sick kid and a concerned family, and we are putting all the onus on our physician here when the greater wide world none of those constraints exist. I agree with labeling. I agree with making the indications well known, but I don't think we should ever try to put the Federal Government in the position of second guessing the judgment of a physician.

Dr. WOODCOCK. Well, we agree with that. Because treatment is empirical, we can't indicate. It has to be suspected. You can't say you can't treat a patient because this wasn't studied in clinical trials if there is nothing else available, or if clinicians, as you said, must use their best judgment when a patient presents before them. We agree with that. We want to give the best directions and information to the clinician so they are aware of not only what clinical situation they are dealing with but how much information pertains to the drug and what kind of drug it is.

Mr. BURGESS. Thank you, Mr. Chairman. I will yield back.

Mr. PITTS. The Chair thanks the gentleman.

Now, recognize the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Dr. Woodcock, for being here this morning. It is always a pleasure to have you before our subcommittee.

I want to commend you and the FDA on the efforts on the GAIN Act. I know at least two drugs have been released, and I also want to thank you for your efforts on the ADAPT Act legislation I co-sponsored with my colleague and good friend, Dr. Gingrey.

When Dr. Hamburg participated in last week's Cures round table, she spoke about the troubles with large clinical trial designs in the antibiotic space.

Can you tell me your thoughts on how the unique nature and incentives, or even disincentives, inherent to the antibiotic space can sometimes make large clinical trials prohibitive?

Dr. WOODCOCK. Certainly. Well, not only is it actually kind of hard to discover new antibiotics, it is expensive to develop them, and the reason is you have a—it is really what Dr. Burgess was talking about. You have a patient before you with pneumonia. They could have all sorts of different organisms causing the pneumonia, and without rapid diagnostics, you don't know what is causing the pneumonia.

And so when a physician is trying to use an investigational drug, you have a sick person in front of you, you have a prolonged consent process where you have to have informed consent; people are not going to wait, often, to go through that process to start a sick person on antibiotics.

And so then we have the issue that the patients are pretreated with different therapies until they get into the clinical trial, and then you have all the heterogeneity, and then you have existing therapies. It is not ethical to have the comparison group have no treatment usually. And so you have to compare it. You have to do a comparative trial against existing therapy. Those are typically called non-inferiority trials because you may not expect to be better

than existing therapy; you simply want to show you're statistically as good as.

So those challenges tend to increase the number of people needed to be enrolled in a clinical trial to a very large number, and they are hard to get. They are hard to enroll because clinicians often don't want to take sick people and go through all the paperwork to get them in a clinical trial.

Mr. GREEN. OK.

The ADAPT Act envisions a scenario where more adaptive clinical trials may be used to help drug developers seeking to create the next antibiotic effective against drug-resistant bacteria.

Can you tell me your thoughts on how the pathway laid out in the ADAPT Act may benefit drug companies in pursuit of these new and novel antibiotics?

Dr. WOODCOCK. Yes. Well, we envision that you can make trade offs based upon the medical need, and we do this in many cases. So if you have a tremendous medical need, people are going to die quickly, and you have nothing to treat them with, then you will accept a lot of uncertainty about the estimates around safety and effectiveness in exchange for something that may work for that patient. Right? And so that means you can have shorter, very small development programs, if the need is huge.

On the other hand, if we are talking, for example, about another drug to treat pneumonia, which is a more common infection for which therapies are available, that situation would not be covered by the ADAPT Act. With ADAPT we are talking about rare resistant organisms where there are really very few treatment options available. And we actually think there are multiple development programs that could be done, depending on this level of need.

In some cases, you may only have ten infections in the United States a year of this certain organism. In other cases, you may have hundreds. You could get a more robust program there, right? But then you are going to be exposing more people when you approve the drug because there are hundreds of people, maybe thousands of people, out there that have the condition.

So you would basically match the development program and the medical need together and put that together, but then we would like to have a very strong signal or symbol or whatever, not of a fearful signal or whatever, but an informative signal to the clinician that the drug had gone through this kind of development pathway so they would understand that.

Mr. GREEN. Thank you.

And I hope with this hearing today and we will be able to move the ADAPT Act across the line in the future.

In the coming weeks and months I expect to continue our dialog with interested parties and stakeholders, including our second panel today, on ways to strengthen this proposal and complete the next step in fighting our public health crisis.

I want to thank you and your staff for your hours you have spent working with our offices during the August recess, and I know we can continue that effort because this is important. And again, thank you for being here.

And I yield back my time, Mr. Chairman.

Dr. WOODCOCK. And I thank you for your leadership.

Mr. PITTS. The chair thanks the gentleman.

And now recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you very much, Mr. Chairman.

Good morning to you, Dr. Woodcock.

Dr. WOODCOCK. Good morning.

Mr. LANCE. As members of the committee, we have heard firsthand the urgent need for greater incentives to encourage new drug and diagnostic development in the antibiotic space.

Some of the witnesses on the second panel have recommended a wide range of incentives that would encourage greater development.

Do you believe that incentives we identify in the antibiotic space might also benefit other areas of unmet need such as rare diseases?

Dr. WOODCOCK. Well, as I said earlier, I believe that there is a tradeoff between the incentives you offer. There is always some tradeoff there, and there are various orphan diseases for which there are many, for which no development is occurring. So I think you have to determine whether, those tradeoffs, those economic tradeoffs and I am not qualified to say what is the right course. I think that Congress makes those decisions.

However, I can tell you that antimicrobial development is urgent and it is a public health issue. The orphan drugs, those people are suffering from those, have a tremendous need for therapies to be developed, and few are being developed.

We are doing some things such as working with the National Organization for Rare Diseases to get better natural history studies that will incentivize development and make it easier to understand what is the course of this orphan disease so we understand what is needed to study it. However, there are still major financial obstacles.

Mr. LANCE. Thank you.

As you know, I chair the rare disease caucus on the Republican side, and I have in my office virtually every week parents of children who suffer from rare diseases where there are no medicines at all, and as a society, we have to do a better job, and I have read the testimony of those on the second panel, and I hope we can move forward.

And you say you may not be qualified, but I think you are one of the great experts in the country on all of these issues, and we look forward to working with you in that area.

Yesterday the President announced an executive order on a five-year plan to combat antibiotic resistance. What role, Dr. Woodcock, will the FDA play in helping to facilitate the President's order?

Dr. WOODCOCK. Yes. Well, we have been working with the planning group on this, and the FDA has a wide range of responsibilities, everything from animal health and those issues, the surveillance activities which are done of antimicrobial resistance, for which CDC is the primary lead, but FDA, for example, works with CDC and USDA on the National Antimicrobial Resistance Monitoring System, NARMS, which is mentioned in those reports which monitors antimicrobial resistant organisms in foods and so forth, and these things are intended to be strengthened.

In addition, we will work on redoubling our efforts to streamline antimicrobial development from a regulatory perspective, and obviously there is interest in better diagnostics which is put forth in that report. So we have multiple roles to play.

Mr. LANCE. Thank you.

And finally, Dr. Woodcock, may Bucknell win all of its games in football this autumn except, of course, against Lehigh.

I yield back the balance of my time.

Dr. WOODCOCK. Thank you.

Mr. PITTS. The chair thanks the gentleman.

Now recognize the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman.

And, Dr. Woodcock, it is good to see you back here again, but I think you are being too coy. The business model to whether it is going to be in diagnostics or testing is the same business decisions that we make in our home. It is simply about risk and reward, and so what is the reward that will encourage them to stay and what is the amount of risk, and I think you all are going to play a big role in that, and we would hope you will work with us to do that.

I have been very excited about this debate of the diagnostic space, and in your opening statement, and I had to go onto the World Wide Web. All new technology allows us to do that without telling staff to go find it and then get it back to us.

Fleming was born in 1881. Pasteur was born 1822.

Dr. WOODCOCK. Right.

Mr. SHIMKUS. Surely if they could recognize our testing procedures now, we have got work to do to ramp it up, I think, and that is the whole biosimilar debate and the genetic markings and all this other genome stuff that is going on. So I am very, very excited.

Also I have been involved and helped along with following Dr. Gingrey's lead. Appreciate the work he has done. And Gene Green, I look forward to working with Gene as we move forward in the next Congress, and we are having discussions to do that.

So you hear the same questions right from us? And so I think what we really want to do, and we will hear it from the next panel, is let's get a handle on this risk and reward, and I am not so adverse to incentivizing the private sector in something that they are moving on that is going process and helping them do that if then they are going to take and then go in places that no one else is going to go.

So one of the first questions was, as you have seen of companies leave the field of antibiotics, are they small, medium, or large? How would you classify them?

Dr. WOODCOCK. Well, I would say that the larger companies, most of them have left the area for better pastures, so to speak, where they see a business model that provides a return on investment, and similar with many of the medium companies.

There are many small startups that are trying to get into the antimicrobial space and that is good news, but I must recognize they aren't always as successful and they may only have one product that they are trying to develop.

Mr. SHIMKUS. So, and we have talked a lot about the ADAPT Act today, and there has been some success in that process.

Do you think there are some additional things we can do to incentivize? What other things can we build on to encourage additional incentives for the ADAPT Act or other processes that we are talking about?

Dr. WOODCOCK. Well, I think you have to think about what are the alternatives. All right? I know there is some government development—there are government awards. Those are usually under contract. They are for certain entities—molecular entities.

So there are a few of those, but what are the other ideas to develop a robust—you need drug discovery effort, and that means scientists working full time in laboratories trying to figure out the new molecules. This is way before a drug gets tested in people, and it doesn't really involve the FDA, and what I understand from the community, the discovery community, is actually antimicrobial discoveries are quite hard.

And I didn't know that until I talked to them, that they have screened large numbers of molecules and pathways and so forth, and it is harder, it is hard to find the next generation of products. And so that means a very robust scientific effort has to go on in the basic science of microbes and also in discovery of these new molecules, and to do that, somebody has to have the faith that they are going to make money from that 10, 15 years hence. OK? And they don't have that faith right now, I can tell you.

So I don't think whatever has been done is enough. And because you have to consider, if it is not going to be commercial development, how is it going to happen? Where is it going to happen?

Mr. SHIMKUS. And would help us as we go through this process, help this committee to identify ways that we can help incentivize?

Dr. WOODCOCK. Absolutely.

Mr. SHIMKUS. I mean, because you are talking with these folks. And we will too, but we will need a lot of ears on it.

And I am going to end just with this, this labeling debate, the way I understand it. We went through this debate with the paper labelings and the information on pill bottles that no one reads. Everybody knows that. So labeling through the Web and labeling through—there has got to be a better way than just to keep putting stickers on pill bottles or things, because they are just overwhelmed, and I would like some simplicity in that. That is just a statement.

Dr. WOODCOCK. Could I respond to that?

Mr. SHIMKUS. Please do.

Dr. WOODCOCK. I think the FDA—CDER is working on developing a patient information leaflet. All right? A one-pager that you get either electronically or at the pharmacy that tells you—every other country has this kind of thing. OK? So it tells you how to take the drug, what it is for, and so forth.

But then we have proposed and we are interested in going to an electronic physician label which is that thing that is folded up inside the pill box. We would like to move that to electronic with some paper options for those who are still electronically impaired, shall we say.

But most of the world can easily get that information at Drugs@FDA, and many other sites.

Mr. SHIMKUS. Thank you.

Mr. PITTS. Chair thanks the gentleman.

And now recognize the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it.

And thank you for your testimony, Dr. Woodcock. We submitted some questions for the record in November, and to my knowledge, the committee hasn't received many responses. So I want to ask you one question again.

Can you tell me how many treatments were approved with novel biomarkers used for the first time within the last 5 years? Have any accelerated approvals occurred with a novel marker and a never before treated disease within the last 5 years? How many new biomarkers did the FDA accept for first time use in the last 5 years? If you can provide that answer.

Dr. WOODCOCK. Yes. We are working very hard on this. That was a very provocative question and, actually, we had a very long debate last week among our senior people on the definition of a biomarker, and which of these end points, such as FEV1, which is how fast you can breathe into one of those machines, is that a clinical end point or is that a biomarker? Clearly, in my opinion, it is a biomarker, but not everyone agreed with that. So we are working very diligently on that.

The answer is yes. We approve a large number of drugs on biomarkers end points all the time. A very significant proportion of the drugs we approve are based on that, and we have approved novel ones in the last 5 years, but to get you the count has taken a little bit more effort because we had to resolve these definitional issues, disputes with that.

Mr. BILIRAKIS. When do you think we might get some answers with regard to the count?

Dr. WOODCOCK. I am not in control of that time frame, but I can tell you we are working very diligently, and I believe you will get this response.

Mr. BILIRAKIS. OK. Well, continue to follow up.

Dr. WOODCOCK. It was a good question. It really provoked some thought internally.

Mr. BILIRAKIS. Thank you.

There was approximately \$450 million in direct funding in Fiscal Year 2014 to address the antibiotic crises. These funds were allocated across HHS, the VA, of course, DOD, and USDA. About 75 percent was used for basic and applied research with the rest directed toward stewardship and surveillance.

Currently how do these various agencies coordinate their efforts?

Dr. WOODCOCK. Well, there has been a longstanding antimicrobial task force at the agency level across the government that was headed at HHS, and FDA has been a part of that.

The Executive order conceives and directs formation of a higher level task force in the government that will direct the implementation of the strategy that was announced.

But there has long been coordination across the government agencies, and I believe the PCAST report discusses that.

Mr. BILIRAKIS. OK. On this how is the U.S. coordinating with the World Health Organization and other organizations as well as other countries working to combat antibiotic resistance?

Dr. WOODCOCK. Yes. We do have, we, the FDA, CDC, and many others have relationships with the World Health organization, and I think the Executive order yesterday and the strategy conceives of much tighter collaboration with WHO in a very concerted way.

Mr. BILIRAKIS. OK. Thank you very much.

And I yield back, Mr. Chairman. Appreciate it.

Dr. WOODCOCK. Thank you.

Mr. PITTS. Chair thanks the gentleman, and now recognize the gentlelady from Colorado, Ms. DeGette, 5 minutes for question.

Ms. DEGETTE. Thank you very much, Mr. Chairman.

I think this has been an excellent discussion, and I just wanted to ask you to clarify one thing, Dr. Woodcock.

Mr. Outtersen on our next panel is going to talk about the report on initiatives by the Eastern Research Group, and what that report concludes is that shortening clinical trial time frames is an unlikely contributor to innovation.

We have been hearing counter arguments to this that without something like the approach taken in the ADAPT Act that I am a cosponsor of, it just isn't feasible to do clinical trials on drugs intended to treat the most serious and resistant pathogens.

So from that perspective, ADAPT might be considered a necessity but not a sufficient condition for developing the most needed antibiotics, but also it would need to be paired with other incentives to spur investment in that area.

So I am wondering if you can just spend a minute giving us your views on this issue because, really, it seems to go to the heart of whether we should even go forward with the ADAPT Act?

Dr. WOODCOCK. Well, clearly there are multiple barriers to antimicrobial drug development for antimicrobial resistance. I do agree that the streamlining of clinical trials for testing drugs that treat resistant organisms will stimulate development in that area. Why? Partly because developers have told me that.

But two, because we know from experience that if we have a clear path to market and people understand it, they are willing to put their money down, betting that they will have a molecule that can get approved.

But this is clearly not sufficient. Number one, we are only talking about the most resistant organisms here and a small cadre of drugs to treat them.

We also need a robust pipeline of discovery that will lead to new drug candidates for all different kinds of infections.

So the limited population antibacterial drug idea and the streamlining of clinical trials, which wouldn't just decrease the time frame, it would also decrease the cost and the number of people needed. So it would do a number of things.

That is one thing that we can do at FDA that we think would be beneficial and would be beneficial for patients, but it is not going to fix this problem we have of investment.

Ms. DEGETTE. Thank you.

Mr. Chairman. I yield back.

Mr. PITTS. I think that concludes this round of questioning. We will have follow-up questions, I am sure, from members. We will send them to you and ask that you please respond.

But, again, Dr. Woodcock, you are a terrific witness. Thank you for your being so forthright and clear in your answers.

And we will now take a 3-minute recess as we set up for the second panel.

Dr. WOODCOCK. Thank you.

[Recess.]

Mr. PITTS. The subcommittee will reconvene on our second panel.

Today we have and I will introduce them in the order that they will make their presentations.

First, Dr. Kenneth Hillan, Chief Executive Officer of Achaogen; Dr. Barbara Murray, President, Infectious Disease Society of America; third, Dr. Adrian Thomas, Vice President of the Global Market Access and Global Public Health, Janssen Global Services; and then Mr. Kevin Outtersen, Professor of Law, Boston University School of Law; Mr. Allan Coukell, Senior Director, Drugs and Medical Devices of the Pew Charitable Trust; and Dr. John Powers, Assistant Clinical Professor of Medicine, George Washington University School of Medicine.

Thank you all for coming. Your written statements will be made a part of the record. You will each have 5 minutes to summarize your testimony.

And we will begin with Dr. Hillan. You are recognized 5 minutes to make your opening statement.

STATEMENTS OF DR. KENNETH J. HILLAN, CHIEF EXECUTIVE OFFICER, ACHAOGEN, INC.; DR. BARBARA MURRAY, PRESIDENT, INFECTIOUS DISEASE SOCIETY OF AMERICA; DR. ADRIAN THOMAS, VICE PRESIDENT, GLOBAL MARKET ACCESS AND GLOBAL PUBLIC HEALTH, JANSSEN GLOBAL SERVICES, LLC; KEVIN OUTTERSEN, PROFESSOR OF LAW, BOSTON UNIVERSITY SCHOOL OF LAW; ALLAN COUKELL, SENIOR DIRECTOR, DRUGS AND MEDICAL DEVICES, THE PEW CHARITABLE TRUSTS; AND DR. JOHN H. POWERS, ASSISTANT CLINICAL PROFESSOR OF MEDICINE, GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

STATEMENT OF DR. KENNETH J. HILLAN

Dr. HILLAN. Thank you.

Good morning and thank you, Mr. Chairman and members of the committee for inviting me to testify today.

It was also heartening to hear the recognition of the work of Alexander Fleming, my fellow countryman. Of course not only did he discover penicillin, but actually when he received his Nobel Prize, he also spoke of the danger of the ignorant man who may easily underdose himself by exposing the microbes to non-lethal doses, make them resistant. That was back in 1945.

I am the chief executive officer of Achaogen, a company focussed on discovery, development, and commercialization of novel antibiotics for multi-drug resistant gram-negative infections.

It is a small company with fewer than 50 full-time employees and is based in the San Francisco Bay area. We are a member of the Antimicrobial Innovation Alliance, a coalition created to address the unique challenges that we have heard about today.

As you have already heard, antibacterial resistance is one of the most significant medical challenges our country faces today, and at Achaogen, we are committed to trying to find solutions.

Our lead product candidate, plazomicin, which has been engineered specifically for multi-drug resistance is currently being evaluated in phase 3 clinical trial in patients with bacterial infections caused by carbapenem resistant Enterobacteriaceae, and the carbapenems are considered to be our last line of antibiotic defense in settings where antibiotics are no longer active.

The phase 3 trial utilizes a superiority designed to demonstrate a reduced number of deaths in patients treated with plazomicin based therapy versus the best available standard of care, which, unfortunately, is not very good today.

We have also developed the diagnostic assay that has been used in the phase 3 trial to measure plazomicin blood levels to try to help to individualize dosing for patients which we believe will improve outcomes.

The innovative design and incorporation of the diagnostic assay required close consultation and coordination with both the drug and diagnostic branches of the FDA, and we find our interactions with the agency to be extremely collaborative and believe this approach serves as a model for how the FDA can help to facilitate companies with development of antibiotics in settings of urgent unmet medical need.

The plazomicin program is also benefited by receiving the first contract awarded through the Broad Spectrums Antibacterial program from the Biomedical Advanced Research and Development Authority, also known as BARDA, and this contract is designed to advance plazomicin through approval by the FDA and could provide over \$100 million in total funding.

However, even with plazomicin in a groundbreaking phase 3 study, a great team back at Achaogen, and exciting early stage pipeline, a successful IPO, and significant government investors aboard, it has not been easy, and there remains significant barriers for companies developing antibiotics, and we can and must work together to address these obstacles so that effective antibiotics will always be available for patients.

We would like to propose significant changes in four key areas.

First, we believe new economic incentives are key. There is a need for reimbursement reform for antibiotics and for additional incentives, both push and pull mechanisms. The economics of developing new antibiotics is not currently attractive to the pharmaceutical industry, and many leading companies have exited from the antibiotic space. This has led to a decline in the number of new antibiotic approvals, and has heralded the increase in antibiotic resistance.

Commercial returns for an antibiotic are limited by the fact that generic antibiotics are cheap. New antibiotics are used sparingly to preserve their use. Reimbursement at hospitals is limited to a fixed payment system that is intended to cover the total cost of patient care, and because longer-term returns are eroded by the unavoidable development or resistance.

Furthermore, other therapeutic areas such as oncology or diabetes provide pharmaceutical companies with much more attractive opportunities for a return on their investment.

We believe the DISARM Act sponsored by Congressman Pete Roskam and Danny Davis has been proposed for reimbursement for qualifying antimicrobial products in a hospital setting. We believe this would provide a powerful incentive as currently the payment to the hospital is the same regardless of the price of the antibiotic. So hospitals are incentivized to use the cheapest but not always the best and most effective antibiotic. By providing separate reimbursement for qualifying antibiotics, the DISARM Act would eliminate an important barrier to the use of more expensive antibiotics.

Achaogen supports passage of the DISARM Act, and we would like to see reimbursement for qualifying antibiotics extended beyond Medicaid and Medicare patients to patients covered by private insurance.

Second, the FDA needs authorization for greater flexibility for approval of antibiotics based on limited clinical data sets, and we have heard the rationale for that today.

Plazomicin is following a streamlined development program with a single phase 3 trial. However, due to the need to power the study to demonstrate statistical significance for a mortality end point and the relative rarity of these infection times, the enrollment period for this study is expected to take 3 years.

In contrast in Europe, recent EMA guidance extends more flexibility in the scenario of unmet clinical need and does not require inferential statistical testing for antibiotic approvals.

In order for new drugs to be available ahead of the emergence of unacceptably large numbers of drug resistant infections, Congress must enact legislation that authorizes the FDA to approve new antibiotics for limited patient populations based on smaller clinical trial data sets, but where the totality of the available evidence supports a favorable benefit risk profile for the antibiotic while acknowledging and reflecting the greater uncertainty associated with limited testing in the product label.

Achaogen supports passage of the ADAPT Act to provide the FDA with the increased flexibility that we believe it needs.

Third, there is a need for more rapid point of care diagnostic tests and a more streamlined approval path for diagnostics. For serious infections, a delay in the administration of the right antibiotic by just one hour significantly increases patient mortality. Traditional diagnostic tests, as we have heard, from the days of Louis Pasteur may take 72 hours to complete, and we believe the Federal Government could make a significant impact by providing support and incentives for the development of rapid and cost effective point of care diagnostics that advance antibiotics stewardship and clinical care.

There is also an opportunity to streamline the regulatory process for development and approval of companion diagnostics tests. There is a need for an expedited and iterative approach to diagnostic development and approval through regulations that are anchored in consideration of the urgency of the unmet medical need and the overall benefit/risk for patients.

The regulation should provide the FDA with flexibility to streamline the required analytical studies as well as a testing related to quality manufacturing software and documentation for the diagnostic device.

And, fourth and finally, we need sustained funding for antibiotic research and development. We must be prepared to take a long-term perspective in order to fully realize the public health benefits that will be derived from increasing funding for antibiotic research and development.

The funding that Achaogen has received from BARDA, NIAID, and the Department of Defense have been essential, and we believe it illustrates how public/private partnerships can successfully advance antibacterial research and development.

We support increased funding on an ongoing and predictable basis for BARDA's broad spectrum antibacterial program and the expansion of BARDA's mission to allow investment and programs designed to address the public health threat posed by antibacterial resistance.

We also support continued funding through NIH devoted to antibacterial discovery and development.

We appreciate the opportunity to contribute to the discussion today, and strongly encourage Congress to take additional measures to mitigate the very significant public health threat posed by multi-drug resistant gram-negative bacteria.

Mr. PITTS. Chair thanks the gentleman.

[The prepared statement of Dr. Hillan follows:]



**Testimony of
Kenneth Hillan, MBChB, FRCS, FRCPath
Chief Executive Officer at Achaogen, Inc.**

**Before the United States House of Representatives
Energy and Commerce Committee
Subcommittee on Health**

**Hearing on 21st Century Cures:
Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development**

**Rayburn House Office Building, Room 2123
September 19, 2014**

Introduction

Good morning and thank you to the Chairman and Members of the Committee for inviting me to testify today. I am the Chief Executive Officer of Achaogen, a company focused on the discovery, development and commercialization of novel antibiotics for treating infections caused by multidrug-resistant Gram-negative bacteria. Achaogen is a member of the Antimicrobial Innovation Alliance, a coalition created to address the unique challenges facing the research, development, and approval of new antimicrobial products, as well as their market viability, and includes Actavis-Forest Labs, AstraZeneca, Astellas, GlaxoSmithKline, Johnson & Johnson, Merck, Tetrphase and The Medicines Company.

This Committee's work through the GAIN Act has already made a significant impact and, initiatives, such as the 21st Century Cures, represent an important step towards addressing the paucity of new antibiotics for serious infections. I appreciate the opportunity to highlight the areas where we believe Congress has an opportunity to make a major difference.

Antibacterial resistance is one of the most significant medical challenges our country faces today. The rise and spread of bacteria that are resistant to multiple classes of antibiotics often leaves physicians with few to no options for treating patients with severe, life-threatening infections. A recent report from the CDC highlights that up to 50% of patients who contract bloodstream infections caused by pathogens known as carbapenem-resistant Enterobacteriaceae, or CRE, die from their infections.



By way of background, I practiced as a physician for 10 years in the United Kingdom before moving to the United States to join Genentech, a California biotech company, where I spent 16 years and held multiple leadership positions spanning from early research to late stage clinical development. I was responsible for all stages of clinical development for products in all therapeutic areas outside of oncology. After Roche acquired Genentech, I was appointed as Senior Vice President of product development in the Asia Pacific region, based out of Shanghai, China. I joined Achaogen nearly four years ago to help address the challenge of antibacterial resistance.

Achaogen is a small business with fewer than 50 full time employees, and is based in South San Francisco, CA. Our lead product candidate, plazomicin, is currently being evaluated in a phase 3 clinical trial focused on CRE. These bacteria are resistant to carbapenem antibiotics, which are often considered to be our last line of defense in settings where other antibiotics are no longer active. Our phase 3 trial utilizes a “superiority” design intended to demonstrate a reduced number of deaths among patients treated with plazomicin-based therapy as compared to the best available antibiotic care. We have also developed a diagnostic assay that is being used in the phase 3 trial to measure plazomicin blood levels to optimize dosing on an individual patient basis.

The innovative trial design and the incorporation of the diagnostic assay required close consultation and coordination with both the drug (CDER) and diagnostic (CDRH) branches of FDA. The trial design was agreed upon through the Special Protocol Assessment, or SPA, process, which is intended to provide assurance to sponsors that the trial design will be sufficient for market approval of the drug. Plazomicin also was granted Fast Track Designation, allowing frequent interaction with the agency throughout the planning process. We found our interaction with the FDA to be extremely collaborative and believe this serves as a model for how the FDA can facilitate development of antibiotics in a setting of urgent unmet medical need.

The plazomicin program received the first contract awarded through the Broad Spectrum Antimicrobials program by the Biomedical Advanced Research and Development Authority (BARDA). The contract is designed to advance plazomicin through licensure by the FDA, and if fully realized, the contract will provide over \$100 million in total funding. Achaogen maintains an active and productive research discovery team that is working on the next generation of antibiotic candidates for treating Gram-negative infections. We have previously received funding from the National Institute of Allergy and Infectious Diseases, or NIAID, and the Department of Defense for several of our research and development programs.

My experiences at both large and small companies gives me insight into the way companies make decisions to invest in research and development programs and I appreciate the opportunity to share some of these today. The following are specific recommendations for actions this committee and others within the government can take to incentivize companies to discover, develop and commercialize the next generation of advanced antibiotics.

Reimbursement Reform and Other Economic Incentives

Compared to other therapeutic areas the economics of developing new antibiotics is not currently attractive to the pharmaceutical industry, resulting in many companies exiting from the antibiotic business. This has led to a decline in the number of new antibiotic approvals and has heralded the increase in antibiotic resistance. The commercial returns for an antibiotic are limited by the following factors:

1. Generic antibiotics are largely effective, given for short courses of therapy, and priced very cheaply (dollars per day);
2. Adoption of new antibiotics is slow as their use is restricted for the sickest patients, in order to preserve their useful life;
3. Reimbursement and use of higher priced new products is limited, particularly in the hospital setting where reimbursement for the antibiotic is typically obtained through a fixed payment that is intended to cover the total cost of patient care;
4. Longer-term commercial returns are eroded by the unavoidable development of bacterial resistance to new antibiotics over time.

As pharmaceutical companies prioritize their R&D efforts based on metrics such as Return on Investment (ROI) or Net Present Value (NPV), antibiotics lose out to other more commercially favorable therapeutic areas such as diabetes, cardiology, and oncology, where resistance development is not a concern and where new drugs are taken for prolonged periods and priced more in line with the value provided. Antibiotics are truly life-saving medicines that can give a patient back years of life, yet a typical branded antibiotic may command only \$3,000/course of therapy. In stark contrast, branded oncology agents, which may only provide only months to a few years of extra life, typically are priced between \$40,00-\$70,000 for a course of therapy.

A number of incentives have been proposed or implemented to help promote antibiotic development. The GAIN Act provides for priority review and an extra 5 years of data exclusivity for qualifying products. However, these benefits are modest and additional incentives are urgently needed in order to significantly improve the economics and spur development. The DISARM Act (Developing an Innovative Strategy for Antimicrobial

Resistant Microorganisms), sponsored by Congressmen Peter Roskam and Danny Davis and supported by many of you, has been proposed as a way to address the pricing challenges faced by new antibiotics. This legislation would reform reimbursement of qualifying antimicrobial products in the hospital setting, allowing value-based pricing. This would provide a powerful incentive, as today the pricing of new antibiotics used in the inpatient setting is limited by fixed reimbursement based on the patient's diagnosis group (e.g., MS DRG, Medicare Severity Diagnosis-Related Group). Currently, the payment to the hospital is the same regardless of the price of the antibiotic used, so hospitals are incentivized to use the cheapest, but not always the most effective, antibiotic. By providing separate reimbursement for qualifying antibiotics, the DISARM Act would help to minimize incentives to choose the cheapest antibiotics and provide manufacturers with the opportunity to price new antibiotics in a way that is commensurate with the value provided. Moreover, the DISARM Act would equalize the payment system for outpatient and inpatient product use, so manufacturers would be less inclined to focus on less serious pathogens and infections simply because of pricing advantages in the outpatient setting.

Achaogen supports passage of the DISARM Act and would like to see reimbursement for qualifying antibiotics extended beyond Medicaid and Medicare patients to patients covered by private insurance. In the latter case, private insurance would be supplemented with a government payment to the hospital for the antibiotic.

Given the urgency of the antibiotic resistance problem, we also believe additional incentives are needed to ensure we have a robust pipeline of new antibacterial agents. Such incentives could include tax credits, payments for the completion of key development milestones (e.g., completion of Phase 1, Phase 2, Phase 3, Approval, etc.), and government subsidies should drug sales fall below certain minimums.

FDA Approval Pathways Based on Limited Populations

Achaogen also supports passage of the ADAPT (Antibiotic Development to Advance Patient Treatment) Act and the establishment of new regulatory approval pathways for antibiotics that target specific and limited patient populations with high unmet medical need. The ADAPT Act will provide FDA with increased flexibility, beyond what is currently available, to promptly approve those agents intended to treat serious and life-threatening infections based on evidence that may come from clinical datasets of limited size, supplemented by pharmacologic or pathophysiologic data and phase 2-type studies.

Traditionally, antibacterial agents have been studied in large patient populations enrolled in non-inferiority clinical trials that focus on one site of infection (e.g., pneumonia, intra-abdominal

infection). More recently, regulatory initiatives in both the US and Europe have resulted in new guidance describing streamlined development programs and clinical trial designs for drugs to treat serious bacterial diseases in patients with unmet medical need. The development program for plazomicin has been adapted to become one of the FDA examples of a streamlined program: a single Phase 3 randomized active-controlled superiority study to determine the efficacy and safety of plazomicin in the treatment of CRE infections. However, due to the need to power the study to demonstrate statistical significance for a mortality endpoint and the relative rarity of these infection types, the enrolment period for this study is expected to be 3 years. In contrast, in Europe a corresponding EMA guidance extends more flexibility in the same scenario of unmet clinical need and does not require inferential statistical testing.

The ADAPT Act should authorize FDA to place greater reliance on pharmacokinetic/pharmacodynamic (PK/PD) determinations based on animal and in vitro models (supplemented with clinical PK/PD data as appropriate). ADAPT should also mandate that FDA revisit, within a reasonable time frame, breakpoints of marketed drugs in the same class as a newly approved drug, to ensure consistency within the class.

ADAPT is important to manufacturers of antibiotics designed specifically to treat multidrug resistant (MDR) infections because it provides an alternative regulatory mechanism that allows for more rapid access to patients based on limited data in that population. It also provides the manufacturer flexibility in further product development, either by the continuation of restricted use or label expansion based on further clinical evidence.

In order for new drugs to be available ahead of the emergence of unacceptably large numbers of drug resistant infections, Congress must enact legislation that authorizes the FDA to approve new antibiotics for limited patient populations based on limited clinical trial data but where the totality of the available scientific and clinical evidence supports the benefit/risk profile for the antibiotic, while acknowledging and reflecting the greater uncertainty associated with limited clinical testing in the product label.

Development and Use of Diagnostic Tests

When faced with a patient who has a serious bacterial infection, physicians need to make rapid antibiotic treatment decisions, as a delay in administration of an effective antibiotic by just one hour significantly increases patient mortality. Existing traditional bacterial identification and antibiotic susceptibility tests may take up to 72 hours to complete, so broad-spectrum antibiotics, intended to cover a variety of pathogens, are administered empirically before the bacterial species and antibiotic susceptibility are known. Rapid diagnostic tests are evolving and are

intended to identify the species of bacteria causing the infection and, with some tests, potential resistance to different antibiotics in a much shorter timeframe. . In an ideal world, rapid diagnostic testing would allow bacterial identification and antibiotic susceptibility to be determined at the point of patient care to enable healthcare professionals to decide on the most appropriate antibiotic as quickly as possible. Diagnostic tests can also be used to monitor drug exposure (patient blood levels) to individualize dosing for each patient, which has been shown to improve outcomes. We believe the federal government should be providing significant support and incentives to companies and innovators of rapid and cost-effective diagnostics that will advance antibiotic stewardship and clinical care.

There is an opportunity to significantly streamline the regulatory process for development and approval of companion diagnostic tests. Currently, the FDA expects that the therapeutic product sponsor will address the need for an approved or cleared companion diagnostic device in its therapeutic product development plan, or will develop its own companion diagnostic device. We contend that the current regulatory model of approving one diagnostic, on a single platform, for one drug is not scalable and risks creating an unnecessary barrier to patient care and antibiotic stewardship. In the rapidly evolving field of diagnostic devices it is difficult to predict which test will be most appropriate at the time of product launch. Furthermore, one size does not fit all microbiology laboratories. Laboratories need the flexibility to run the tests that are most suitable for the equipment, expertise and workflow within their laboratory.

During the conduct of trials involving drugs and diagnostics, sponsors and the FDA need to be able to work flexibly with laboratories closest to the point of care, and to be able to use a variety of tests that facilitate enrollment of patients with rare multi-drug resistant infections. There is a need for an expedited approach to diagnostic development to keep pace with the changes in technology. We need regulations that support a more flexible approach under a risk-based assessment that considers at its core, the overall benefit risk for patients. The regulations should provide the FDA with the flexibility to customize the required analytical studies for each assay at the time of NDA filing, as well as the data and testing related to quality systems, manufacturing, software testing and documentation, so that they support the safe and effective use of the drug.

Sustained Funding for Antibiotic Research and Development

Finally, it is crucial to secure a long-term commitment to funding for antibacterial research and development. Less than a decade after the first antibiotics, sulfonamides and penicillin, were introduced in the 1930s and 1940s, bacterial strains resistant to these antibiotics were discovered. Indeed, resistance has eventually developed to every antibiotic that has been used in the clinic.



Thus, we need to maintain a robust pipeline of antibiotics so that effective therapies always remain available to patients. The funding that Achaogen has received from BARDA, NIAID, and the DOD illustrates how public-private partnerships can successfully advance antibacterial research and development.

The investment from BARDA in the plazomicin program has supported the design, initiation, and ongoing performance of our phase 3 superiority trial, the development of the plazomicin diagnostic assay, plus advances in the plazomicin manufacturing process. The funding from BARDA came at a time when we were completing a phase 2 clinical trial of plazomicin under an investment from the Wellcome Trust, and it enabled Achaogen to advance plazomicin to the next stage of development. We support increased funding for the Broad Spectrum Antimicrobial program, and the expansion of BARDA's mission to allow investment in programs designed to address the public health threat posed by antibacterial resistance in addition to their current work to combat biodefense threat pathogens.

The role that BARDA has in advancing novel antibiotics through late stage development will be bolstered by the recent launch of the Antimicrobial Resistance Leadership Group, or ARLG, through support from the National Institute of Allergy and Infectious Diseases, or NIAID, an Institute within the National Institutes of Health. The goal of this group is to streamline the development of novel antibiotics by providing an existing network of clinical sites to more rapidly enroll patients in clinical trials, and by standardizing clinical trial designs through the development of master protocols. We support the continued funding of the ARLG and other initiatives to develop clinical trial networks that will streamline operational aspects of performing antibiotic clinical trials.

It is also important to ensure steady funding for early stage efforts to discover the next generation of antibacterial candidates, in order to maintain a sustained pipeline of effective antibiotics. The NIH historically has supported this stage of development, and indeed, Achaogen has received funding from NIAID. We support continued funding of early antibiotic R&D through specific NIAID funding devoted to antibacterial discovery and early development.

The process from initiation of an antibiotic discovery program through clinical trials and licensure can take well over 10 years. Given this long timeline, it is important to provide incentives to launch antibacterial research programs on an ongoing and predictable basis. Congress must develop a long term strategy for funding antibiotic research and development that is sustainable as a benefit to public health. The funding for BARDA and NIH must be guaranteed and ring-fenced from diversion for other purposes, in order to assure antibiotic discoverers of continued support for their efforts.

Conclusion

We propose a multifaceted approach to incentivize companies to develop new antibiotics that is based upon the following four points:

1. Passage of the DISARM Act and consideration of other incentives such as tax credits and milestone payments
2. Passage of the ADAPT Act and consideration of approval pathways based on limited clinical data sets and novel endpoints
3. Streamlined approval pathways for rapid diagnostic assays that enable selection of appropriate antibacterial therapy, in order to prevent delays in approval of antibiotics where there is a high unmet need
4. Increased, sustained, and dedicated funding to support antibacterial research from early discovery through late stage clinical development, specifically to include funding for BARDA and NIH/NIAID

Together, the initiatives would provide additional incentives for companies to invest in and sustain antibacterial research and development that will be needed to maintain a robust pipeline of life-saving antibiotics. We believe that Congress must take aggressive action now to prevent the public health threat from multi-drug resistant bacterial infections from growing beyond current levels.

Mr. PITTS. And now recognizes Dr. Murray 5 minutes for an opening statement.

STATEMENT OF DR. BARBARA MURRAY

Dr. MURRAY. Thank you very much, Mr. Chairman.

Thank you for inviting me to testify on behalf the Infectious Diseases Society of America, IDSA, on the public health crisis of antibiotic resistance and the urgent need for new antibiotics in diagnostics.

IDSA is grateful for this subcommittee's continued leadership on these critical issues.

Physicians are seeing more and more patients with very serious infections that are resistant to all or almost all antibiotics. For example, I recently saw a young woman with severe lupus, an autoimmune disease, who developed a very painful bile duct infection that persisted despite multiple antibiotics, endoscopies and surgical interventions. The infecting bacterium invaded her blood stream and it developed resistance to every antibiotic available, including colistin, a toxic antibiotic usually of last resort. Finally, all we could do was send her to hospice for palliative comfort care while she waited for the infection to claim her life after a very prolonged and expensive stay in the hospital.

A colleague of mine recently took care of a very active patient in his sixties following a prosthetic knee replacement, he developed a serious pseudomonas infection that, despite removal of the implanted joint and multiple antibiotics, could not be controlled and he had to have an above-the-knee amputation.

This summer I cared for two diabetic women with urinary tract infections, or UTI, who had to be admitted to the hospital, not because they were so seriously ill, but for IV therapy because their infecting organism was resistant to all oral antibiotics.

For anyone who has had a UTI, which is going to be most of the women in this room and some of the men, having to be hospitalized for such a common infection is inconvenient, decreases productivity, and markedly increases our health care costs.

Antibiotic R&D, as you have heard, faces significant barriers. Discovery is hard. Scientific challenges lead to very high development costs. Economically, antibiotics have a very poor return on investment because they are typically priced low, used for a short duration, and held in reserve by us to try to control antibiotic resistance.

IDSA thanks the subcommittee, and especially Representatives Gingrey and Green, for its leadership in enacting the GAIN Act in 2012, which is beginning to address some of the economic barriers. We hope you can now build on these efforts and address current regulatory barriers.

Specifically, extensively resistant bacteria currently infect relatively small numbers of patients, making it virtually impossible, as you have heard, to populate traditional, i.e., large clinical trials, but we need to develop new drugs before there is an epidemic. Think of how our fear for Ebola would be much less if there were already effective therapies.

Representatives Gingrey and Green introduced the ADAPT Act, which would address this regulatory conundrum by allowing FDA to approve certain antibiotics with smaller trials. This approach would only be for antibiotics to treat serious infections where there is an unmet medical need. ADAPT would make trials of highly resistant bacteria feasible, possibly less costly, and it would allow FDA to assess the risk of a new antibiotic relative to its potential benefit to this limited population.

IDSA is deeply concerned that without ADAPT many of the most urgently needed antibiotics would not be brought to the market. The strategy of a limited population approval pathway was also suggested in the PCAST report that you heard yesterday.

ADAPT includes safeguards to help ensure that these drugs are used appropriately. It also contains multiple important provisions to ensure that susceptibility tests, interpretive criteria, or break points, which predict whether a patient will have a good response to an antibiotic, are quickly updated and made publicly available.

Up-to-date information is crucial for clinical care and to ensure that antibiotics are not misused or overused.

IDSA urges the subcommittee to mark up the ADAPT Act swiftly.

As also mentioned in the PCAST and earlier today, additional economic incentives are required, such as public/private partnerships; support for Federal agencies that invest in antibiotic research; improved reimbursements and/or tax credits.

Ernst & Young estimated that an IDSA tax proposal targeting R&D for these needed antibiotics would result in an additional five to seven new antibiotics in the pipeline every year.

While new antibiotics are critical, IDSA is also committed to a multi-prong response to antibiotic resistance, including a well-coordinated Federal leadership, as mentioned in the PCAST report; sustained involvement of nongovernment stakeholders; antibiotic stewardship programs in every health care facility; enhanced surveillance of antibiotic use and resistance patterns; and research on novel strategies to prevent and control antibiotic-resistance organisms. These steps are critical to protect patients, the public health, and the Federal investment in new antibiotics.

Lastly, again, as you have heard, it is extremely important to promote the development and clinical integration of new diagnostics. Rapid point-of-care diagnostics can reduce inappropriate antibiotic use which drives resistance by lessening the need for empiric or shotgun therapy.

IDSA recommends increased investments in diagnostics research, regulatory approval pathways, strengthening in reimbursement, and supporting outcomes research to demonstrate the impact of diagnostics on patient care.

Thank you again for allowing me to testify here and for your continuing efforts in this very important area.

Mr. PITTS. Chair thanks the gentlelady.

[The prepared statement of Dr. Murray follows:]

**Written Statement of Barbara E. Murray, MD, FIDSA, President
Infectious Diseases Society of America**

**Energy and Commerce Committee, Health Subcommittee
U.S. House of Representatives
*21st Century Cures: Examining Ways to Combat Antibiotic Resistance
and Foster New Drug Development***

September 19, 2014

Thank you for inviting me to testify on behalf of the Infectious Diseases Society of America (IDSA) on the public health crisis of antibiotic resistance and the urgent need for new antibiotics, diagnostics and vaccines. IDSA is grateful for this Subcommittee's leadership in addressing these critical issues and advancing policies to combat resistance and save lives.

Antibiotic Resistance: A Public Health Crisis

Antibiotics are generally accepted as the greatest development in medical therapeutics of the 20th century and are now credited with a 26 year increase in average longevity. For example, before the discovery and development of antibiotics, 100% of patients who contracted heart valve infections died from that infection. Now the mortality rate for heart valve infections is around 25%. Similarly, in the pre-antibiotic era, over 80% of patients with brain infections died. Now, over 80% of patients with brain infections survive, thanks to antibiotics. Unfortunately, this tremendous progress is seriously threatened by the rapid rise of antibiotic-resistant bacteria coupled with a persistent market failure to develop new antibiotics. This public health crisis has been well documented by the Centers for Disease Control and Prevention's (CDC's) *Antibiotic Resistance Threats 2013* report, the World Health Organization and multiple other government entities and non-government experts, including IDSA with our 2004 Bad Bugs, No Drugs report and our 2011 Combating Antimicrobial Resistance: Policy Recommendations to Save Lives

report. We are on the very real, very frightening precipice of a post-antibiotic era with mortality rates for infections increasing.

IDSA is advocating for new antibiotics and diagnostics to improve and save the lives of the many patients who are suffering from serious or life-threatening infections. At my own institution in Texas, my colleagues and I are seeing more and more patients of all ages with serious or life-threatening infections that are resistant to all or nearly all available antibiotics. I would like to share a few of these patient stories with you.

I saw a young adult patient with severe lupus (a chronic, non-infectious, auto-immune disease in which the patient's immune system attacks his or her own body). This young woman developed a bile duct and bloodstream infection caused by the bacterium, *Pseudomonas aeruginosa*. She was in significant pain. Over several months, the infection persisted despite all the antibiotics we tried, and the *Pseudomonas* became increasingly resistant to every available antibiotic, including Colistin — a toxic drug of last resort because it damages the kidneys. Despite even surgical interventions, her infection and marked pain persisted. All we could do was send her to hospice for palliative comfort care while she waited for the infection to claim her life.

A colleague of mine had another patient in his sixties who had been healthy and active. Following joint replacement surgery, he developed a *Pseudomonas* infection in the prosthetic joint. Despite removal of the prosthetic joint and multiple antibiotics, the infection could not be controlled and he had to have an above-the-knee amputation. For one facing possible future joint replacements, this is a truly frightening complication.

This summer I cared for two patients with diabetes and urinary tract infections (UTI) caused by a highly resistant strain of *E. coli*. Both patients had to be admitted to the hospital for intravenous therapy because their infections were resistant to all oral antibiotics, and they were not candidates for home intravenous (IV) therapy (and our system is not set up for daily outpatient IV injections). There is now **no** reliable oral antibiotic for complicated UTIs. Having to hospitalize patients or, at the least, insert a catheter for self administration of antibiotics at home (which has its own problems), for such a common infection that could previously be treated effectively with oral antibiotics, markedly increases our health care costs (as well as increases inconvenience, potential complications and decreases productivity). Probably every woman by the age of 60 has had at least one UTI, illustrating the enormity of the problem.

Urgent Need for New Life-Saving Antibiotics

IDSA is extremely appreciative of this Committee's leadership, and especially Congressmen Phil Gingrey and Gene Green, in enacting the Generating Antibiotic Incentives Now (GAIN) Act in 2012. This legislation not only provides an additional 5 years of exclusivity for new antibiotics that treat serious or life-threatening infections, but it also signals to the health care community and the patients who depend on us, that Congress is committed to addressing antibiotic resistance and providing physicians with the tools we need to effectively treat our patients. Today's hearing demonstrates this Subcommittee's ongoing dedication to finding and advancing policy solutions, and IDSA is delighted to continue working with you.

Despite the success of the GAIN Act, companies still face significant economic, regulatory and scientific barriers to antibiotic development—particularly when it comes to developing new drugs to treat some of the most deadly and highly resistant infections, such as those caused by Gram-negative bacteria (one of two major classes of bacteria, with the Gram-positive class represented by “MRSA”). One key example is carbapenem resistant Enterbacteriaceae or CRE—dubbed the “nightmare bacteria” by CDC last year. CRE germs kill up to half of patients who get bloodstream infections from them. About 18% of U.S. long-term acute care hospitals had at least one patient with a serious CRE infection during the first half of 2012, and this deadly pathogen is continuing to spread. Even more frightening—we have no safe and effective antibiotics to treat CRE. An April 2013 analysis of the antibiotic development pipeline conducted by IDSA found only a few new drugs in development for the treatment of infections caused by multidrug-resistant Gram-negative bacteria. Given the high predicted failure rate in clinical trials, it is quite possible that none of these will make it across the finish line to Food and Drug Administration (FDA) approval. Moreover, none of them will work against the pan-resistant pathogens (or those resistant to all current antibiotics).

Why are pharmaceutical companies facing such difficulty in developing new antibiotics to treat CRE and other serious or life-threatening infections caused by multi-drug resistant disease-causing bacteria? As the Subcommittee may recall from its deliberations on the GAIN Act, antibiotics research and development (R&D) faces very significant economic hurdles. Antibiotics are typically priced low, used for a short duration, and held in reserve by physicians to protect against the development of resistance. The GAIN Act took an important first step to

begin providing an economic incentive for companies to invest in new antibiotic development. But Congress must still do more.

ADAPT Act: Removing Regulatory Barriers to Antibiotic R&D

Companies who now wish to develop some of the most urgently needed new antibiotics are facing serious regulatory barriers. Some of the most dangerous pathogens are to date occurring in relatively small numbers of patients, making it difficult or impossible to populate traditional, large scale clinical trials. It is important to develop drugs to treat infections caused by these deadly pathogens before they infect larger numbers of people. However, when a pathogen is resistant to all approved antibiotics, there is no effective antibiotic against which to compare the new antibiotic, which is the standard procedure for traditional clinical trials. Compounding the problem is the lack of rapid diagnostic tests to quickly identify patients infected with certain pathogens who may be eligible for antibiotic or antifungal clinical trials early enough to improve their outcomes and to avoid enrolling patients only to find out 24-48 hours later that they are not eligible, which adds markedly to the overall cost of the trial without gaining useful efficacy information.

IDSA thanks Representatives Gingrey and Green for continuing to lead the effort to incentivize antibiotic development by introducing the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, and we urge the Subcommittee to markup this important bill.

ADAPT would help address some of these serious regulatory hurdles by creating a new FDA approval pathway in which companies could study in smaller clinical trials new antibacterial or antifungal drugs to treat serious or life-threatening infections for which there is an unmet medical

need. ADAPT drugs would receive approval just for the limited population in most need of the therapy, as opposed to all patients. Smaller clinical trials can also be less costly to companies, which is an important consideration given the economic hurdles still facing antibiotic R&D.

The ADAPT Act would speed patient access to desperately needed, life-saving new drugs for infections for which there are very limited or no therapeutic options, and it includes important provisions to help guide the appropriate use of these drugs. For example, ADAPT requires that the labeling of drugs approved under the limited population pathway explicitly state: “This drug has been approved for a limited and specific population.” In addition, FDA would have the authority to pre-review any promotional materials for ADAPT drugs to ensure these drugs are not marketed inappropriately. This policy is identical to what FDA does under the successful accelerated approval pathway. Lastly, the use of ADAPT drugs would be monitored under CDC’s existing National Healthcare Safety Network (NHSN). IDSA believes that the bill could be further strengthened to ensure that the labeling of drugs approved under this new pathway clearly and prominently illustrate that these drugs are indicated for a limited population. It is important to make it as simple as possible for the health care community to easily recognize that these drugs have been approved in a different manner than traditional antibiotics and should be used appropriately.

The ADAPT Act provides a critical incentive to companies to develop the most urgently needed new antibiotics. In addition to simply making these clinical trials feasible by allowing them to be smaller, ADAPT would reduce some of the significant expense and administrative and regulatory burdens associated with traditional, large scale clinical trials that are not practical or

even possible with these infections. In addition, to help ensure to as great an extent as possible that the drugs are safe and effective for the limited indicated population, the FDA could also consider different types of data (such as pre-clinical and volunteer pharmacologic or pathophysiologic data, data from phase 2 clinical studies, and other confirmatory evidence) when determining a new drug's approval under the ADAPT Act.

The ADAPT Act also contains important provisions designed to ensure that susceptibility test interpretive criteria (commonly referred to as "breakpoints") for antimicrobial drugs are regularly updated in a timely fashion, and that updated breakpoints are made publicly available via FDA's website. A breakpoint provides information that helps to predict whether a patient infected with a specific pathogen will have a good clinical response to standard doses of a drug. Given the ongoing development of drug resistance, it is critical that breakpoints be regularly updated to provide physicians with accurate information to guide the optimal use of drugs in patients.

We are very grateful to all of the Subcommittee members who have already cosponsored the ADAPT Act, and hope that after today's hearing, many more of you will want to lend your support. Numerous medical societies and public health organizations share IDSA's view of this important legislation. As the Committee heard during its recent May 20th hearing, "*21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation*," PCAST endorsed a limited population approach to antibiotic development in its 2012 report. IDSA believes that without an approach to antibiotic development like the one the ADAPT Act would establish, many of the drugs our patients need to stay alive simply cannot

and will not be developed. On behalf of those patients, we urge you to swiftly advance the ADAPT Act.

Additional Economic Incentives for Antibiotic R&D

While the ADAPT Act would create a feasible pathway for the development of the most urgently needed new antibiotics, expert stakeholders agree that additional economic incentives are required (including tax credits, additional funding for critical agencies, and new public-private partnerships). Due to significant scientific challenges and regulatory hurdles, development of new antibiotics—particularly to treat some of the most highly-resistant and most deadly infections—can be extremely expensive. Net present value (NPV) describes the relationship between a drug's R&D costs versus its potential return on investment. Companies use NPV to decide whether to move forward with one drug versus a competing drug the company is able to available to invest in at a given time. Due to high R&D costs, insufficient federal support for antibiotic R&D, and inadequate opportunity to earn a satisfactory return on investment, antibiotics have a very low NPV. Some research even indicates some antibiotics' NPV is a negative number, meaning the company would actually lose money by bringing the drug to market.

Federal Agencies Supporting Antibiotic R&D

IDSA also recognizes that multiple federal agencies provide critical investments in antibiotic R&D. We encourage the Subcommittee to consider how Congress can best support these efforts. The National Institutes of Health (NIH) National Institute for Allergy and Infectious Diseases (NIAID) recently established the Antibacterial Resistance Leadership Group (ARLG) to develop,

design, implement, and manage a clinical research agenda to increase knowledge of antibacterial resistance. The ARLG is focusing on antibacterial drug and diagnostic development, optimal usage strategies, infection control and activities to limit the development of resistance.

In 2010, The Biomedical Advanced Research and Development Authority (BARDA) established a Broad Spectrum Antimicrobials (BSA) Program to focus on developing novel antibiotics to address biological threats as well as the public health threat of antibiotic resistance. In four years, the BARDA program has grown from supporting one industry partnership with an antibiotic candidate in Phase 2 development to six partnerships with three industry partners in Phase 3 clinical development. Since 2010, BARDA has awarded over \$550 million to companies for antibiotic development.

IDSA also encourages the Committee to be mindful of CDC's role in research and innovation. For example, CDC's proposed Detect and Protect Against Antibiotic Resistance initiative – which has broad support – includes the establishment of a bacterial isolate library that could be very useful to researchers and companies for the development of new antibiotics and diagnostics.

While not under this Subcommittee's jurisdiction, the Defense Threat Reduction Agency (DTRA), and the Defense Advanced Research Projects Agency (DARPA) have also been important sources of funding for antibiotic research, particularly focusing on threats to our warfighters.

Public Private Partnerships

While individual federal agencies are effectively partnering with individual pharmaceutical companies to pursue antibiotic R&D, the U.S. lacks a large-scale public private partnership (PPP) to convene the diverse stakeholders required to tackle the challenges facing antibiotic R&D. The European Union has launched an impressive PPP, New Drugs for Bad Bugs (ND4BB), under its Innovative Medicines Initiative (IMI). ND4BB brings together government leaders, academia, industry and other experts for an unprecedented sharing of information and multi-disciplinary collaboration. The focus of the overall program is to develop better networks of researchers, create fluid and innovative clinical trial designs and provide incentives for companies in order to meet the challenges of antibiotic resistance quickly and efficiently.

At a late July joint NIH/FDA meeting on antibiotic development, NIH Director Dr. Francis Collins announced that the U.S. would launch a new public private partnership on antibiotic development and would pursue the creation of a master clinical trials protocol for antibiotics. We appreciate that Congressman Gene Green asked Dr. Collins for additional information on this effort during a recent 21st Century Cures roundtable. IDSA is encouraged by the NIH announcement and looks forward to additional information from NIH and other federal partners about how we can best support these activities. We urge the Subcommittee to express its support for these initiatives as well.

Tax Credits

A variety of economic experts agree that a combination of “push” and “pull” incentives are needed to effectively stimulate antibiotic R&D. The GAIN Act provides a valuable “pull”

incentive (additional exclusivity). Improving reimbursement for the most urgently needed new antibiotics would be another important pull incentive. We urge you to work with other Congressional committees to provide targeted tax credits for antibiotic R&D. Tax credits would provide an extremely valuable “push” incentive and would be a very important complement to other efforts undertaken by this Subcommittee. IDSA has developed a proposal to provide a credit of 50 percent of the qualified clinical testing expenses (which we would define as expenses incurred in phase 2 and 3 clinical trials) for new antibiotics and antifungal drugs to treat serious or life-threatening infections—the very same drugs eligible for the additional 5 years of exclusivity under the GAIN Act (life-saving new drugs that this Subcommittee deemed worthy of federal investment). Economic modeling has indicated that financial support during expensive clinical trials, as provided through tax credits, would be a powerful incentive to complement enhanced exclusivity and reimbursement. In fact, Ernst & Young analysis estimated that our tax credit proposal would result in an additional 5-7 new antibiotics or antifungal drugs to treat serious or life-threatening infections in the pipeline every year.

Reimbursement Reform

Reimbursement mechanisms can be used to help stimulate antibiotic R&D, such as through the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act, H.R. 4187. This bill would provide Medicare add-on payments for antibiotics used in inpatient settings to treat infections associated with high rates of mortality. Strong communication between the Centers for Medicare and Medicaid Services (CMS) and FDA is critical for the success of such efforts, to help ensure that criteria to determine a drug’s coverage and payment are applied in a scientifically and medically appropriate and consistent manner that provides

companies with the certainty and predictability they need in order to develop life-saving new antibiotics. It is also very important to monitor the use of antibiotics that receive this increased reimbursement.

Combating Antibiotic Resistance

While incentivizing the development of new antibiotics is critical, it is equally important that the Committee take a leadership role in developing and implementing a national strategy to address antibiotic resistance. Key elements of a successful strategy should include well coordinated federal leadership; sustained and meaningful involvement of non-government stakeholders; antibiotic stewardship; enhanced surveillance and data collection on antibiotic use and resistance patterns; and research on novel strategies, best practices and evaluation of methods to prevent, control, and eradicate antimicrobial resistant organisms.

Federal Leadership and Coordination

The U.S. Interagency Task Force on Antimicrobial Resistance (ITFAR) is charged with coordinating federal efforts in this area. However, the ITFAR lacks the high-level, centralized leadership it needs to ensure measurable progress and accountability. We urge you to designate a Director at a high level of government --either in the White House or under the Secretary of Health and Human Services (HHS)-- to lead the ITFAR and coordinate the Federal response. This enhanced leadership would help facilitate better coordination, including a stronger ongoing dialogue with nongovernment experts. The problem of antibiotic resistance is so significant that government must work collaboratively with a broad array of key stakeholders. IDSA continues to advocate for the creation of a formal advisory board of non-government experts to meet with

the ITFAR on a regular basis. In addition, earlier this month we officially launched the new Stakeholder Forum on Antimicrobial Resistance (S-FAR), which includes 80 member organizations representing health care providers, patients, hospitals, public health, advocates and industry. S-FAR will hold its inaugural meeting with key federal leaders in October 2014.

Antimicrobial Stewardship Programs in Every Health care Facility

Antimicrobial stewardship programs must also play a central role in our efforts to combat resistance across the continuum of care. Over the last several decades, there has been a dramatic increase in antibiotic use in hospitals and outpatient settings. Antibiotics may be prescribed needlessly and continued when no longer necessary. Such overuse and misuse is driving the development of antibiotic resistance. Antibiotic stewardship is a critical tool to protect antibiotics from misuse and overuse. Antibiotic stewardship can better patient care, improve outcomes, and lower the healthcare costs associated with antibiotic overuse as well as costs associated with infections and antibiotic resistance. IDSA has proposed that the CMS require health care facilities to implement antimicrobial stewardship programs as a condition of participation in Medicare, and we hope that the Committee will join us in encouraging CMS to adopt this policy.

Strengthening Surveillance and Data Collection

To thoroughly monitor the impact of stewardship programs and other interventions, we need real time, publicly available data on antibiotic usage and antibiotic resistance. Our current surveillance and data collection in these areas are sporadic and contain many gaps. Improved surveillance and data collection are critical for determining the prevalence of resistant infections,

determining antibiotic and diagnostic development priorities, and defining metrics and allowing benchmarking.

The CDC's new Detect and Protect Against Antibiotic Resistance initiative (as proposed in the President's Budget Request for Fiscal Year 2015 at \$30 million) would improve surveillance. One piece of the initiative would create a detection network of five regional labs to speed up identification of the most concerning threats and increase susceptibility testing for high priority bacteria.

The President's Budget also requested a \$14 million increase for NHSN. This additional funding would support increased uptake of NHSN's antibiotic resistance and antibiotic use modules — two tools that allow for centralized reporting of antibiotic use and resistance (AUR) data. Currently, 12,000 facilities report some type of data through NHSN, but only a small fraction of those facilities are reporting AUR data. CDC recently launched a new AUR reporting module and is onboarding new facilities, but more funding is needed to expand reporting. Once more facilities across the country are capable of reporting these data, CDC can create a prescribing index to help benchmark antibiotic use across health care facilities, allowing facilities to compare their data with similar facilities. It will also help state, local and federal public health entities to identify antibiotic use and resistance hot spots within a city or a region. Finally, health care providers, researchers and the public will be able to view and study the data via a web-based portal. It is critical that antibiotic resistance and use data, and gaps in those data, be made public on a regular basis. IDSA greatly appreciated the 2013 CDC report on this issue and recommends that these data be reported on a regular basis. The proposed funding increase will improve our

understanding of antibiotic resistance threats and bring the clear public health benefits of such data to the public faster.

Investing in Diagnostics R&D and Clinical Integration

New diagnostic tools are also crucial for combating resistance. Emerging diagnostic technologies help guide appropriate use of antibiotics and decrease antibiotic misuse and overuse by lessening the need for clinicians to treat patients empirically and permitting use of narrow spectrum agents to minimize collateral damage to normally present host microorganisms. However, there are significant challenges to the development, regulatory approval and clinical integration of new diagnostic tests.

IDSA's 2013 report, Better Tests, Better Care: Improved Diagnostics for Infectious Diseases makes policy recommendations to help spur the development of new and more rapid diagnostic tests and encourage their use in patient care and public health.

IDSA urges you to work with your colleagues on the Appropriations and Ways & Means Committees to provide robust funding for diagnostics research through NIAID, BARDA and tax credits. The NIAID Small Business Innovation Research (SBIR) program is an important source of funding for diagnostics research, and additional resources would expand this program's impact. IDSA also urges the Committee to support NIAID, where appropriate, in its efforts to address the most urgent diagnostics needs. For example, NIAID should work to ensure that the peer review process for diagnostics grant submissions includes study sections with appropriate expertise to evaluate feasibility and clinical applicability, as well as scientific merit. IDSA

applauds NIAID's recently announced \$12 million funding initiative geared toward research on diagnostics to quickly detect bacteria responsible for antibacterial resistant infections in hospital settings, and we hope to see continued focus in on this priority area.

It is also critical to reduce regulatory barriers to diagnostics R&D, specifically by working with the FDA Center for Devices and Radiological Health (CDRH) to facilitate the development of point of care tests. Currently, some novel diagnostic tests for certain pathogens must be approved through the premarket approval (PMA) pathway, which can be cost prohibitive and time-consuming, especially for smaller companies. In addition, study designs that call for comparing superior new diagnostics to outdated reference tests can add considerable time and cost to trials. The FDA has taken several promising steps to simplify diagnostics regulatory approval through two draft guidance documents this year. The first draft guidance, "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibility Debilitating Diseases or Conditions" streamlines the premarket approval (PMA) pathway for diagnostics that address unmet needs by allowing alternative study designs. The second guidance document, "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval" allows smaller clinical studies for approval of diagnostics that address unmet medical needs, with the admission that smaller trials may leave more uncertainty about the risks or benefits of these tests. However, that uncertainty is preferable to a complete lack of diagnostics for certain infections where there is unmet medical need. Additional data can then be collected post-approval to provide additional information about the diagnostic's efficacy and appropriate utilization in real world settings. We encourage the Subcommittee to work with FDA to build on these efforts with a focus on providing a

feasible approval pathway for diagnostics that can rapidly identify pathogens causing infection and determine their resistance to antimicrobial drugs.

IDSA also thanks the Subcommittee for its efforts to craft and enact the Protecting Access to Medicare Act of 2014 (PAMA). We are particularly supportive of PAMA's provisions to improve diagnostic test reimbursement, and we view this new law as an excellent foundation on which to build future diagnostic reimbursement reform. IDSA looks forward to the new expert panel that PAMA requires the Secretary of Health and Human Services to establish on issues surrounding diagnostic tests. This expert panel will also provide input on reimbursement levels, temporary Current Procedural Terminology (CPT) code assignment for new diagnostic tests, and help develop policies to facilitate the appropriate use of diagnostic tests. We hope the Subcommittee will support our call for this panel to include infectious diseases physicians and scientists as well as clinical microbiologists to provide this necessary expertise. We also encourage the Subcommittee to conduct oversight, as needed, to ensure prompt and appropriate implementation of the diagnostics reimbursement provisions in PAMA. Specifically, IDSA recommends that reimbursement cover the cost of testing, at a minimum; that wide regional variations in reimbursement for diagnostic testing be eliminated; and that the process of assigning new CPT codes for diagnostic tests be simplified, expedited and made more transparent.

Additional research is also needed to understand more fully the impact of diagnostics. While we recognize that innovative infectious diseases diagnostic tests can have a significant impact on patient outcomes, public health, and health care resources utilization, we lack sufficient concrete

data to inform and demonstrate these points. We urge the Subcommittee to explore ways to encourage the conduct of outcomes research to provide data on diagnostic use in varied clinical settings and the effect of diagnostic testing on patients, public health and the health care system. With strong supporting data, clinicians can be educated about the utility and optimal use of new tests, increasing their rate of integration and appropriate use within the health care community. The Patient Centered Outcomes Research Institute (PCORI) is well positioned to support the evaluation of clinical outcomes of new diagnostics, but to date, PCORI has focused largely on chronic conditions rather than infectious diseases. IDSA also urges the Subcommittee to explore opportunities for the Agency for Healthcare Research and Quality (AHRQ) and the Health Resources and Services Administration (HRSA) to assist health care institutions and professional societies with educational programs about the utility of infectious diseases diagnostic tests.

Once again, IDSA sincerely appreciates the Subcommittee's continued dedication to addressing the public health crisis of antibiotic resistance and the urgent need for new antibiotics and diagnostics. We look forward to opportunities to work with the Subcommittee to advance our common policy goals to improve patient care and public health and save lives.

**Barbara E. Murray, MD, FIDSA, President
Infectious Diseases Society of America
Summary of Testimony
September 19, 2014**

The Infectious Diseases Society of America (IDSA) is grateful to the Subcommittee for holding a hearing on antibiotic resistance and the urgent need for new antibiotics. My colleagues and I are seeing more and more patients with serious or life-threatening infections that we cannot effectively treat due to antibiotic resistance. Significant economic, regulatory and scientific barriers thwart the development of desperately needed new antibiotics and diagnostics.

IDSA thanks the Subcommittee, and especially Representatives Gingrey and Green, for its leadership in enacting the Generating Antibiotic Incentives Now (GAIN) Act in 2012. We hope you can build on those worthwhile efforts and address regulatory barriers that impact this critical issue. Companies who wish to develop some of the most urgently needed new antibiotics continue to face serious regulatory barriers. Some of the most dangerous pathogens currently infect relatively small numbers of patients, making it difficult or impossible to populate traditional clinical trials. It is important to develop drugs to treat infections caused by these deadly pathogens before they infect larger numbers of people. Compounding the problem is the lack of rapid diagnostic tests to quickly identify patients infected with certain pathogens. Current clinical trials involve potentially enrolling patients who may be infected and then later needing to disenroll those patients days later when the laboratory results indicate an infection outside the research protocol. This diagnostic uncertainty adds markedly to the overall cost of the trial. In response to these issues, Representatives Gingrey and Green introduced the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, which would remove this regulatory barrier by allowing companies to receive Food and Drug Administration (FDA) approval for certain antibiotics with the use of smaller clinical trials. This approach would only be for antibiotics used to treat serious or life-threatening infections where there is an unmet medical need. Under ADAPT, FDA could approve these antibiotics for a limited population. IDSA urges the Subcommittee to markup this legislation swiftly.

In addition to ADAPT, other Congressional proposals could assist with antibiotic R&D including tax credits to support antibiotic R&D, reforming the way we reimburse antibiotics, providing more effective support through federal agencies, and establishing a public private partnership for antibiotic R&D. IDSA supports developing a coordinated government response to antibiotic resistance including well-coordinated federal leadership; sustained and meaningful involvement of non-government stakeholders; antibiotic stewardship programs in every health care facility; enhanced surveillance and data collection on antibiotic use and resistance patterns; and research on novel strategies, best practices and evaluation of methods to prevent, control, and eradicate antimicrobial resistant organisms. These steps to address resistance are critical to protect federal investment in new antibiotics. Lastly, it is critical to address the economic and regulatory barriers to development and clinical integration of new diagnostics. IDSA recommends increased investment in diagnostics research, regulatory approval pathways for needed diagnostics, strengthening diagnostics reimbursement and supporting outcomes research to demonstrate the impact of diagnostics on patient care.

Mr. PITTS. Now recognizes Dr. Thomas. Five minutes for questions.

STATEMENT OF DR. ADRIAN THOMAS

Dr. THOMAS. Thank you, Chairman Pitts and members of this committee for this opportunity to come before you today.

I am Dr. Adrian Thomas, vice president at Global Market Access and head of the Global Health function at Janssen which is the pharmaceutical business of Johnson & Johnson.

On behalf of Johnson & Johnson, I applaud you for organizing this hearing and commend all the leaders in this room for giving voice to the dire situation of antibiotic resistance.

We also recognize this committee's and Congress' leadership, as well as the leadership of President Obama on this important issue, and we offer our support for the national strategy announced yesterday.

Today I bring the lens of a private sector physician through more than 30 years' experience in public health from my early career in the Australia's Flying Doctor Service to my current role overseeing Janssen's portfolio of production and services for diseases of high public health impact, which include HIV, tuberculosis, and also more recently, Ebola.

I am a clinical pharmacologist and physician by training, with additional expertise in a variety of areas in the health care industry. The majority of my 17 years in the private sector has been with Johnson & Johnson.

As many of you know, Johnson & Johnson is the world's largest and most broadly based health care company, with a portfolio that also includes diagnostics and devices as well as the consumer products.

We are an innovation-based business, and it is critical, as you think about this issue, that we address incentives that apply and are relevant to many different stakeholders in the area of innovation, not just large companies, but discovery, academic research, biotech and start-up in the public sector.

Our place in and reach across the health care innovation ecosystem allows us unique visibility into both the number and the status of projects underway across areas of unmet need, including antibiotics. It also leads me to comment that as we consider incentives for antimicrobial resistance, we should also consider incentives in vaccines and other preventive mechanisms and diagnostics if we are truly going to make progress against this terrible issue.

Our work also brings us into proximity with patients facing life-threatening illnesses, including patients with these infectious diseases. Their stories affirm what we have heard day; that we must do more to meet their needs.

First and foremost, we must work together and think differently to bring forward new therapies. We have heard in some detail today that despite the need in recent efforts to improve it, including legislative efforts, the innovation climate for antibiotics and other antimicrobial R&D remain suboptimal. That is, in large part, because the basic science with this field continues to be very difficult with high rates of failure. If failure is no longer an option

given this critical and growing global health security, I would term it, crisis, then we need to take different measures.

We can learn lessons and warnings from the Ebola crisis, which was also neglected, and which now we have companies scrambling, including our own, to try and provide new vaccines within unfeasibly short time frames and unfunded mechanisms.

While strategies for better stewardship of antibiotics on the market are vital in the fight against resistance, current conditions demand that we need a new framework for innovation in antibiotics R&D. We have to track the world's best and brightest to this challenge, including the private sector.

As is done in other areas, the U.S. can and should lead the world in creating enabling conditions. We cannot wait for the European's Medicines Initiative to solve the problems for us.

It is our hope that this committee and the Congress will give serious consideration to new legislative proposals. Beyond this, we believe there remains the need to put forward a comprehensive set of both push and pull incentive options specific to antibiotics that address the need for R&D across a wide range of stakeholders.

We must create a broad set of highly attractive although financially manageable incentives to engage the many different biomedical innovator companies large and small in this work, including academic networks.

The policies can and should be able to take into consideration a holistic view of the costs and risks of this, and also the costs and risks of developing, introducing, and supporting these products worldwide. And how those risks are different for different stakeholders and the incentives must address, therefore, those different stakeholder perspectives.

I would like to talk a little bit about transferable market exclusivity. We have heard different perspectives on this topic. As our company has undertaken its own in-depth analysis of different incentive proposals for antibiotic R&D, it is apparent that many existing proposals only offer marginal valuations.

In addition to being a physician, I serve on the investment committee of our pharmaceutical business. I balance the difficult choices we have to make about, is Ebola, is multi-drug resistant tuberculosis, is diabetes, is cancer a more important public health question, and is it also financially feasible for us to balance our research efforts in this area.

Spending almost \$5 billion annually in research in pharmaceuticals, these decisions are not easy, and often have timeframes of 10 to 15 years.

Thinking about transferable market exclusivity, the notion of an exclusivity that can be applied towards another product not only gives certainty the investments be made in very high-risk areas, but also disincentivize activities that might otherwise undermine both the public health stewardship and the protection of these products and assets need to offer against emerging and developing antibiotic resistance to encouraging appropriate use.

The bottom line to our proposal is we believe we have to have more shots on goal, more basic research, more discovery, more biotech start-ups, more academic partnerships, more companies investing, and the in-house facilities to recognize and take up new

assets, and to conduct the expensive research necessary to deliver and develop these products to the marketplace.

In conclusion, we welcome the changes in public policy to stimulate new antibiotic R&D, and thank you very much for your time today.

Mr. PITTS. Chair thanks the gentleman.

[The prepared statement of Dr. Thomas follows:]

**Written Testimony of
Adrian Thomas, MD, FRACP
Vice President, Global Market Access & Commercial Strategy Operations and
Head, Global Public Health at Janssen, the pharmaceutical companies of
Johnson & Johnson**

**Before the
Subcommittee on Health
Committee on Energy and Commerce**

**United States House of Representatives
September 19, 2014**

Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development

Introduction

Thank you, Chairman Pitts, Ranking Member Pallone and members of this important Committee for this opportunity to come before you today to discuss the current antibiotics crisis and strategies for reversing its course. I am Dr. Adrian Thomas, vice president of Global Market Access and head of Global Public Health at Janssen, the pharmaceutical companies of Johnson & Johnson.

On behalf of the Johnson & Johnson Family of Companies, I applaud you for organizing this hearing, and commend all those leaders in this room and well beyond it who have given voice to the growing threat of antibiotic resistance.

It is my privilege to be able to view the issues at hand from the standpoint of more than 30 years of experience in public health—from my early career in Australia’s Flying Doctor Service, providing emergency care to the rural poor, to my current role overseeing Janssen’s global portfolio of products and services for diseases of high public health impact, including HIV, tuberculosis, and Ebola. I am a clinical pharmacologist and vascular physician by training, with additional expertise in pharmaceutical safety surveillance, epidemiology, clinical trial design and methodology. The majority of my 17 years in the innovator pharmaceutical industry has been spent at Johnson & Johnson.

Headquartered in New Brunswick, New Jersey, Johnson & Johnson is the world’s largest and most broadly based healthcare company. Our company was founded more than 125 years ago

with the initial aim of creating clean and safe conditions for patients undergoing surgery. Those early innovations in antiseptic surgery represented a major leap forward in healthcare. Today, our Company's quest for similarly transformative advances in healthcare remains vibrant, spanning many categories of products and services relevant to the topics of today, among them medical device and diagnostic technologies, consumer healthcare products, and pharmaceuticals.

Fundamental to our strategy is participation in and investments across the healthcare innovation ecosystem. We seek out the best science wherever it may be, accelerating cutting-edge projects at universities, academic institutes, and small start-up companies around the world. Our place and perch in this ecosystem lends us important insights into the number and status of projects in areas of unmet medical need—including antibiotics. Our in-house capabilities in the research and development (R&D) of new products, such as at Janssen, the pharmaceutical companies of Johnson & Johnson, lends us a deep understanding of the costs and risks associated with biomedical innovation.

Janssen Global Public Health, lessons from the SIRTURO™ experience

One of the groups at Janssen that I oversee, Janssen Global Public Health, is responsible for a particular medicine, known by its trade name as SIRTURO™, worth highlighting here. SIRTURO™ is a new antimycobacterial drug indicated as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis, or MDR-TB. It is the first new medicine for TB with a new mechanism of action to be developed in more than 40 years, and is the first new drug specifically indicated to treat a drug-resistant form of tuberculosis. We commend the U.S. Food & Drug Administration (FDA) for the great care it took, and continues to take, in providing guidance throughout the product's development process.

In keeping with the special requirements FDA and other regulatory agencies have set for SIRTURO™, our company's post-marketing commitments are substantial. They include a lengthy Phase 3 research program; a pediatric formulation and first-ever randomized, open label, controlled clinical study in a pediatric MDR-TB population; and a 5-year prospective study to characterize the acquisition of resistance to this new drug. Our experience with SIRTURO™ highlights the breadth of post-approval responsibilities and the magnitude of sustained investments required to ensure appropriately its safe and effective use worldwide. We estimate that approximately half of all investments necessary to develop and support SIRTURO™, amounting to several hundreds of millions of dollars, will be required *after* the point of U.S. regulatory approval in December 2012.

These are investments for which we expect no “return” as the term is traditionally defined. Normal cost recovery and profit-deriving sources for the pharmaceutical industry are well characterized and continue to rely on advanced-economy markets with more equitable and advanced healthcare systems. However, MDR-TB case numbers in the U.S. and EU amount to fewer than 2,000 patients per year. In the United States, fewer than 150 cases are reported annually. As is the case with most therapies developed for neglected diseases, cost recovery and profits associated with eventual sales of SIRTURO™ will prove to be relatively small, elusive, and insufficient to cover the costs accompanying the drug’s introduction.¹

Our experiences with SIRTURO™—today and since its discovery in our labs more than a decade ago—illustrate just some of the challenges associated with the development and introduction of new antibiotics, particularly those addressing an area of great need: namely, drug-resistant infections which, even if not yet commonplace, represent a significant health threat.

These challenges help to explain why the overall state of antibiotics R&D is deficient relative to the need. They also point us to potential policy options for overcoming and counterbalancing current risks specific to antibiotics development. Today, the innovation climate for antibiotics and other antimicrobial R&D remains suboptimal, even despite laudable recent efforts to improve it. The basic science associated with this field continues to prove exceedingly difficult, with high rates of failure.

The dangers in view

Failure, it seems, is no longer an option in the wake of the critical and growing public health threat that antibiotic resistance poses. The emergence of so-called Superbugs, or drug-resistant bacteria, forces our attention to the inadequacy of our therapeutic arsenals. Management of hospital and healthcare-acquired infections costs the U.S. health system an estimated \$10MM USD per year.² Drug-resistant healthcare-acquired infections (HAIs) are on the rise, imposing further costs in dollars spent and lives lost. Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major public health threat globally, even as notifications of other multidrug-resistant

¹ Our company received a Priority Review Voucher with the accelerated approval of SIRTURO™. The voucher program marked an important step forward in the design and implementation of new incentives to spur R&D in areas of high unmet medical need. At the same time, the program provides limited incentive to invest in high-risk early research into innovative therapies because, in considering such investments, the voucher value is discounted both by the high risk of program failure and the substantial delay (typically over a decade) before the voucher would be received. We believe the Priority Review Voucher would be most effective as an incentive for innovator firms if it were part of a more complete, diverse and integrated set of incentives that Congress can help to make available.

² Goodman, Brenda. "Hospital-Acquired Infections Cost \$10 Billion a Year: Study." *U.S. News, U.S. News & World Report*, 03 Sept. 2013. Web. 16 Sept. 2014.

Gram-negative organisms continue to increase (e.g., *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*).³

Absent new treatments or vaccines, we stand all but defenseless against these dangers.

Numerous programs have been put into place to help keep drug-resistant bacteria at bay. We commend the U.S. Centers for Disease Control and Prevention (CDC) for its leadership in this regard. Johnson & Johnson is proud to work with CDC and other partners in the implementation of such programs to reduce HAIs in the U.S. and abroad.⁴

While strategies for preventing the spread of drug-resistant bacteria in healthcare settings—and for better management of and stewardship over antibiotics on the market—are vital in the fight against resistance, *we believe that current conditions demand an even greater focus on stimulating R&D on new antibiotics and adjacent technologies (e.g., diagnostics)*. Creating a special framework for innovation in antibiotics R&D, sufficient to attract the world's best and brightest to this great challenge, must be a major point of focus as we examine solutions to the current crisis.

Lessons and warnings from the Ebola crisis

This morning's hearing is timely as tragedy unfolds in West Africa with the Ebola outbreak that has infected and killed more people than all previous Ebola outbreaks combined.⁵ Though Ebola is treated with antivirals, not antibiotics, this outbreak presents important lessons that merit our attention.

The presence of the Ebola virus in West Africa is not new, but years of neglect and a variety of armed conflicts have dramatically weakened the infrastructures, including health systems, in impacted countries. Considering the topic of this discussion today, it is useful to consider the importance of multi-pronged strategies to combat and prevent the spread of drug-resistant bacteria, especially where fragile health systems are concerned. Such multi-pronged strategies should include, for example, attention to both antibiotic innovation and stewardship.

Also relevant to today's topic are the biosecurity concerns that Ebola brings into view. While it is generally believed that the Ebola virus is limited to human transition through contact with the

³ Pollack, Andrew. "A Rising Hospital Threat." *The New York Times*. The New York Times, 26 Feb. 2010. Web. 16 Sept. 2014.

⁴ Johnson & Johnson is currently working with Advanced Sterilization Products to pioneer the reduction of pathogens from health care settings with GLOSAIR™ area disinfection products.

⁵ Cook, Nicolas, and Tiaji Salaam-Blyther. *Ebola: 2014 Outbreak in West Africa*. Rep. no. 7-5700. Washington DC: Congressional Research Service, 2014. Web. 16 Sept. 2014.

blood, secretions, organs, or other bodily fluids of already infected patients, the epidemiological data clearly demonstrate that Ebola can cross borders as easily as any traveler unwittingly incubating the disease. Our world's advanced transportation systems facilitate the exchange of sickness as well as that of people and goods. Viewed in this context, the Ebola outbreak is clearly a national security issue for many countries.⁶

At present, there are no drugs proven to prevent or treat infection with the Ebola virus, despite its documented emergence nearly forty years ago in 1976.⁷ Health experts can control it under favorable infrastructure conditions, but those are sorely lacking in the developing nations where the virus's spread has reached crisis proportions. On an emergency basis, several experimental therapies have been used that show significant promise. The absence of ready, proven therapeutic and other tools to fight this virus leaves the world at large at a loss.

At Johnson & Johnson, we have added our own resources and commitment to this critical endeavor. With the support of funding partners such as the National Institutes of Health (NIH), we are fast-tracking the development of a potential new combination vaccine to help protect people against the Ebola virus.

Our determination notwithstanding, the hurdles to our success are considerable. Beyond the extremely challenging science involved in development, inadequate market- and policy-derived incentives for investments of this type and scale compound the difficulties in play.

Similar difficulties plague the antibiotics space.

Reshaping the incentives paradigm for antibiotics R&D through policy

The development process for any innovative therapy is recognized for its cost, risk, complexity and lengthy duration. Importantly, innovators must absorb the economic impacts of failures in the R&D process, sometimes amounting to hundreds of millions of dollars or more. Less than one in every 10 drug candidates entering Phase I clinical trials ever makes it to market.⁸

Extensive and expensive clinical testing is necessary and, for those drugs that do succeed to the point of market approval, post-market research requirements can be extensive and costly.

⁶ *Ibid.*, page 3.

⁷ *Ibid.*, summary page.

⁸ Herper, Matthew. "The Truly Staggering Cost of Inventing New Drugs." *Forbes*. Forbes Magazine, 2 Oct. 2012. Web. 16 Sept. 2014.

The distinctiveness of pharmaceutical R&D for drug-resistant infectious disease places new points of strain on this already challenging innovation model. The development shift forced by drug resistance demands a targeted approach that is very different from approaches employed for broad-spectrum antibiotics in the past. Failure risks and rates are higher than average.

For these reasons and more, the current incentive structure for antibiotics is simply too ill-fitting and anemic to stimulate the level of new antibiotic R&D investments so critically needed to strike back at drug-resistant infections.

Changes in public policy toward the creation of a new incentives framework specific to antibiotics R&D can help to offset these challenges. As it has done for other areas and industries, the U.S. can lead the world in creating the enabling conditions for progress toward new antibiotics, and in so doing can affirm its role as the world's preeminent driver of biomedical innovation. In recent years, the U.S. has already made important strides toward this end.

The GAIN Act: An important first step

This Committee, Congress, and the president have all recognized the importance of infusing new incentives into the development of needed antibiotic therapies, evidenced by the "Generating Antibiotic Incentives Now," or "GAIN" Act, signed into law in 2012 as part of the *Food and Drug Administration Safety and Innovation Act*. The GAIN Act adjusted the existing incentive structure for manufacturers by extending the term of market exclusivity for an additional five years on new antibacterial or antifungal drugs for use by humans intended to treat serious or life-threatening infections, when designated under the law as "qualified infectious disease products." Today, some companies have been able to take advantage of the new investment incentives provided by the extended market exclusivity period, and have advanced some potentially promising new options through the earlier stages of the drug approval process.⁹

In this way and others, GAIN was an important first step toward a more comprehensive restructuring of the incentive model for antibiotic R&D.

Appropriately, this Congress has carried the baton forward with a variety of new legislative proposals aimed at combating antibiotic resistance. Bills introduced in recent months include the ADAPT Act, DISARM Act, and STAAR. It is our hope that this Committee and the Congress will give serious consideration to each of these proposals. Beyond these proposals, we believe

⁹ PEW Charitable Trusts. "GAIN: How a New Law Is Stimulating the Development of Antibiotics." *pewtrusts.org*. PEW Charitable Trusts, 7 Nov. 2013. Web. 16 Sept. 2014.

there remains a need for Congress to put forward a bolder and more comprehensive set of “push and pull” incentive options specific to antibiotics.

Toward a broader, bolder “basket” of incentive options

For drug-resistant diseases especially, the need for more R&D across the board remains stark. To address this need, we must explore an array of options for stimulating antibiotic drug development, and the development of adjacent technologies such as companion diagnostics. In short, *we must create a broad set of highly attractive incentives to engage many biomedical innovator companies, large and small, in this work.*

Policies should take into consideration a holistic view of the costs and risks required to develop, introduce, and support these products worldwide, and how those costs and risks shift between different actors in the innovation ecosystem at different stages along the pathway, from discovery to development to delivery.

There are many different types of incentive proposals and complementing programs already available for policymakers’ consideration. Many worthy options remain in concept form only, yet to be implemented or tested. Until such testing occurs and programs are assessed and refined, the key questions of *what will work?* and *how, when and where will it work best?* will be impossible to answer. Thus, a multidimensional or “package” approach to incentives and programs—allowing innovator firms of all forms to access an assortment of incentives—offers the greatest potential to address various issues facing different organizations and programs at different stages of development.

Such an approach could allow for efficient testing and refining of incentive models; indeed, finding what “works” within an acceptable period of time will almost certainly require testing several options simultaneously.

It is individual innovator companies that are best positioned to assess the likely success of different incentive programs ahead of implementation. Innovators of different sizes and character will almost certainly have varying perspectives on what constitutes an attractive and workable incentive or combination of incentives with regard to various challenges and needed efforts in the area of antibiotic development. Similarly, different types of diseases related to drug-resistant bacteria—each with its own set of risks, markets and cost profiles—will require different incentives as well. Hence, again, the importance of providing a comprehensive package that includes a wide variety of incentive options. It is critical that incentives be designed with an emphasis on pragmatism and with a sense of urgency.

One incentive option meriting focused consideration at the policy level:

Transferable Market Exclusivity

As our company has undertaken its own in-depth analysis of different incentive proposals for antibiotics R&D, it is apparent that many existing proposals offer only marginal valuations (\$50-100MM USD) relative to overall R&D costs. Such programs will likely not spur the extent of new innovation required. By contrast, our analysis suggests one potential model as an especially strong option for reinvigorating antibiotics R&D across the spectrum of innovators: namely, Transferable Market Exclusivity (TME).

Transferable Market Exclusivity is a policy incentive that was first proposed in 2003 by Duke University professor and researcher, Henry Grabowski. TME is a pull-based incentive that affords companies a defined period of market exclusivity that can be applied to any compound, thus facilitating R&D spending on a different “socially desirable but unprofitable medicine”¹⁰

Studies of the Orphan Drug Act have demonstrated that the single most valuable aspect of the act was guaranteed market exclusivity.¹¹ In the decade before 1982, FDA approved 10 treatments for orphan diseases, but since 1983 more than 400 products designated as indicated for orphan diseases have been approved.¹² In the past decade, such drugs accounted for 11% of new drug approvals and 24% of biologic drugs. Pediatric exclusivity as implemented under the *Best Pharmaceuticals for Children Act* has similarly proven the value of time-limited exclusivity provisions. Because the opportunity for commercial return on any new antibiotic product itself is so sharply limited,¹³ and because the spectrum of innovators required for antibiotics R&D today is so diverse, it is the transferable nature of the market exclusivity period made possible under TME – from one innovator to another, one product to another – that gives this model its unique strength as an innovation driver.

In addition to providing a meaningful incentive to innovators, TME decouples the investment toward development of an antibiotic from the market success of the antibiotic. This decoupling can help to mitigate any tensions between investment recovery and antibiotic stewardship post-market.

¹⁰ Grabowski, Henry. "Increasing R&D Incentives for Neglected Diseases: Lessons from the Orphan Drug Act." *International Public Goods and Transfer of Technology under a Globalized Intellectual Property Regime*. New York: Cambridge UP, 2005. 457-80. Print.

¹¹ Peabody JW, Ruby A, Cannon P; The economics of orphan drug policy in the US. Can the legislation be improved? *Pharmacoeconomics*, 1995 Nov; 8(5): 374-84.

¹² "Developing Products for Rare Diseases & Conditions." *FDA.gov*. The Federal Food and Drug Administration, 30 July 2014. Web. 16 Sept. 2014.

¹³ For example, by the time of end of market exclusivity, resistance may well have developed, impairing medical and commercial value and thus limiting the value of extended exclusivity of the antibiotic.

We believe that TME can be structured in policy to maximize its public health advantages and to minimize downside risks, including risks to generic manufacturers. So-called “guardrails” could be incorporated into a TME model to ensure, for example, that a TME period or voucher cannot be applied to on-market pharmaceutical products for which fewer than four years of patent life remain.

Facilitating More “Shots on Goal”

Ultimately, we support the inclusion of TME in a larger package of policy incentives for antibiotic R&D because of its clear potential to appeal to a broad swath of innovators and to move them to action. In the design of policies to meet this need of growing magnitude, focus must be fixed on the end goal, namely: more therapeutic and preventive options for patients, sooner. To achieve this, we must foster more “shots on goal,” galvanizing and mobilizing the larger innovator community to apply its time, talents and resources to the challenge of antibiotic resistance.

Thank you, Chairman Pitts, Ranking Member Pallone, and members of this Subcommittee, for your leadership on these important issues and your focus on innovation through the 21st Century Cures initiative. I look forward to answering any questions you may have.

Appendix A

Ranking Incentive Models to Drive Innovation and Investment toward New Antibiotics and Adjacent Technologies: Our “Top Three” Recommendations Based on Internal Analysis.

1. Transferable Market Exclusivity
2. Public-sector underwriting of both early- and late-stage development
3. Prize models

Combinations of these and other incentives would help to enlarge the pool of innovators participating in antibiotics R&D.

Less effective incentive models, per our internal assessments: Reimbursement adjustments; tax credits.

Appendix B

The Johnson & Johnson Family of Companies recognizes and applauds the many Members of Congress who have and are leading efforts at the policy level to counter the growing threat of antibiotic resistance.

H.R.4187 - DISARM Act of 2014

Rep. Roskam, Peter J. [R-IL-6] (Introduced 03/11/2014)

Rep. Davis, Danny K. [D-IL-7]* 03/11/2014

Rep. Bucshon, Larry [R-IN-8] 03/27/2014

Rep. Sanchez, Linda T. [D-CA-38] 03/27/2014

Rep. Jenkins, Lynn [R-KS-2] 03/27/2014

Rep. Gingrey, Phil [R-GA-11] 04/07/2014

Rep. Ellmers, Renee L. [R-NC-2] 05/19/2014

Rep. Gerlach, Jim [R-PA-6] 05/21/2014

Rep. Meehan, Patrick [R-PA-7] 05/29/2014

Rep. Green, Gene [D-TX-29] 05/29/2014

Rep. Buchanan, Vern [R-FL-16] 05/30/2014

Rep. Nunes, Devin [R-CA-22] 05/30/2014

Rep. Larson, John B. [D-CT-1] 06/09/2014

Rep. Pascrell, Bill, Jr. [D-NJ-9] 06/17/2014

Rep. Brady, Robert A. [D-PA-1] 06/17/2014

Rep. Sires, Albio [D-NJ-8] 06/18/2014

Rep. Payne, Donald M., Jr. [D-NJ-10] 06/25/2014

Rep. Lujan, Ben Ray [D-NM-3] 07/29/2014

ADAPT Act**H.R.3742 - Antibiotic Development to Advance Patient Treatment Act of 2013**

Rep. Gingrey, Phil [R-GA-11] (Introduced 12/12/2013)

Rep. Green, Gene [D-TX-29]* 12/12/2013

Rep. Shimkus, John [R-IL-15]* 12/12/2013

Rep. Eshoo, Anna G. [D-CA-18]* 12/12/2013

Rep. Whitfield, Ed [R-KY-1]* 12/12/2013

<u>Rep. DeGette, Diana [D-CO-1]*</u>	12/12/2013
<u>Rep. Blackburn, Marsha [R-TN-7]*</u>	12/12/2013
<u>Rep. Engel, Eliot L. [D-NY-16]*</u>	12/12/2013
<u>Rep. Griffith, H. Morgan [R-VA-9]*</u>	12/12/2013
<u>Rep. Butterfield, G. K. [D-NC-1]*</u>	12/12/2013
<u>Rep. Matsui, Doris O. [D-CA-6]</u>	03/24/2014
<u>Rep. Ellmers, Renee L. [R-NC-2]</u>	03/24/2014
<u>Rep. Dingell, John D. [D-MI-12]</u>	03/24/2014
<u>Rep. Latta, Robert E. [R-OH-5]</u>	03/24/2014
<u>Rep. Matheson, Jim [D-UT-4]</u>	03/24/2014
<u>Rep. Cassidy, Bill [R-LA-6]</u>	03/24/2014
<u>Rep. Yarmuth, John A. [D-KY-3]</u>	03/24/2014
<u>Rep. Olson, Pete [R-TX-22]</u>	03/24/2014
<u>Rep. Tonko, Paul [D-NY-20]</u>	03/24/2014
<u>Rep. Lance, Leonard [R-NJ-7]</u>	03/24/2014
<u>Rep. Pompeo, Mike [R-KS-4]</u>	03/24/2014
<u>Rep. Barrow, John [D-GA-12]</u>	03/24/2014
<u>Rep. Guthrie, Brett [R-KY-2]</u>	04/28/2014
<u>Rep. Lujan, Ben Ray [D-NM-3]</u>	04/28/2014
<u>Rep. Bilirakis, Gus M. [R-FL-12]</u>	05/08/2014
<u>Rep. Speier, Jackie [D-CA-14]</u>	05/28/2014
<u>Rep. Shea-Porter, Carol [D-NH-1]</u>	05/28/2014
<u>Rep. McMorris Rodgers, Cathy [R-WA-5]</u>	07/09/2014
<u>Rep. Roskam, Peter J. [R-IL-6]</u>	07/10/2014
<u>Rep. McCaul, Michael T. [R-TX-10]</u>	07/15/2014
<u>Rep. Barton, Joe [R-TX-6]</u>	07/17/2014
<u>Rep. Langevin, James R. [D-RI-2]</u>	07/17/2014
<u>Rep. McNerney, Jerry [D-CA-9]</u>	07/22/2014
<u>Rep. Roe, David P. [R-TN-1]</u>	07/22/2014
<u>Rep. Byrne, Bradley [R-AL-1]</u>	07/22/2014
<u>Rep. Pascrell, Bill, Jr. [D-NJ-9]</u>	07/29/2014
<u>Rep. Johnson, Eddie Bernice [D-TX-30]</u>	07/30/2014
<u>Rep. Heck, Joseph J. [R-NV-3]</u>	09/08/2014

<u>Rep. DesJarlais, Scott [R-TN-4]</u>	09/09/2014
<u>Rep. Ellison, Keith [D-MN-5]</u>	09/11/2014
<u>Rep. Kilmer, Derek [D-WA-6]</u>	09/11/2014

STAAR

H.R.2285 - Strategies to Address Antimicrobial Resistance Act

<u>Rep. Matheson, Jim [D-UT-4]</u>	(Introduced 06/06/2013)
<u>Rep. Moran, James P. [D-VA-8]</u>	07/23/2013
<u>Rep. McCollum, Betty [D-MN-4]</u>	11/20/2013
<u>Rep. Shea-Porter, Carol [D-NH-1]</u>	12/05/2013
<u>Rep. Green, Gene [D-TX-29]</u>	01/14/2014

STAAR

S.2236 - Strategies to Address Antimicrobial Resistance Act

Sen. Brown, Sherrod [D-OH] (Introduced 04/10/2014)

Other policy champions on issues relating to antibiotic resistance:

U.S. House of Representatives

Pitts (R-PA)
Shimkus (R-IL)
DeGette (D-CO)
Lance (R-NJ)

U.S. Senate

Blumenthal (D-CT)
Hatch (R-UT)
Bennett (D-CO)
Corker (R-TN)

Mr. PITTS. And now recognizes Mr. Outterson. Five minutes for an opening statement.

STATEMENT OF KEVIN OUTTERSON

Mr. OUTTERSON. Good morning, Mr. Chairman, and thank you, for inviting me to testify today.

I am a professor at Boston University. I also serve on the Centers for Disease Control and Prevention Antimicrobial Resistance Working Group, and at the Royal Institute for International Affairs in London as a visiting fellow at Chatham House.

My remarks today are my own, but at Chatham House, the work that we have been doing for the past year is focussed onto linkage.

I think today we need to focus and act decisively because the business model for antibiotics is broken. Not only for antibiotics but for other things that treat and prevent infectious diseases such as diagnostics, vaccines, infection controls, and related devices.

And so I have a couple of slides here to look at the business model, and the slides are based on the study that was done by the Eastern Research Group of which I was a part, I am a co-author of that study, for the department of Health and Human Services.

This first slide no one in the committee needs to see this, honestly. We know that this a huge problem. The actual number of deaths in the CDC threat assessment was 37,000 per year because they included *Clostridium difficile*. It is a huge problem.

So let's look at the business model, and we are looking at the net present value from a private perspective. This is a company looking to make a decision about whether to invest in a molecule at an early stage. And this is a typical decision tree which tries to analyze for the company what is the chance of failure at each stage and how much it will cost to advance the molecule through.

Every company uses a model like this. Everyone might use slightly different assumptions or numbers in it, but this is a typical thing done in the industry. In fact, there is in England right now at the Office of Health Economics using AstraZeneca data there is another study almost completed which comes out with I must, sad to say, much gloomier numbers than what we present here today.

So the business model is broken. The first thing we looked at, the FDA and Health and Human Services asked us to look at six bacterial indications, and it is hard to read, and I am sorry for that, but what you need to see is that the companies were hoping for \$100 million net present value. That was the money that they would get in return.

And you see here on the arrow bars and on the colored things that for several of these indications they have a negative net present value. They are actually going to lose money after they build a factory to make this drug. And for others there was a positive one but nowhere here the \$100 million threshold that was necessary for companies to move forward.

The red arrow bars, the little light thing, is the 90 percent confidence interval. For every single indication, the confidence interval included a negative number. So it is really difficult for companies to commit to research programs in that sort of space.

The second thing we were asked to look the is the social net present value. How valuable are these drugs to society. Now, we

didn't have speculative numbers here. We didn't look at the effect on reducing resistance. We didn't model how it would keep us all working. You know, the kind of ancillary effects. We just looked at the direct cost for society. And yet the numbers we came up with were huge. These numbers are in the billions, and the arrow bar ranges are huge. So the social net present value for many of these drugs was two orders of magnitude higher. Several billion dollars for several of these drugs.

In other words, society would be getting a tremendous bargain if it was able to procure one of these drugs for even a fraction of that amount.

As a comparison, I compared for each of the six indications the social and the private, and if you look real carefully, you can't even see the private on the same scale because it is in blue. It is so small it is almost impossible to see. There is a huge gap here.

So I did just one and tried to stretch it out across the slide, and you can barely see the blue for HAP/VABP. OK? And so what I did here is I truncated everything at 100 million. Those red bars really would go up another 15 feet on the wall if I allowed them, and that is the gap between the social and private value. It is another way of saying we are tremendously under reimbursing for antibiotics.

We also looked at incentives, and given that I have 30 seconds, I will get down to the key chart in which we modeled which incentives could we change in order to solve this \$100 million benchmark. We looked at every incentive ever published, I promise you, and then put them in the different categories and fed them into some model.

The short answer is that if you do something that affects the cost of capital, it has to be fairly significant in order for it to work. So if we had tax credits or BARDA funding, it better be significant in order to kick in; something on the range of a billion dollars per molecule we would want coming out the other side. So we are not talking small change. It is large.

Yesterday's proposal from the president \$800 million under BARDA, they are hoping for one drug per year out of that. I think it is a reasonable number.

Things that don't seem to work based on the model. We even had unlimited perpetual forever patents. It still didn't get the companies anywhere near the \$100 million threshold.

Similarly, to reduce clinical trial times, you would have to reduce it by 75 percent. So ADAPT could be very useful to bring a new drug to market for the people who need it today, but it should not be viewed as a powerful economic incentive for a company early in the stages to decide now is the moment to green light this drug. It doesn't have that sort of effect. What the companies need is money, not the promises of earlier approval.

Thank you.

Mr. PITTS. The chair thanks the gentleman.

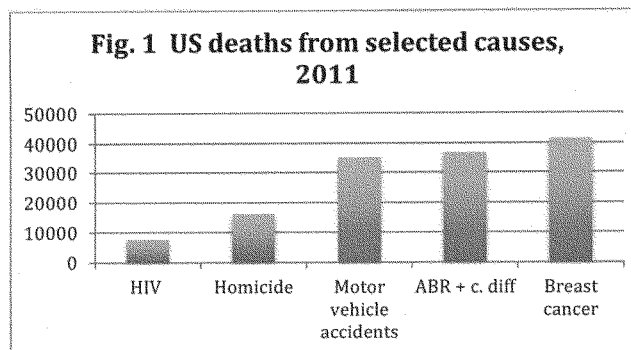
[The prepared statement of Mr. Outtersen follows:]

**Testimony of
Kevin Outterson
Boston University School of Law
To
The House Energy and Commerce Committee
September 19, 2014**

Thank you for inviting me to testify today. My name is Kevin Outterson. I am Professor of Law and the N. Neil Pike Scholar of Health and Disability Law at Boston University. For a decade I have worked on the legal ecology of antimicrobial resistance.¹ I serve as a member of the CDC Antimicrobial Resistance Working Group and a Visiting Fellow at the Royal Institute of International Affairs at Chatham House in London. I speak today in my individual capacity, not representing any institution.

We must act decisively to fix the broken business model for antibiotics and other methods to prevent and treat bacterial diseases. These other methods include vaccines, diagnostics, infection control, and devices.

Last year, the CDC issued the first national threat assessment on antimicrobial resistance.² The media reported that 23,000 Americans die each year from antibacterial resistance, but the CDC estimated an additional 14,000 deaths per year from a horrible intestinal disease related to antibiotic use, *Clostridium difficile*. These calculations are conservative and likely undercount the true impact in the US, the equivalent of a 100-passenger jet crashing every day (Fig. 1).



Source: National Vital Statistics Report (NVSr) "Deaths: Final Data for 2011." Data for ABR is from CDC, Antibiotic Resistance Threats in the US, 2013

¹ A bibliography of my works on resistance is collected in the Appendix.

² CDC. Antibiotic Resistance Threats in the US, 2013.

Antibiotic resistance deaths in Europe are in the same range,³ but the situation in poorer countries is also dire. Resistant pathogens in low-income countries cause several hundred thousand neonatal sepsis deaths each year.⁴ Similar numbers of people die in low-income countries from susceptible bacteria, so we face an antibiotic access crisis in addition to the global problem of resistance.⁵ Much of our world lives in a pre-antibiotic era.

Future projections are much worse. If we lose antibiotics as a drug class, the social cost may be more than a trillion dollars, shaving several years off life expectancy and making many modern medical procedures either impossible or much more dangerous.

The ability to prevent and treat bacterial diseases is a global common pool resource of immense value, akin to fisheries.⁶ Exhausting this resource is cheap and lazy; preserving it will take concerted effort and substantial resources. These future expenditures are an investment in the continued effectiveness of one of the greatest classes of drugs ever discovered. Consider this as an “insurance premium,” protecting us against the post-antibiotic era.

1. The business model is broken.

For more than a decade, it has been noted that the net present value (NPV) of antibiotic investments was too low, especially compared with other investment opportunities within drug companies.⁷ Several larger companies abandoned antibacterial development over the past two decades, although several are now considering re-entry due to the prospect of aggressive action by Congress and the EU.

In order to understand these issues, The Department of Health and Human Services contracted with the Eastern Research Group in October 2011 for a study entitled: *Incentives for the Development of New Drugs, Vaccines, and Rapid Diagnostics for Bacterial Diseases*.⁸ I served as an independent consultant and co-author of the final report: *Analytical Framework for Examining the Value of Antibacterial Products* (April 2014).⁹

³ ECDC. Available at http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm.

⁴ Laxminarayan R et al. (in peer review 2014).

⁵ My testimony today focuses on bacterial threats. While drug-resistant malaria, tuberculosis and HIV are very significant threats to global health, they are beyond the scope of this testimony.

⁶ Outterson K. The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation. *Cardozo L Rev.* 2010;31:613.

⁷ Projan, S.J. 2003. Why is big Pharma getting out of antibacterial drug discovery? *Curr. Opin. Microbiol.* 6:427–430.

⁸ Task Order No. HHSP23337004T; Contract No. HHSP23320095634WC.

⁹ Available at: http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm.

A. Private and social net present values (NPVs).

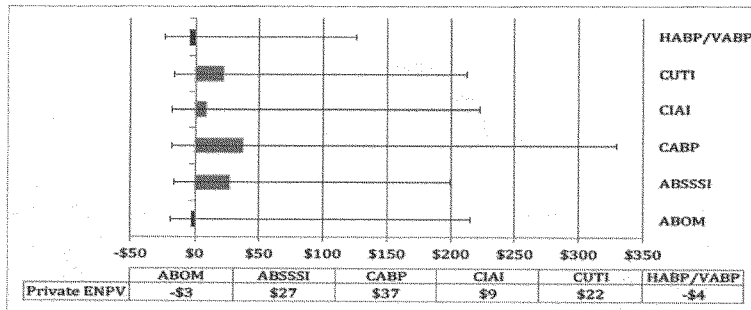
We were first asked to estimate NPVs for new drugs to treat six specific types of infections, a bacterial vaccine against ear ache, and a new MRSA diagnostic device. This is the “private” NPV because it is calculated from the perspective of the private company making an investment decision on funding R&D. We built a model based on point estimates from the published and grey literature, and also ran Monte Carlo simulations using a range of values. The model, data sources and methods are described in full in the ERG Report. Limitations include focusing solely on the US market and examining a limited set of bacterial indications, vaccines and diagnostics.¹⁰

We set a benchmark target of a NPV equal to or exceeding \$100 million, which is a conservative target for a new antibiotic drug.

We also estimated the direct social value of each of these products – what they bring to society in terms of avoided mortality, morbidity and associated costs. We avoided speculative social values, such as the reductions in resistance that might flow from decreased antibiotic use. We also did not include social costs entirely external to the health system, such as the effects on business from a pandemic. We discounted these values at a 3% rate, consistent with OMB guidelines, with a sensitivity analysis ranging from 1% to 7%. The result is the “social” NPV, what the innovation is potentially worth to society.¹¹

The results are striking: in no case did any of the six antibiotic drugs yield a private NPV close to the benchmark \$100 million. For all six antibiotics, the 90% confidence interval included *negative* NPVs (Fig. 4 in the ERG Report):

Figure 4: Sensitivity of Estimated Private ENPVs by Indication for a New Antibacterial Drug (in \$ Million) - Error Bars Represent 90% Confidence Bounds

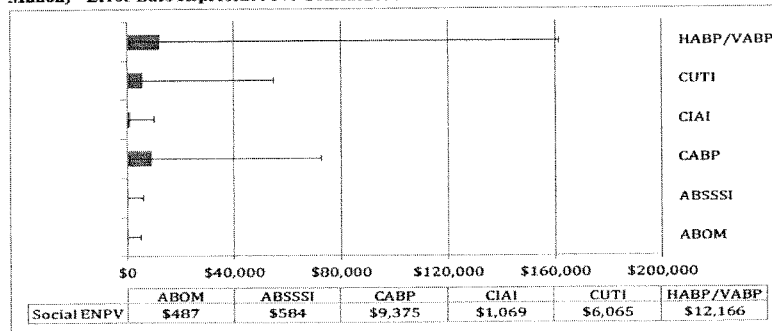


¹⁰ Professor Adrian Towse and Dr. Jorge Mestre-Ferrandiz at the Office of Health Economics have created a similar modeling exercise, currently in peer-review. Their model focuses on Europe and antibiotics targeting narrow-spectrum resistant pathogens. In general, their private NPVs are lower than those described in the ERG Report.

¹¹ ERG Report, section 3.6.

The low private NPVs stand in sharp contrast to the social NPVs, which were conservatively estimated to range from \$487 million to \$12.1 billion (Fig. 6 in the ERG Report):

Figure 6: Sensitivity of Estimated Social ENPVs by Indication for a New Antibacterial Drug (in \$ Million) - Error Bars Represent 90% Confidence Bounds

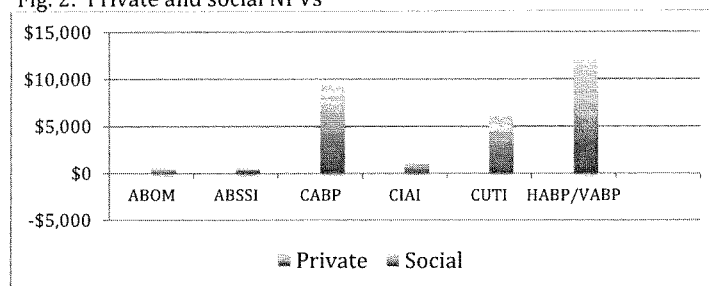


Source: ERG 2013 (fig. 6).

Put simply, society will benefit greatly from preventing or treating these conditions, but companies are not financially rewarded for bringing these products to market and the US health care system is not rewarded for preventing these infections through other means, such as vaccination, better diagnostics or infection control.

The gap between private and social NPVs is even starker when plotted on the same scale, which makes the blue private NPV difficult to see since it is so small compared to the social NPV (Fig. 2):

Fig. 2: Private and social NPVs



Source: Author's analysis using data from ERG 2013.

The data were more encouraging for the proposed Acute Bacterial Otitis Media (ABOM) vaccine against ear aches. Private NPV was \$515 million and social NPV

was \$2.2 billion,¹² but this social value did not include the ancillary benefits from reducing antibacterial use in children for ABOM, which accounts for about half of all antibiotic use in children.¹³ Otitis media accounts for more than 25% of all physician office visits where an antibiotic was prescribed for patients 14 years old and younger.¹⁴ If the vast majority of these prescriptions could be avoided through a vaccine or device, resistance could be slowed, reducing the need for new antibiotics.

The social value gap was greatest for the proposed rapid point-of-care diagnostic for MRSA: private NPV of \$329 million and social NPV of \$22.1 billion.¹⁵

Put bluntly, the US should be willing to pay up to \$2.2 billion for an ABOM vaccine (or, alternatively, a device that treated ear aches in children without antibiotics such as the EntraTympanic device currently moving towards clinical trials).¹⁶ The US should be willing to pay up to \$22.1 billion for an outstanding MRSA diagnostic that changed clinical practice. A prize of \$500 million would be a bargain. The largest current prize offered for a bacterial diagnostic is the UK Longitude Prize for £10 million.¹⁷

B. Which incentives work best?

The second main task in the ERG Report was to model which incentives would most efficiently improve private NPV. We searched all of the published literature, including reports by industry, the WHO, think tanks, academics, civil society, and trade associations. We categorized each incentive according to how it might impact NPV.

For example, shortening clinical trials impacts the model in two ways: reducing expenditures and shortening the time until drug approval and sales revenue. Intellectual property extensions delay generic competition, protecting a portion of sales after the patent would have otherwise expired. Tax incentives and non-dilutive capital like the BARDA Broad Spectrum Antibacterial Program reduce cash outlays and the overall cost of capital for the company.

We also modeled how public health and conservation programs impacted private NPV. Many excellent public health programs reduce unit sales of antibiotics, worsening the business case. Examples include successful antibacterial vaccination campaigns (such as the proposed ABOM vaccine), rollout of point-of-care clinical

¹² ERG 2013 (tables 19-20).

¹³ Finkelstein JA, Metlay JP, Davis RL, Rifas-Shiman SL, Dowell SF, Platt R. Antimicrobial Use in Defined Populations of Infants and Young Children. *Arch Pediatr Adolesc Med* 2000; 154(4):395-400.

¹⁴ McCaig LF et al. Office-Related Antibiotic Prescribing for Persons Aged ≤14 Years — United States, 1993–1994 to 2007–2008 *MMWR* 60;34 Sept 2, 2011.

¹⁵ ERG 2013 (tables 21-24).

¹⁶ See <http://www.entratympanic.com/>.

¹⁷ See <http://www.nesta.org.uk/project/longitude-prize-2014>.

diagnostics (such as the proposed MRSA diagnostic), entry of a device that dramatically cut antibiotic use (such as a device like the EntraTympanic), Medicare programs to reduce hospital-associated infections, and successful public education campaigns by the CDC to reduce unnecessary antibiotic use (see below). All of these are excellent ideas, preventing infections or greatly reducing unnecessary antibiotic use, but each of them reduces market demand for antibiotics and therefore reduces the private NPV (Fig. 3):

Fig. 3: Impact of various incentives on private NPV

INCENTIVE	IMPACT ON PRIVATE NPV
Intellectual Property (IP) extensions	Delays generic entry
Tax incentives	Decreases cost of capital
Modifications to the clinical trial process & approval standards	Reduces time to market
Grants for antibiotic research and development	Decreases R&D costs
Prizes and product development partnerships (PDPs)	Decreases R&D costs
Reductions in demand-side uncertainty	Reduces demand uncertainty
Education campaigns	Reduces unit sales
Improvements in hospital infection control	Reduces unit sales
Vaccination promotion	Reduces unit sales
Better monitoring & reporting of infection rates & antibiotic resistance	Reduces unit sales
Performance- and value-based reimbursement schemes	Reduces unit sales
Revocation of marketing authorization for antibiotics that pollute	Truncates revenue time horizon

Source: Adapted from ERG 2013.

The results of our modeling found that several incentives would never reach the \$100 million benchmark by themselves. Even perpetual patents and marketing exclusivities failed to reach the benchmark, mainly due to discounting (i.e., the time value of money). When faced with a decision whether or not to green light a new

molecule for pre-clinical development, companies do not highly value the prospect of an additional five or ten years of exclusive sales two decades from now. This is especially true for small venture-capital backed research companies.

Shortening clinical trial timeframes was also an unlikely contributor to innovation: clinical trials times would have to be cut by more than 75% in some cases in order to reach the benchmark. Since the ERG model did not account for recent streamlining for antibiotic trials by the FDA, additional reductions on this magnitude are probably impossible. In addition, requiring only very limited trials prior to antibiotic approval will limit the types of efficacy and safety data that physicians and patients need and that payers will want in order to support value-based pricing.

Tax credits, BARDA grants and other non-dilutive capital fared better in the model, as would direct modifications to reimbursement.

The most direct path to improving private NPV is to boost reimbursement, but to do so in a way that does not give any incentive to oversell or waste antibiotics and in a way that does not impede access for patients who truly need the product. When paired with tax credits and BARDA-style contracts, this menu of options can easily exceed the benchmark threshold without surprising payers with extremely high prices.

Perhaps the most important finding in the ERG Report is buried on Table 14: in order to reach the benchmark for one of the bacterial indication (ABSSSI), the total incentives that would be needed totaled \$919 million, including additional value-based reimbursements or prizes totaling \$155 million after FDA approval. It should be noted that this was just one possible example out of many, but it illustrates an important point: the magnitude of the incentives must be large, in the range of \$1 – 2 billion total per year if the goal is to see a couple of new, high-quality antibiotics each year. Since this research has lead times exceeding a decade, substantial incentives must be put in place and left unchanged for more than a decade. Given the high social value of antibiotics, this is a critical social investment, retaining one of the most important drug classes in history.

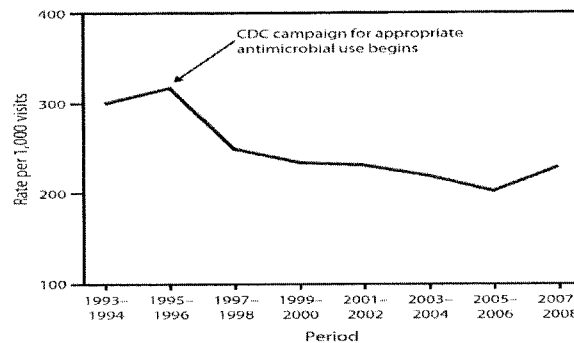
The proposed DISARM Act, as modified,¹⁸ is an intermediate step to reforming reimbursement, but the sector needs incentives with 10-year federal cost estimates exceeding \$10 billion, not \$144 million.¹⁹ The size of the response is too low by at least two orders of magnitude.

¹⁸ The modification to limit DISARM incentives to higher-priority pathogens is an excellent choice; see my discussion below on targeting.

¹⁹ Avalere Health. Estimated Costs of Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act of 2014 (DISARM Act) (draft, June 2014).

The magnitude of the incentives required also suggests how much we should be investing in prizes and reimbursement for vaccines that prevent disease and diagnostics that allow physicians to treat each bug with the right drug. Likewise, the NIH budgets for antibacterial resistance research seem too small at an estimated current level of less than \$200 million.²⁰ The CDC has run its national education campaign to reduce unnecessary antibiotic use for many years with less than 2 FTE employees and a total budget under \$1 million per year. Much has been achieved under such tight budgets (Fig. 2 in the MMWR article):

FIGURE 2. Average annual antibiotic prescribing rates for persons aged ≤14 years per 1,000 physician office visits — National Ambulatory Medical Care Survey, United States, 1993–1994 to 2007–2008



Source: McCaig LF et al. Office-Related Antibiotic Prescribing for Persons Aged ≤14 Years — United States, 1993–1994 to 2007–2008 MMWR 60;34 Sept 2, 2011.

While the GAIN Act is viewed as a good first step, we now know that decisive action is needed, giving investors a credible expectation that if they fund research programs today, then billion dollar rewards await a decade from now.

2. Now is the moment for decisive action.

Many lawmakers and stakeholders on both sides of the Atlantic are engaged with the problem of antibacterial resistance. US efforts include the 21st Century Cures hearings, the 2012 GAIN Act, the CDC Threat Assessment, ongoing work by CMS to reduce hospital-associated infections, the impending report from the President's Council on Science and Technology, BARDA's contractual program, FDA initiatives, and the soon to be announced NIH National Strategy. Together, they speak to the commitment by the US government to leadership on this issue. Private stakeholders

²⁰ The NIH releases composite figures for antimicrobial resistance research, which includes anti-retrovirals (HIV) and anti-parasitics (malaria). The actual amount of NIH funding targeting resistant bacterial pathogens on the CDC Threat Assessment is not known to the public. I have estimated it at \$200 million; the actual number may be lower.

include the Infectious Diseases Society of America, the Alliance for the Prudent Use of Antibiotics, and many others that have long argued for better policies in this area. The Brookings Institution and the Pew Charitable Trusts have hosted several stakeholder meetings to build consensus. Many of the companies are working together and putting concrete legislative language on the table, most prominently through the Antimicrobial Innovation Alliance.

The European Union has committed almost €700 million to a public-private partnership to boost innovation to prevent and treat bacterial diseases, the “New Drugs for Bad Bugs” (ND4BB) program under the larger Innovative Medicines Initiative. One project under ND4BB will specifically examine the broken business models in this area and propose solutions. This project, DRIVE-AB, launches next month and I serve as a Senior Consultant. We will build on the ERG model in the European context, with a significant program of research over the next three years. DRIVE-AB is funded at more than €6 million for the next three years.

Recognizing the urgency, Prime Minister David Cameron recently announced an independent commission headed by economist Jim O’Neill to recommend changes to the economic landscape. Commission staff members will be in Washington next week (September 23-25) to meet with key leaders and researchers in the US. Their preliminary report is due in April 2015, so the timeline is short. The commission is independent of the government, funded by the Wellcome Trust. This work builds on the advocacy carried out for many years by Dame Sally Davies, the Chief Medical Officer of England, both in Europe and at the WHO.

Chancellor Angela Merkel is the third leader of the G7 to highlight the urgent need to act on this issue. She is joined by many civil society organizations in Europe calling for reforms, such as ReACT and Antibiotic Action. Amongst the think tanks in Europe, the Royal Institute of International Affairs (Chatham House) has worked for several years designing new business models for antibiotics.²¹ The final report from their Working Group – which I lead – will be published in November 2014.

Clearly, we have unprecedented political, social, and medical mobilization to address antibiotic resistance. This level of energy and consensus has never been seen on this issue. If we do not act now, we may waste the opportunity for a generation.

3. Specific recommendations.

The following recommendations are drawn from my work as a researcher and my experience on the various bodies with whom I am privileged to serve, but the recommendations are my own.

²¹ Outtersson K. New business models for sustainable antibiotics. Chatham House 2014. Available at <http://www.chathamhouse.org/sites/files/chathamhouse/public/Research/Global%20Health/0214SustainableAntibiotics.pdf>.

- **Be bold**

Now is not the time for small, incremental tinkering. Press reports suggest that some large drug companies are considering leaving antibacterial development; others that cut back programs a decade ago are expressing interest again. But the ERG Report clarifies the scale of the ambition needed: billions, not millions, committed for decades, not years.

- **Think beyond the pill**

New antibiotics are needed. They will cost us perhaps a billion dollars each and be worth every penny. But we should think beyond the pill and also invest similar amounts of money in bacterial vaccines,²² diagnostics and other devices, basic NIH research, surveillance, and infection control. Bacterial vaccines have a clear impact on health, reducing the need for antibiotics by preventing infections.

Global surveillance is our early-warning system against bacterial threats. Infection prevention and control in hospitals, long-term care, and other institutional settings may be our most cost-effective response (see the decline in hospital-associated MRSA in recent years), but to a hospital CFO, infection control is a cost center, not a revenue generator. When faced with the investment choice between a new cardiac catheterization lab or better infection control, only the catheterization lab offers a return on investment. If we really want to see robust infection control, give it a billing code.

Reimbursement is low and unattractive for antibiotics, but it is worse for diagnostics. Remember that the social value of a MRSA diagnostic is estimated at \$22.1 billion. A \$500 million dollar prize would draw significant interest and be a bargain. New diagnostic and device companies struggle to raise \$3.5 million for an initial round of financing to proceed to clinical trials.

The goal is to prevent and treat bacterial infections. We should fund and use all of the tools, focusing on the most cost-effective options. The most cost-effective response might be to prevent infections and slow resistance and roll out new antibiotics only when needed. We need innovation not just for new pills, but also to preserve and extend effective treatments, including prevention.²³

²² Bacterial vaccines such as the pneumococcal conjugate vaccine have substantially reduced invasive pneumococcal disease and therefore antibiotic use. What if we had a vaccine against MRSA or *Clostridium difficile*?

²³ Laxminarayan R. Antibiotic effectiveness: Balancing conservation against innovation. *Science* 2014;345:1299-1301; Kesselheim AS, Outterson K. Improving Antibiotic Markets for Long Term Sustainability. *11 Yale J Health Pol'y L Ethics* 2011;11:101.

- **Target the incentives**

Resist the Lake Wobegon temptation to see all antibiotics as above average and worthy of special incentives. Since our resources are limited, we must target the most important pathogens identified on the CDC Threat Assessment.

The Qualified Infectious Disease Product (QIDP) list promulgated under the GAIN Act includes every major bacterial pathogen and does not require that the pathogen be resistant. As a result, all *staphylococcus* species are included, as are all *E. coli*. It seems likely that every antibiotic ever approved by the FDA would qualify as a QIDP. This is a failure to prioritize and put scarce resources where they are needed most.

The 1980s saw the introduction of a large number of antibiotics, but many were low quality drugs that never made a significant clinical or commercial impact. Of the 61 new molecular antibiotics approved by the FDA from 1980 – 2009, 43% of them were withdrawn from the market by FDA action or discontinued by the company ceasing commercial sales in the US (Figure in Appendix A). We want quality, not quantity, focused on the greatest threats to human health.

- **Offer a menu of generous incentives across the product life cycle**

Boosting NIH funding stokes the pipeline and feeds start-up companies. Creating tax credits for qualified clinical trial expenses (similar to the Orphan Drug Act, but built on a different statute) will lower the cost of capital and raise NPVs. BARDA is a proven success story, with a strong hand in many of the best molecules now in development (see Fig. 4). BARDA funding should be replenished, with a more flexible mandate.

Fig. 4: BARDA's Broad Spectrum Antibiotic Supported Product Pipeline, 2014.

BARDA's BSA Supported Product Pipeline					
Sponsor	Compound	Development			
		Preclinical	Phase I	Phase II	Phase III
Antibiotics	Achaogen Plazomicin (ACHN-490)	Next-generation aminoglycoside: Broad Spectrum plague, tularemia and carbapenem-resistant Enterobacteriaceae (CRE)			
	CUBRC/ Tetraphase Eravacycline (TP-434)	A novel fully synthetic tetracycline: Broad Spectrum plague, tularemia, nosocomial and intra-abdominal and urinary tract infections (UTI, cUTI)			
	Cempra Solithromycin (CEM-101)	Next-generation fluoroketone: Broad Spectrum antitoxin, tularemia, gonorrhea and community-acquired bacterial pneumonia (CABP)			
	Basilea BAL30072	A novel sulfonamide: Broad Spectrum MDR Gram-negative infections, melioidosis, glanders			
	Rempex Carbavance™ (meropenem/ BPK7009)	Carbapenem/β-lactamase inhibitor: Broad Spectrum CRE, cUTI, hospital-acquired pneumonia, ventilator-associated pneumonia (VAP), endocarditis, glanders			
	GSK A portfolio approach	Broad Spectrum Antibiotic Portfolio A partnership to fund multiple compounds to combat antibiotic resistance at various stages of development			

Disclaimer: The above projects are supported by BARDA's BSA Program utilizing non-dilutive funding via a contract and/or agreement. The stage of development is approximate as of July 2014 (please refer to the sponsor's site for updated information). The table represents the compounds most advanced commercial indication being pursued by the developer.

Source: BARDA.

Once products are registered, some form of value-based reimbursement or prize should kick in, either fully replacing or supplementing existing reimbursement. GlaxoSmithKline has publicly taken the stance that volume-based reimbursement is inappropriate for antibiotics due to resistance and has called for post-approval payments that are “delinked” from sales volume. The Chatham House Working Group that I lead has been working on delinkage models for more than a year and will issue a final report in November 2014.

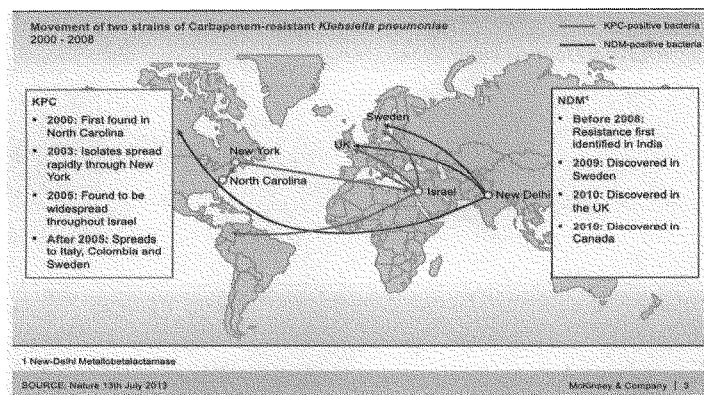
- **National leadership with global coordination**

National programs have successfully reduced antibiotic use, reduced hospital-associated infections, vaccinated the populations, and improved the bacterial safety of water and food.

The US can also lead the world by supporting innovation as described above, especially if this is coordinated with the EU. The market heft of the US and the EU together are more than sufficient to drive substantial research programs to solve these problems.

But some issues require global coordination, since pathogens respect no borders. The global spread of CRE strains is but one example:

The increased mobility of the population makes AMR a health threat without borders



KPC-3 producing CRE strains are now found in South Dakota, where an outbreak recently struck.²⁴

²⁴ Lee M. Kiedrowski et al. Carbapenem-Resistant *Enterobacter cloacae* Isolates Producing KPC-3, North Dakota, USA. EID 20;9 (Sept 2014).

Global coordination is needed to protect important antibiotics from wasteful overuse. US leadership will be key to this effort, coordinating with partners such as the EU, the G7, and WHO. While TATFAR is a useful arrangement, the level of coordination needed is much greater, with very senior leadership.

- **Include agriculture and environmental sources**

Agriculture accounts for more than 80% of antibiotic use in the US, including some key human drug classes (Fig. 5):

Fig. 5: Total Antimicrobial Consumption by Class in the US²⁵

Antimicrobial Class	Animal Use (Kg)	Human Use (Kg)	Total Use (Kg)	Average DDD (g)	Total Animal Usage (DDD)	Price (\$/kg)	Animal Expenditures
Aminoglycoside	214,895	6,485	221,380	0.599	358,457,048	\$28.5	\$6,124,507.5
Cephalosporins	26,611	496,910	523,521	2.77	9,606,859	\$75	\$1,995,825
Ionophores**	4,123,259	na	4,123,259	1.56	2,644,227,099	\$30	\$123,697,770
Macrolides	582,836	164,028	746,864	1.07	544,706,542	\$55	\$32,055,980
Lincosamides	190,101	71,455	261,556	1.65	115,212,727	\$50	\$9,505,050
Penicillins	880,163	1,460,421	2,340,584	3.76	234,085,904	\$30	\$26,404,890
Sulfas	371,020	481,664	852,684	1.91	194,251,309	\$33	\$12,243,660
Tetracyclines	5,642,573	113,832	5,756,405	1	5,642,573,000	\$28	\$157,992,044
Not independently reported*,**	1,510,572	na	1,510,572	1.56	968,722,900	\$30	\$45,317,160
Total:	13,542,030	3,289,175	16,831,205		10,711,843,388		\$246,321,956.5

Source: Aidan Hollis, Ziana Ahmed, The path of least resistance: paying for antibiotics in non-human uses, Health Policy, Available online 8 September 2014, ISSN 0168-8510, <http://dx.doi.org/10.1016/j.healthpol.2014.08.013>.

Resistance genes have been found throughout the agricultural sector, including dairy cows that did not receive antibiotics.²⁶ We should launch serious research efforts to find and deploy techniques to reduce the need for antibiotics in agriculture and to reduce health risks to humans, including animal husbandry, vaccines,

²⁵ Notes: Data on quantities from [9,48]. Data on prices are drawn from a search of prices offered on Alibaba in August 2013. DDDs are taken from the WHO ATC/DDD Index 2013 and averaged by class.

*Includes aminocoumarins, amphenicols, diaminopyrimidines, fluoroquinolones, glycolipids, pleuromutilins, polypeptides, quinoxalines, and streptogramins. **The DDD is the average of other commonly used antibiotics.

²⁶ Wichmann F, Udikovic-Kolic N, Andrew S, Handelsman J. 2014. Diverse antibiotic resistance genes in dairy cow manure. mBio 5(2):e01017-13. doi:10.1128/ mBio.01017-13.

alternative forms of growth promotion, and other innovations. The FDA recently brokered voluntary restrictions on non-therapeutic antibiotic uses in farm animals. One recent proposal suggests a user fee on animal antibiotics, to gently reduce volumes while funding research.²⁷

Antibiotic pollution is also found in surprising places in the natural environment. Several recent studies have found both antibiotics and resistance genes in wastewater from treatment plants and generally in the water supply.²⁸ Antibiotics are generally excreted through urine and may survive current water treatment processes. Much work is needed to understand the scope of the problem and to provide innovative water treatment solutions for these issues.

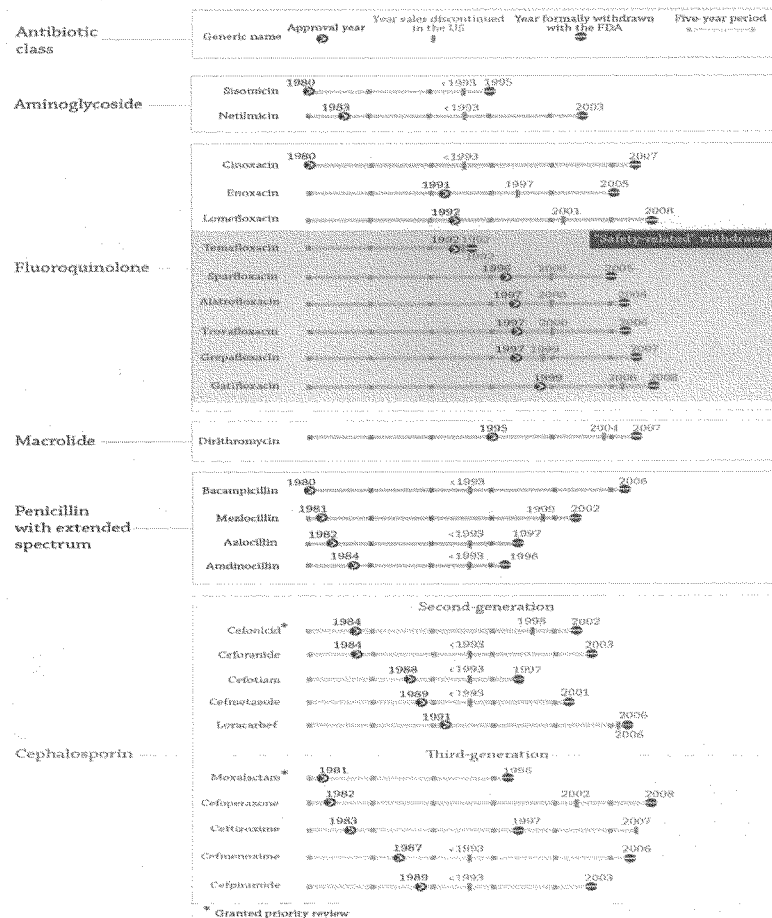
4. Conclusion.

Currently in the news and foremost on our minds is Ebola. Ebola is a viral disease, but the next pandemic could be bacterial and arise in our own hospitals and communities. In the movies, heroic research scientists discover the cure before the credits roll; in real life, research programs require at least a decade and generally longer to deliver an effective antibiotic. Congress should take bold action to retain the effectiveness of the original wonder drugs that have saved so many lives – antibiotics.

²⁷ Aidan Hollis, Ziana Ahmed, The path of least resistance: paying for antibiotics in non-human uses, Health Policy, Available online 8 September 2014, ISSN 0168-8510, <http://dx.doi.org/10.1016/j.healthpol.2014.08.013>;

²⁸ Farenfeld N. et al. Reclaimed water as a reservoir of antibiotic resistance genes: distribution system and irrigation implications Front Microbiol. 2013;4:130.

APPENDIX A

New Systemic Antibiotics Approved by the FDA 1980-2009,
but Subsequently Withdrawn or Discontinued

* Granted priority review

On average, these antibiotics were formally withdrawn 14.8 years after FDA approval (IQR: 10.5, 18.75). Most drugs ceased sales or were informally discontinued several years before formal action to withdraw from FDA approval.

Antibiotics for which the sales discontinuation date is listed as <1993 had their sales discontinued prior to 1Q 1993; the exact date was unavailable for earlier periods.

Data source:
Kevin Outterson, John H. Powers, Enrique Sonane Vazquez,
Rosa Rodriguez-Monguilo, and Aaron S. Kesselheim
*Approval and Withdrawal of New Antibiotics and Other
Antimicrobials in the U.S., 1980-2009*
Journal of Law, Medicine & Ethics, Fall 2013.

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APPENDIX B

Kevin Outterson's publications on resistance and drug regulation:

Peer reviewed journals, legal journals and major reports:

Analytical Framework for Examining the Value of Antibacterial Products (US Department of Health & Human Services/ASPE, April 15, 2014) (with Sertkaya et al.) http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm.

New Business Models for Sustainable Antibiotics, Chatham House Centre on Global Health Security Working Group Papers (London, Feb. 2014).

The Drug Quality and Security Act – Mind the Gaps, 370 N. ENGL. J. MED. 97-99 (2014).

Approval and Withdrawal of Antibiotics and Other Antiinfectives in the US, 1980-2009, 41(3) J.L. MED. & ETHICS 688-696 (2013) (with Powers, Seoane-Vazquez, Rodriguez-Monguio, & Kesselheim).

Regulating Compounding Pharmacies After NECC, 367 N. ENG. J. MED. 1969 (2012).

All Pain, No GAIN: Need for Prudent Antimicrobial Use Provisions to Complement the GAIN Act, 30 APUA CLINICAL NEWSLETTER 13 (2012).

Towards New Business Models for R&D for Novel Antibiotics, 14 DRUG RESISTANCE UPDATES 88-94 (2011) (with So AD, et al.).

Improving Antibiotic Markets for Long Term Sustainability, 11 YALE J. HEALTH POL'Y, L. & ETHICS 101 (2011) (with Kesselheim AS).

Fighting Antibiotic Resistance: Marrying New Financial Incentives to Meeting Public Health Goals, 29 HEALTH AFFAIRS 1689-1696 (2010) (with Aaron S. Kesselheim).

Questions About the 10 x '20 Initiative, 51 CLIN. INFECT. DISEASES 751-752 (2010) (with Powers JH, Gould IM & Kesselheim AS).

The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation, 31 CARDOZO L. REV. 613 (2010).

How Medicare Could Get Better Prices on Prescription Drugs, 28 HEALTH AFFAIRS W832-841 (July 30, 2009, web exclusive) (with Kesselheim AS).

Death from the Public Domain?, 87 TEXAS L. REV. SEE ALSO 45 (2009).

Foreword – Will HPV Vaccines Prevent Cervical Cancers Among Poor Women of Color?: Global Health Policy at the Intersection of Human Rights and Intellectual Property

Outterson Testimony

9/16/14

Law, 35 AM. J. L. & MED. 247 (2009) (symposium editor).

Pharmaceutical Innovation: Law & the Public's Health, 37 J. L. MED. & ETHICS 173 (2009) (symposium editor).

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Translated into Portuguese: '*Fair Followers*': *Expandindo o Acesso a Medicamentos Genéricos para a População de Baixa e Média Renda*, in PROPRIEDADE INTELECTUAL: NOVOS PARADIGMAS INTERNACIONAIS, CONFLITOS E DESAFIOS (Campus-Elsevier, Brasil 2007).

Mr. PITTS. Now recognizes Mr. Coukell 5 minutes for open statement.

STATEMENT OF ALLAN COUKELL

Mr. COUKELL. Mr. Chairman, I would like to thank you and the ranking member and the members of the committee for the opportunity to be here today.

My name is Allan Coukell. I direct drug, medical device, and food programs at the Pew Charitable Trusts. We are independent research and policy organization with a longstanding focus on the urgent need for new antibiotics.

As you have already heard, the dwindling pipeline of antibiotics is a potential public health crisis. Every one of us will need one of these drugs in our lifetime, and most of us already probably know somebody who has had a resistant infection.

Children and seniors are particularly vulnerable, as are members of the military. One-third of those injured in Iraq and Afghanistan came back with an infection, some of them resistant to almost all existing drugs, and among the broader population, 23,000 Americans die every year from resistant infection.

So a comprehensive response requires infection prevention and surveillance in reducing unnecessary use and better diagnostics. But my focus today is steps to reinvigorate the drug pipeline.

And the state of the pipeline is not good. A Pew analysis included in my written statement finds 38 drugs, antibiotics, now in clinical testing. Five of them in advanced development have some potential to treat Gram-negatives, which are probably the most serious immediate threats. That may sound encouraging, but let's recognize just based on general trends that 80 percent of those won't reach market. They will fail because of reasons of toxicity or lack of effectiveness.

What is more, very few of the drugs now in development actually have novel mechanisms of action that would significantly delay the onset of resistance.

So what can be done? By passing the GAIN Act two years ago, this committee has already taken a leadership role. GAIN, introduced by Dr. Gingrey, Mrs. DeGette, and Mr. Green extends market exclusivity for certain antibiotics. This gives companies a better chance of a positive return in investment. GAIN also ensures swift FDA review of these drugs.

That was an important first step, and more is needed, especially for the infections that are hardest to treat, and as has been mentioned, trials of antibiotics are hard because only a small proportion of the population with, say, pneumonia has a resistant bug at any given time.

So to help address these challenges, Dr. Gingrey and Mr. Green and a long list of bipartisan cosponsors have introduced the ADAPT Act. ADAPT would create a new FDA approval pathway for antibiotics to treat patients with few or no other treatment options. This approach, which is also called LPAD, for Limited Population Antibacterial Drug, meets both a public health goal and helps streamline development.

So let me make it concrete with two different scenarios. Imagine drug A which is approved for a range of bacterial pneumonias,

some easily treated, some resistant. When FDA approves drug A, it has to consider the universe of people who might get it. Some of them have lots of treatment options and won't be willing to accept greater uncertainty.

Now take a second drug, drug B, which is an LPAD drug only for life-threatening pneumonias caused by a resistant organism. The patient with this infection may well die if he doesn't take drug B. So the potential benefit may be greater against the uncertainty.

And the FDA, in making a benefit/risk calculation only for patients like our patient, can accept less data in approving the drug. That reduces development costs.

To be clear, this does not change the standard of approval. It merely targets a specific population that is different from the general population.

For LPAD to work as intended, health care providers have to know and understand that the drug is approved for the limited population based on limited data. The drug's special status has to be clearly communicated through drug labeling and any marketing materials.

To vet this concept, Pew has worked with the Infectious Disease Society, antibiotic stewardship personnel, drug companies, health insurers, the FDA, and others, and this legislation has the support of numerous and diverse stakeholders, and yesterday PCAST, the President's Council of Advisors on Science and Technology, also called for such legislation.

This committee has long understood the threat of antibiotic resistance and has done much to bring it to the national stage, and we appreciate your leadership and continued commitment.

Let me conclude with the observation that we face many intractable problems in many diseases that seem intractable. This is not one of them. Bacterial infection is a solvable problem. Penicillin and the heyday of the drugs that followed effectively conquered bacterial illness for a time, and we can get back there if we commit and ensure that we do it again.

I thank you and I welcome your questions.

Mr. PITTS. The Chair thanks the gentleman.

[The prepared statement of Mr. Coukell follows:]



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

September 19, 2014

**Allan Coukell, Director of Drugs and Medical Devices
 The Pew Charitable Trusts**

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.

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

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
Testimony of Allan Coukell, The Pew Charitable Trusts
September 19, 2014

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.

A data table from

THE PEW CHARITABLE TRUSTS

JULY 2014

Antibiotics Currently in Clinical Development

As of September 15, 2014, an estimated 38 new antibiotics¹ with the potential to treat serious bacterial infections are in clinical development for the U.S. market. The success rate for drug development is low; at best, only 1 in 5 candidates that enter human testing will be approved for patients.² This snapshot of the antibiotic pipeline will be updated periodically as products advance or are known to drop out of development. Please contact Rachel Zetts at rzetts@pewtrusts.org or 202-540-6557 with additions or updates.

Drug name	Development phase	Company	Drug class	Cited for potential activity against gram-negative pathogens?	Known QIDP designation?	Potential indication(s) ^{2,3}
Tedizolid	Approved for acute bacterial skin and skin structure infections; June 30, 2014	Cubist Pharmaceuticals	Oxazolidinone		Yes	Acute bacterial skin and skin structure infections, hospital-acquired bacterial pneumonia/ventilator-acquired bacterial pneumonia
Dalbavancin	Approved May 23, 2014	Durata Therapeutics	Lioglycopeptide		Yes	Acute bacterial skin and skin structure infections
Oritavancin	Approved August 6, 2014	The Medicines Company	Glycopeptide		Yes	Acute bacterial skin and skin structure infections
Ceftolozane+avibactam ⁴	New Drug Application (NDA) submitted for complicated urinary tract infection and complicated intra-abdominal infection (indications)	Cubist Pharmaceuticals	Novel cephalosporin+beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infections), hospital-acquired bacterial pneumonia/ventilator-associated pneumonia
Debio 1450	Phase I	Debiopharm Group	FabI inhibitor (Debio 1452 pro-drug)		Yes	Acute bacterial skin and skin structure infections
AZD0914	Phase I	AstraZeneca	DNA gyrase inhibitor	Yes	Yes	Uncomplicated gonorrhea
Aztreonam+avibactam ⁴ (ATM-AVI)	Phase I	AstraZeneca/Forest Laboratories	Monobactam+novel beta-lactamase inhibitor	Yes		Bacterial infections
BAL30072	Phase I	Baxley Pharmaceuticals	Monosulfactam	Yes		Multidrug-resistant Gram-negative bacterial infections ⁵
CRS3123	Phase I	Crestone	Methionyl-tRNA synthetase (MetRS) inhibitor			Clostridium difficile infection

Drug name	Development phase?	Company	Drug class	Cited for potential activity against gram-negative pathogens ²⁴	Known QIDP designation?	Potential indication(s)? ²⁵
EDP-788	Phase 1	Enanta Pharmaceuticals	Bicyclicide			Bacterial infections
LC801-0371	Phase 1 ²⁶	LagoChem Biosciences (South Korea)	Oxazolidinone			Bacterial infections
MRX-1	Phase 1	Micula Pharmaceuticals	Oxazolidinone			Bacterial infections including community-acquired MRSA and vancomycin-resistant enterococci infections ²⁷
TD-1607	Phase 1	Theravance Biopharma	Glycopeptide-cephalosporin heterodimer			Serious Gram-positive bacterial infections (acute bacterial skin and skin structure infections, hospital-acquired pneumonia/ventilator-associated pneumonia, bacteremia) ²⁸
WCK-2349	Phase 1	Weeks	Fluoroquinolone (WCK-771 pro-drug)		Yes	Bacterial infections
WCK-771	Phase 1	Weeks	Fluoroquinolone		Yes	Bacterial infections
POL7090	Phase 2	Polyphor (Roche license)	Macrolide (protein epoxide mimetic) lipid inhibitor	Yes (Pseudomonas)		Ventilator-associated bacterial pneumonia, lower respiratory tract infection, bronchiectasis
Debio 1452	Phase 2	Debiopharm Group	FabI inhibitor		Yes	Acute bacterial skin and skin structure infections
Avanofloxacin	Phase 1	Furukawa Pharmaceuticals (acquired by Iovance Laboratories)	Fluoroquinolone	Yes	Yes	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections
Brilacidin	Phase 2	Cellcutix	Defensin-mimetic			Acute bacterial skin and skin structure infections
Ceftazidime-avibactam ²⁹	Phase 2	AstraZeneca/Forest Laboratories	Cephalosporin/novel beta-lactamase inhibitor	Yes		Complicated urinary tract infections
CG-400549	Phase 2	CrystalGenomics	FabI inhibitor			Acute bacterial skin and skin structure infections, osteomyelitis ³⁰
Pikafloxacin	Phase 2	MerLion Pharmaceuticals	Fluoroquinolone	Yes	Yes	Complicated urinary tract infections, acute pyelonephritis (kidney infections), acute intra-abdominal infections, acute bacterial skin and skin structure infections
OSK2140944	Phase 2	GlaxoSmithKline	Type 2 topoisomerase inhibitor			Respiratory tract infections, acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia
Lefamulin (BC-3761)	Phase 2	Nabriva Therapeutics	Pleuromutilin			Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia ³¹

Drug name	Development phase	Company	Drug class	Cited for potential activity against gram-negative pathogens?	Known QIDP designation?	Potential indication(s)?
Relebactam (MK-7655)+ (imipenem/cilastatin) ⁹	Phase 2	Merck	Carbapenem+novel beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, acute pyelonephritis, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia
Nemonoxacin ⁹	Phase 2	TaiGen Biotechnology	Quinolone	Yes	Yes	Community-acquired bacterial pneumonia, diabetic foot infections, acute bacterial skin and skin structure infections
Omadaacycline	Phase 2	Paratek Pharmaceuticals	Tetracycline	Yes	Yes	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, complicated urinary tract infections
Rafezolid	Phase 2	Melinta Therapeutics	Oxazolidinone	Yes	Yes	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia
Ramoplanin	Phase 2	Nanotherapeutics	Lipoglycopeptide			C. difficile-associated diarrhea, C. difficile relapse prevention ⁹
TAK-578 (fosfomic acid) ⁹	Phase 2	Cempra Pharmaceuticals	Fosidone			Prosthetic joint infections
TD-1792	Phase 2	Theravance	Glycopeptide-cephalosporin heterodimer			Acute bacterial skin and skin structure infections, other serious infections caused by Gram-positive bacteria including hospital-acquired pneumonia/ventilator-associated pneumonia and bacteremia ⁹
Zabofloxacin	Phase 2	Ding Wei Pharmaceutical	Fluoroquinolone			Community-acquired bacterial pneumonia
SMT 19969	Phase 2	Summit			Yes	C. difficile-associated diarrhea
Carbazolid	Phase 3	Actelion Pharmaceuticals	Quinolone+oxazolidinone		Yes	C. difficile-associated diarrhea
Carbavance	Phase 3	Rempex Pharmaceuticals (wholly owned subsidiary of The Medicines Company)	Carbapenem (biapenem)+novel boronic beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, febrile neutropenia, bacteremia, acute pyelonephritis (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae)
Cefazidime+avibactam (CAZ-AVI) ⁹	Phase 3	AstraZeneca/Forest Laboratories	Cephalosporin+novel beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infections), hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia

Drug name	Development phase	Company	Drug class	Cited for potential activity against gram-negative pathogens?	Known QIDP designation?	Potential indication(s) ^{3,4}
Delamanid	Phase 3	Melinta Therapeutics	Fluoroquinolone	Yes	Yes	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, uncomplicated gonorrhea, hospital-acquired bacterial pneumonia, ⁵ complicated urinary tract infections, ⁶ complicated intra-abdominal infections ⁶
Eravacycline ⁷	Phase 3	Tebah Pharmaceuticals	Tetracycline	Yes	Yes	Complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired bacterial pneumonia ⁸
Plazomicin ⁹	Phase 3	Achaogen	Aminoglycoside	Yes		Bloodstream infections and nosocomial pneumonia caused by carbapenem-resistant Enterobacteriaceae
Solidronmycin	Phase 3	Cempra Pharmaceuticals	Macrolide (ketolide)	Yes	Yes	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhea
Surotomycin	Phase 3	Cubist Pharmaceuticals	Lipopeptide		Yes	C difficile-associated diarrhea

Note: The following drugs have been removed from the pipeline:

September 2014 Review: GSK-2694266 and GSK-1323222 (Gilead/SmithKline), ACHN-975 (Achaogen), and PF571 (Novartis) were removed during the September 2014 review. These drugs were either no longer included in the R&D pipelines on the company website or there was direct communication from the company regarding the status of the drugs.

June 2014 Review: Cefepime—an antibiotic developed by Basilea Pharmaceuticals—had been included in our analysis; however, the company announced in June 2014 that it is not pursuing further development in the United States until a partner has been acquired. This drug will be included in future updates if development resumes.

* Michael Hay et al., "Clinical Development Success Rates for Investigational Drugs," *Nature Biotechnology* 32, no. 1 (2014): 40-51. See more at <http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development>.

Notes

- Antibiotics listed here include products containing at least one component not approved in the United States previously. All analyses were strictly limited to systemic antibiotics (drugs that work throughout the body) and drugs to treat *Clostridium difficile*-associated disease. The Centers for Disease Control and Prevention cited *C. difficile* as an urgent public health threat in a 2013 report (*Antibiotic Resistance Threats in the United States, 2013*, Sept. 16, 2013, <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>). We excluded biological products, vaccines, and locally acting drugs such as topical, ophthalmic, and inhaled products. Also excluded were drugs used to treat mycobacterial infections such as tuberculosis and *Mycobacterium avium* complex, *H. pylori*, and biothreat pathogens. Autibartam, a novel beta-lactamase inhibitor, is being studied in combination with three approved antibiotics and all three were counted for this report as each combination targets a distinct set of pathogens.
- Based on the most advanced development phase for any indication according to trials registered in clinicaltrials.gov. If no trials were included in clinicaltrials.gov, then the phase listed on the company website or provided directly by the company is noted. Antibiotics that have been approved will remain listed for one year following approval of the initial indication.
- Based on information provided on the company website or press releases or based on inclusion in citations *iv* or *v* below. "Yes" in this category means that the antibiotic has potential activity against at least one Gram-negative organism. Examples include the pathogen that causes gonorrhea, *Neisseria gonorrhoeae*, which the CDC classified as an urgent public health threat; Gram-negative bacilli such as members of the Enterobacteriaceae family such as *Klebsiella pneumoniae* and *Escherichia coli*; *Acinetobacter* species and *Pseudomonas* species; and so-called fastidious Gram-negative bacteria that commonly cause community-acquired respiratory infections.
- Certain antibiotics intended to treat serious or life-threatening infections can be designated by the Food and Drug Administration as qualified infectious disease products, or QIDPs. QIDPs are eligible to receive benefits under the Generating Antibiotic Incentives Now Act (signed into law as part of the Food and Drug Administration Safety and Innovation Act), including expedited FDA review and extended exclusivity for approved products.
- Based on clinical trials currently registered in clinicaltrials.gov and/or reported QIDP designations unless otherwise noted. Bolded indications are reported QIDP designations.

6. Not currently registered in clinicaltrials.gov. Information obtained from the company via a corporate website, press release, and/or direct communication.
7. Avibactam is a new beta-lactamase inhibitor being tested in conjunction with three individual antibiotics. We list all three combinations here.
8. Identified as antibiotics in advanced development (phase 2 or 3) with the potential to treat infections caused by Gram-negative bacilli (Enterobacteriaceae, *Pseudomonas*, *Acinetobacter*) resistant to currently available treatments. According to the Infectious Diseases Society of America, multidrug-resistant strains of these organisms represent today's most pressing medical threat.
9. Approved for community-acquired bacterial pneumonia in Taiwan, marketing application submitted in China.
10. TAKSTA was granted an orphan drug designation for the indication of prosthetic joint infections.
11. Registered in clinicaltrials.gov, but with no current study sites within the United States.

Citations

- i. Citeline, "Pharmaprojects," Pipeline (2012), <http://www.citeline.com/products/pharmaprojects>.
- ii. BioCentury, "Antibiotics NCE Pipeline," accessed Oct. 28, 2013, <http://www.biocentury.com/antibioticsncepipeline.htm>.
- iii. U.S. National Institutes of Health, "Search for Studies," <http://www.clinicaltrials.gov>.
- iv. Helen W. Boucher et al., "10 x '20 Progress—Development of New Drugs Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America," *Clinical Infectious Disease* 56 (2013): 1685–94, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3707426>.
- v. Michael J. Pucci and Karen Bush, "Investigational Antimicrobial Agents of 2013," *Clinical Microbiology Reviews* 26 (2013): 792–821, <http://cm.asm.org/content/26/4/792>.
- vi. Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States*, 2013 (Sept. 16, 2013), <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>.

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The Pew Charitable Trusts is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, reduce the poverty, and stimulate civil life.

Mr. PITTS. Now recognizes Dr. Powers 5 minutes for an opening statement.

STATEMENT OF DR. JOHN H. POWERS

Dr. POWERS. Thank you very much, Mr. Chairman. Thank you for inviting me to testify.

I am a practicing infectious diseases and internal medicine physician, and a medical researcher who actively cares for patients. I was a scientist at FDA for almost a decade and the co-chair of the Inter-agency Task Force on Antimicrobial Resistance, and I am a member of the WHO Advisory Group on Antimicrobial Resistance.

I am speaking today on behalf of the National Physicians Alliance. NPA is a professional home to physicians in more than 40 medical specialties. We share a commitment to patient-centered health care, evidence-based health policy, and professional integrity. NPA does not accept pharmaceutical company funding. We believe in the advancement of knowledge through research that is free of financial conflicts of interest, transparent, and peer reviewed. NPA's FDA Task Force was established to support our work in defense of a strong scientifically rigorous FDA.

As members of this committee have pointed out, studies of infectious diseases in the early 1900s, at a time when there were no effective therapies, were the first to use the modern methods of adequate and well-controlled trials that are a part of law today. Investigators and then members of Congress realized that appropriate study methods are critical in order to separate the harmful from the helpful for patients.

The problems of antibiotic resistance and the scientific and regulatory responses to it are also not new. Dr. Scott Podolsky in his recent book, *The Antibiotic Era*, recounts that during the rise of resistance the common staphylococcal infections in the 1950s, drug companies marketed numerous ineffective antibiotics based on supposed superiority in the test tube.

Dr. Maxwell Finland, the first president of the Infectious Diseases Society of America, with 19 other prominent infectious disease clinicians, pointed out the need for adequate and well-controlled studies in patients. He said, "Properly conducted clinical studies may support the claims and justify the enthusiasm for these antimicrobial agents, but it is incumbent upon those of us who are intimately concerned with the welfare of our patients to wait until such data are presented before we accept and acclaim any new agents or recommend them for general use."

In 1962, Dr. Finland made these same points at the Senate hearings that resulted in adding the requirement for effectiveness for new drugs based on substantial evidence from adequate and well-controlled studies showing that, like with other drugs, antibiotic effectiveness cannot be assumed based on test tube tests, animal studies, or mathematical modeling, but can only be verified by studies that ask the right questions with the right outcomes in the patient who might benefit from experimental drugs.

The problem of antibiotic resistance today is the same as it was in years past. The unmet medical need exists in those patients who have no effective therapies. The need for treatments with improved

effectiveness compared to older treatments on the outcomes of decreasing death or irreversible disability, not alternative outcomes. The program described by Dr. Hillan exactly focuses on this population and these outcomes.

Drugs marketed as life saving should actually be shown to save lives in adequate and well-controlled studies using appropriate diagnostics such as those we have discussed this morning and advocated in yesterday's PCAST report to select the patients who would receive added benefit from those drugs. And susceptibility criteria should be based on patient outcomes, not mathematical modeling from sources without conflicts of interest.

Drugs that are highly effective need few patients to show those effects in adequate and well-controlled studies. Therefore, the sample size of a study is related to how effective the drug actually is.

It is ethically questionable to expose our patients who have any current effective and safe options to less effective treatments in order to have a robust pipeline or as an economic stimulus to companies. It is scientifically invalid to test drugs in patients with disease due to susceptible organisms and then assume effectiveness in older sicker patients with disease due to resistant pathogens based on assumptions from modeling and individual and anecdotes.

Recent clinical trials of new antibiotics carry warnings on FDA Web site of increased death compared to older effective drugs despite promising test tube tests, animal models, and mathematical modeling. A recent study by AHRQ showed a lack of evidence that this kind of mathematical modeling has been shown to result in better patient outcomes. This shows that now, as in past years, preliminary information is not a substitute for clinical studies in patients.

Patients who wish to take an informed risk should have access to these drugs through requirements for expanded access under existing FDA programs for patients who do not qualify for ongoing clinical research studies, as was done in the early years of the HIV epidemic to allow access to new therapies while the drugs are continued to be evaluated in adequate and well-controlled studies prior to widespread marketing.

FDA labeling should accurately reflect the benefits, the types of patients who benefit, how clinicians should select those patients, and the information used as the basis for approval. Telling clinicians a drug has not been studied properly does not help clinicians prescribe new drugs appropriately.

Our written testimony provides NPA's plan for a comprehensive approach to development, disease prevention, stewardship, diagnosis and reimbursement strategies for improved therapies of infectious diseases in line with the recommendations from the president's PCAST report released yesterday.

Dr. Finland sums up the issues we discuss today and that we as physicians still agree with today when he said, "Clinical investigators and authors of medical and scientific publications have the duty to protect the medical profession and the public against the abuse of preliminary scientific information and against the improper and premature exploitation of conclusions based on inadequate data."

Thank you very much for the opportunity to testify.

[The prepared statement of Dr. Powers follows:]



Testimony of John H Powers MD
Associate Clinical Professor of Medicine
George Washington University School of Medicine
To
United States House of Representatives
Energy and Commerce Committee
September 19, 2014

21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development

Thank you for inviting me to testify. I am a practicing infectious disease and internal medicine physician and a medical researcher who actively cares for patients. I was a scientist at FDA for almost a decade and while at FDA I was one of the co-chairs of the Inter-agency Task Force on Antimicrobial Resistance and the Lead Medical Officer for Antimicrobial Development and Resistance Issues. I would like to share with you today my perspectives as a clinician, researcher and patient myself on appropriately developing antibiotics where there is the greatest need in order to provide benefit to patients. I am speaking on behalf of the National Physicians Alliance.

The National Physicians Alliance (NPA) serves as a professional home to physicians across more than 40 medical specialties who share a commitment to patient-centered health care, evidence-based health policy, and professional integrity. The NPA strictly refuses funding from pharmaceutical or medical device companies. We believe in the scientific advancement of knowledge through empirical research that is conducted free of financial conflict of interest; subjected to professional peer-review; and transparent in process.

The NPA's FDA Taskforce was established to support the organization's work in defense of a strong, scientifically rigorous FDA that does not stray from its mission "to protect public health by ensuring the safety and effectiveness of drugs and medical devices." The FDA is under increasing pressure, much of it from industry, to speed innovation. We are here today because we are concerned about a growing threat to the scientific rigor with which the agency reviews drugs and medical devices. We all believe in the goal of providing patients with therapies that result in improved outcomes but this can only be accomplished through a comprehensive approach and adequate and well-controlled studies in patients who benefit.

When innovation maximizes meaningful clinical outcomes for our patients, it is a tremendous good for society; but innovation does not always do this. New is not always better. Sometimes new is dangerous. Sometimes new is deadly. As prescribers who pass both risk and cost on to our patients

when we recommend a particular drug or device, our aim is to help ensure thorough, independent review of the medical products under the FDA's purview. We too want powerful, effective treatment options for our patients: we want treatments to work, and we want them to work safely. This means that integrity of the label "FDA-approved" is critically important to physicians.

Learning from History

The study of infectious diseases has gone hand in hand with the development of better methodologies to evaluate whether medical interventions result in more benefits than harms for patients. Studies of infectious diseases were the first to use the modern methods of adequate and well-controlled trials that are part of law today.¹ The reason for the development of these methods was the realization of investigators and members of Congress that only through adequate study of new medical interventions can we separate the harmful from the helpful for patients.

The problems of antibiotic resistance and the discussion of appropriate scientific and regulatory responses to that problem are not new. Dr. Scott Podolsky of Harvard Medical School in his recent book *The Antibiotic Era*², recounts that during the rise of resistance to common staphylococcal infections in the 1950s, drug companies marketed ineffective antibiotics with claims of improved effectiveness based on test tube testing and animal models, with resultant increased costs to the medical system and unclear benefits for patients. Dr. Maxwell Finland, the first President of the Infectious Diseases Society of America, with 19 other prominent infectious diseases investigators as co-signatories pointed out the need for adequate and well-controlled studies in patients as the basis for determining whether these new interventions were beneficial to patients:

"To be sure, properly conducted clinical studies may, in the future, support the claims and justify the enthusiasm for these or other ...antimicrobial agents, but it is incumbent upon those of us who are intimately concerned with the welfare of our patients to wait until such data are presented before we accept and acclaim any new agents or special formulations and recommend them for general use, particularly in view of their great potential for harm when they are used extensively and indiscriminately"³

In 1962, Dr. Finland made these same points as he testified at the Senate hearings that resulted in adding the requirement for demonstration of effectiveness of new drugs based upon "substantial evidence" from "adequate and well-controlled studies". Dr. Finland's remarks point out that like with other drugs, antibiotic effectiveness cannot be assumed based on test tube tests and animal studies or mathematical modeling but can only be verified by studies that ask the right questions, with the right outcomes, in the patients who might benefit from the test drugs.

¹ The James Lind Library. Principles of Fair Testing of Medical Treatments.

<http://www.jameslindlibrary.org/context/principles-of-testing.html>

² Podolsky S. *The Antibiotic Era*. Johns Hopkins Press. In press for release December 2014

³ Maxwell Finland, "The New Antibiotic Era: For Better or For Worse?" *Antibiotic Medicine and Clinical Therapy* 4 (1957): 18

Defining the Problem: Unmet Medical Need in the Setting of Antibiotic Resistance

The problem of antibiotic resistance today is the same as it was in years past. Patients with disease caused by antibiotic resistant organisms for which there are no effective therapies are more likely to die or suffer serious disability from their disease. Therefore **the unmet medical need exists in those patients that have no effective treatments**. The need is for treatments with *improved effectiveness* than those that have become less effective over time. The outcome that is most relevant to patients is decreasing death or irreversible disability. Defining unmet medical need in the setting of antibiotic resistance clearly leads to how and in whom studies should be performed and the outcomes that should be measured. There is also an unmet medical need based on lack of effectiveness in setting outside of antibiotic resistance, such as the need for improved effectiveness in disease due to *Clostridium difficile*.

It is ethically questionable to expose our patients who have current effective and safe treatments to less effective treatments in order to have a “robust pipeline” of new drugs or to provide an economic stimulus to drug companies. Therefore studies of new interventions to treat infectious diseases should be done in the patients who are expected to live longer or live better lives with the new interventions.

Furthermore legal precedent points out that patients with life threatening diseases should be not receive less protection under the law from less effective or unsafe drugs. In 1979, Justice Thurgood Marshall wrote in a landmark Supreme Court decision:

“The [Food Drug and Cosmetic] Act makes no express exception for drugs used by the terminally ill and no implied exemption is necessary to attain congressional objectives or to avert an unreasonable reading of the terms ‘safe’ and ‘effective’. Nothing in the legislative history suggests that Congress intended protection only for persons suffering from curable diseases”⁴

Comprehensive Approach to Addressing Improved Therapies for Infectious Diseases

In order to ensure improved patients outcomes a comprehensive approach is needed to address the worse outcomes in patients caused by antibiotics resistance. New antibiotic drugs alone, especially if not studied properly, will not only fail to address the problem but may make it worse since ineffective drugs can still cause side effects in patients and spread antibiotic resistance further. We propose a comprehensive set of suggestions to help patients and develop better therapies:

- 1. Requirement for expanded access programs for all drugs and biologics under any expedited review programs including qualified infectious diseases products (QIDP):**

Patients who wish to gain access to experimental therapies and who wish to take an informed risk for themselves should have access to these drugs. Drug sponsors should be required to have such programs under existing FDA expanded access programs for all patients who do not qualify for ongoing clinical research studies. These programs were developed during the early years of the HIV epidemic so that patients could obtain access while the new therapies continued to be evaluated in adequate and well-controlled studies prior to widespread marketing. Such programs should be streamlined, including rapid distribution and efficient Institutional Review Board

⁴ US v Rutherford 1979.

(IRB) review to that patients can obtain access to experimental therapies.⁵ The current program allows companies to recoup costs.

2. **Studies should be performed in patients who have *no* effective therapies to show *improved effectiveness*:** Programs based on less data should focus on only on therapies that have added benefits for patients. The ethical conduct of clinical research requires that studies be done in types of patients who might benefit from the test therapies. The current paradigm of approving antibiotics based on studies designed to rule how much *less effective* a new therapy might be in studied patients compared to an older standard of care therapy already known to be safe and effective puts current patients in harms way without benefit. FDA's own guidance on the mis-named "non-inferiority" studies states:

"Because the intent of the trial is... to show that the new drug is not materially worse than the control, they are now called non-inferiority (NI) trials. But that... is a misnomer, as guaranteeing that the test drug is not any (even a little) less effective than the control can only be demonstrated by showing that the test drug is superior. What non-inferiority trials seek to show is that any difference between the two treatments is small enough to allow a conclusion that the new drug has at least some effect or, in many cases, an effect that is not too much smaller than the active control."⁶

These studies do not address the need for therapies with improved effectiveness in patients who do not have effective therapies. Patients who have current effective therapies should not be asked to accept more risk, as the risk-benefit decision in patients who do not have effective therapies is different than in patients who have effective and safe therapies. Therapies with substantial toxicity may be acceptable if they are life saving in patients who have no effective therapies. Drugs with increased toxicity are not acceptable in patients who already have effective and safe options. So-called "non-inferiority" studies ask the wrong question in the wrong types of patients.

In cancer there is also a substantial problem of drug resistance. New cancer drugs to address resistance are performed in patients who have cancer drug resistance to show improved outcomes in those patients, rather than doing studies to show somewhat lesser effectiveness in patients with drug-susceptible disease. The substantial toxicity of cancer drugs is acceptable because the goal is to decrease death, and because the patients studied do not have other effective therapies.

In HIV-AIDS, patients who have resistant viruses and who have received prior HIV therapies are studied in clinical trials to show improved effectiveness of new therapies as well.

Clinical studies should be performed in patients with well-defined disease syndromes and not based on pooling diseases with widely differing types of patients or diseases merely because the

⁵ US Food and Drug Administration. Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)
<http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/accesstoinvestigationaldrugs/ucm176098.htm>

⁶ US Food and Drug Administration. Guidance for Industry Non-Inferiority Clinical Trials.
<http://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf>

same “bugs” cause the diseases. Clinicians treat patients, not “bugs”, and patients present for care with recognized disease syndromes. Clinicians prescribe treatments based on those recognized disease syndromes. Current antibiotic studies show that antibiotics have differing effects in different diseases; such as current FDA warnings on increased mortality in pneumonia with various antibiotics while the drugs claim effectiveness for other diseases.⁷

3. **Outcomes in clinical studies in patients should show decreased deaths and/or decreased disability in patients:** Since patients die or experience irreversible disability with resistant infections the outcomes in studies should be decreased deaths or decreased irreversible disability for patients. Many types of bacterial infections are acute diseases where the direct outcomes of death and disability in patients occur in a matter of weeks to months. In this setting there is no need to use outcomes based on laboratory outcomes or clinician judgments since the direct outcomes are easily measurable. Drugs that are marketed as “life saving” should actually be shown to save lives in adequate and well-controlled studies in patients. FDA’s own guidance on expedited approval programs states:

“Accelerated approval [based on surrogate endpoints] is generally less useful in more acute disease settings in which therapy is intended to provide a more near-term clinical benefit. In such settings, even if there are potentially predictive surrogate endpoints or intermediate clinical endpoints, there may be little or no time advantage for studies evaluating a surrogate or intermediate endpoint compared to studies evaluating the intended clinical benefit.”⁸

Approval for chronic diseases based on outcomes that are not patient centered, such as microbiological testing of sputum cultures in tuberculosis, should include a “sunset provision.” If confirmatory studies based on patient centered outcomes like decreased deaths are not done within a specified amount of time then approval should be automatically withdrawn. Companies should be required to keep open expanded access programs while further work is done to gain full approval.

Work in ongoing through the Foundation for the National Institutes of Health (FNIH) to improve the outcomes assessments in clinical trials in infectious diseases and move away from poorly defined outcomes based on clinician judgment and/or laboratory testing to more patient centered outcomes.⁹ Companies should be given incentives to develop drugs using patient centered outcomes.

⁷ FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning. <http://www.fda.gov/drugs/drugsafety/ucm369580.htm>
FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia.
<http://www.fda.gov/Drugs/DrugSafety/ucm387971.htm>

⁸ US Food and Drug Administration. Guidance for Industry. Expedited programs for serious conditions - drug and biologics.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

⁹ Talbot GH, Powers JH, Fleming TR, et al. Progress on developing endpoints for registrational clinical trials of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections: update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. Clin Infect Dis. 2012; 55: 1114-21.

4. Studies should be adequate and well-controlled studies in patients with well-defined serious and life threatening disease under study, not based solely on test tube tests, animal models or mathematical modeling:

Recent antibiotic studies have shown increased deaths or decreased cures in patients who received new antibiotics compared to older drugs already proven safe and effective in treating serious infections. These new drugs had promising test tube tests, animal models and mathematical modeling but they still resulted in worse outcomes for patients. Therefore concerns about the use of test tube tests, animal models and mathematical modeling are not merely theoretical but have resulted in real harms for patients who already have effective therapies. This type of preliminary information is not “confirmatory evidence”. Increased deaths have occurred more often in the sickest types of patients. Since patients with disease due to resistant pathogens tend to be older, sicker, have more concomitant disease and receive more medications, they are most likely to be harmed by ineffective drugs. Doing studies to show a new drug is a little less effective in patients who are relatively less sick with disease due to susceptible organism and then extrapolating improved benefit to unstudied types of sicker patients with resistant pathogens is not logical or scientifically supported by these same studies showing harm in sicker patients. FDA has several warnings on its website concerning these drugs.¹⁰

A study by the Agency for Healthcare Research and Quality of over 1700 studies showed a lack of evidence that mathematical modeling resulted in better patient outcomes. Therefore it is scientifically inappropriate to rely on such methodology as “predictive” of improved effectiveness in patients in lieu of clinical trials in patients with the disease under study.¹¹

Dr. Finland warned of this same problem of accepting new drugs as effective and safe based on preliminary information before they are studied in patients:

“Clinical investigators and authors of medical and scientific publications [have] the duty to protect the medical profession and the public against the abuse of preliminary scientific information and against the improper and premature exploitation of conclusions based on inadequate data.”¹²

5. Focusing studies on well-defined patients with disease due to resistant pathogens will allow for smaller studies:

Non-inferiority studies usually are larger than studies designed to show improved effectiveness (superiority) of new therapies. The number of patients needed to show a test intervention is effective is based on how much more effective the new therapy really is: therapies with greater effectiveness need a smaller sample of patients and less effective therapies require a greater number of patients to study. Prioritization should be given to the most effective

¹⁰ FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning. <http://www.fda.gov/drugs/drugsafety/ucm369580.htm>

FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia. <http://www.fda.gov/Drugs/DrugSafety/ucm387971.htm>

¹¹ Agency for Healthcare Research and Quality. Pharmacokinetic/pharmacodynamics measures for guiding therapy in nosocomial pneumonia. <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1598&pageaction=displayproduct>

¹² Finland. The New Antibiotic Era. Ibid.

interventions, and “limited datasets” for less effective drugs will only hide their lack of effectiveness. The earliest studies in infectious diseases in patients who lacked effective therapies required few patients because the drugs were highly effective in decreasing deaths in the studied patients.¹³

The size of a clinical study also has ethical implications for clinical research studies. The Institute of Medicine monograph on Small Clinical Trials points out that the sample size of a study:

“A critical aspect of clinical trial design is determination of the sample size needed to establish the feasibility of the study (i.e., sufficient statistical power). The number of participants in a clinical trial should always be large enough to provide a sufficiently precise answer to the research question posed, but it should also be the minimum necessary to achieve this aim. A proposed study that cannot answer the question being asked because the necessary sample size cannot be attained should not be conducted on ethical grounds. That is, it is unacceptable to expose patients or research participants to harms even inconveniences if there is no prospect that useful and potentially generalizable information will result from the study.”¹⁴

6. **New therapies can only be studied and used in practice with appropriate diagnostics:** The lack of diagnostics that not only select patients with a specific disease but also select patients who will benefit from specific new therapies is long overdue in infectious diseases. Empirical therapy exposes patients to excess harm. Approving drugs based on “limited datasets” and then using the drugs widely without ability to focus therapy on patients who benefit will also result in excess harm. Currently there is no incentive for drug companies to develop diagnostics as empirical usage spurs excess sales and increased profits. Any incentives for new antibiotics should be limited to those drugs that can provide patients characteristics and diagnostic testing in real world clinical practice that allows for selection of patients who benefit from new interventions.
7. **Clinical trials transparency is needed to better inform patients, clinicians and drug developers:** Complete release of all clinical trials and preclinical information is needed. We can learn from both successes and failures of previous development programs to avoid repeating past mistakes. Clinicians should be able to access all information about drugs approved through both expedited and standard reviews in order to assess how the study design affects the reliability of the study results and to evaluate how the results apply to their particular patients.
8. **FDA labeling should accurately reflect the benefits and harms and the types of patients studied, how clinicians should select those patients and the information used as the basis for approval:** FDA does not regulate the practice of medicine but FDA does regulate what drug companies can advertise to practicing clinicians. Drug companies should not be allowed to advertise that their drugs are safe and effective in patients with disease due to resistant pathogens

¹³ Colebrook L, Kenny M. Treatment of human puerperal infections, and of experimental infections in mice, with prontosil. *Lancet* 1:1279-1286.

¹⁴ Institute of Medicine. Small Clinical Trials: Issues and Challenges.
<http://www.iom.edu/Reports/2001/Small-Clinical-Trials-Issues-and-Challenges.aspx>

unless they have performed adequate and well-controlled studies in those patients. Clinicians are often forced to make treatment decisions without evidence not because we wish to do so but because the evidence is not available. FDA approval of new antibiotics based on assumptions from test tube tests, animal models and mathematical modeling removes any incentive for drug companies to do appropriate studies in patients with resistant disease. FDA labeling informing patients and clinicians that a drug has not been studied properly does not help either patients or clinicians, and reserving a drug for those in whom the benefits outweigh the risks requires evidence about which patient experience those benefit and harms.

FDA labeling should remove the statement instructing clinicians to administer antibiotics when infections are “suspected”. Rather than focusing usage of antibiotics, this statement allows drug companies to advertise their drugs for empirical usage. What clinicians need is better diagnostics to focus usage so we can prescribe new therapies to patients who actually need them and withhold them from patients who do not need them.

FDA labeling for any drug approved under expedited pathways should include wording as already specified in 21 CFR201.57 that the drug has not been shown to be effective for other diseases not studied.

9. **Stewardship of antibiotics and tracking of use needs to accompany any program for approval of new antibiotics:** We need information on how and when antibiotics are used in both animals and human, what they are used for and how much is used. Appropriate stewardship programs are needed to use drug appropriately since CDC data shows antibiotics are still used inappropriately in both inpatient and outpatient settings.¹⁵ FDA should require 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.
10. **If the economics are broken, fix the economics but improve the science:** Drug companies complain they do not make enough money on antibiotics. However, putting patients at risk so that companies can get more return on investing in antibiotics is not an appropriate response. The standards for antibiotic approval should be improved rather than lowered, and approval should be based on actual evidence from adequate and well-controlled trials in patients with resistant infections rather than on guesses from test tube tests, animal studies and mathematical modeling. Strategies such as de-linkage of antibiotic sales from usage may provide companies with sufficient return while appropriately reserving and preserving antibiotics. Patients, clinicians and payers are not willing to pay more for antibiotics that do not have added value on patient outcomes. A recent study showed almost half of antibiotics approved since 1980 have been discontinued from the market not due to resistance but due to lack of added benefit compared to older drugs.¹⁶ This shows the bottleneck is not regulatory approval but lack of added value.

¹⁵ Centers for Disease Control and Prevention. Improving antibiotic use among hospitalized patients. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6309a4.htm?s_cid=mm6309a4_w

¹⁶ Outtersen K, Powers JH, Seoane-Vazquez E, et al. Approval and withdrawal of new antibiotics and other anti-infectives in the U.S., 1980-2009. *J Law Med Ethics*. 2013; 41: 688-96.

New treatments for infectious diseases should be based on added value on patient outcomes to make any increase cost of new drugs worthwhile. Approval of drugs that are less effective than current options increases the costs to the health care system by delaying administration of effective treatments to patients, and waste resources that could be put towards developing more effective therapies. Incentives should be provided not just for more antibiotics but other therapies such as monoclonal antibodies, bacteriophages, lysins, interventions that modify patients' immune response to disease, etc. These therapies may increase and preserve the effectiveness of antibiotics and may be less susceptible to the development of resistance.

11. **Antibiotic susceptibilities should be based on patient outcomes data, not mathematical modeling alone, without conflicts of interest:** Determining the very definition of “antibiotic resistance” is based upon the fact that patients have worse outcomes from “resistant” infections. Therefore any changes to susceptibility criteria need to be based on evidence of worse outcomes in patients by comparing patients with similar severity of illness across susceptibility criteria. FDA should obtain clinical evidence from multiple sources including other government agencies and hospitals already performing such evaluations of part of quality improvement and stewardship programs. Clinical studies show that changing susceptibility criteria based on mathematical modeling in the absence of patient outcomes data will increase “apparent resistance” but not change patient outcomes, resulting in shifting of antibiotic usage to other drugs that may be less well tested, more toxic and more expensive.¹⁷ FDA acceptance of unverified information from organization with obvious conflicts of interest including charging drug companies membership fees and including drug company employees on susceptibility committees does not serve the public health. Disclosures of conflicts of interest are insufficient to address these conflicts.

Dr. Maxwell Finland and his colleagues had to grapple with the same challenging issues we do today with antibiotic resistance. We can take the example of clinician investigators from a time when there was as great or greater unmet medical need for improved effectiveness in infectious diseases therapies as we have today. Dr Finland pointed out our obligations to patients to develop and prescribe better therapies which improving their lives as our primary goal:

“We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot consider to be as good as, or no better than, those previously shown to be good, even if they are legally certified.”¹⁸

Physicians want new therapeutic options for our patients and we depend on the FDA to ensure that new therapies are both safe and effective before they become available for general use. **We offer the National Physicians Alliance FDA Taskforce as a resource for you when specific legislative pertinent to our focus arise.** We offer this comprehensive pathway to provide a constructive way forward to address the issues of antibiotic resistance. Please visit our website <http://npalliance.org/fda-taskforce/> for further information. **Contact: npa@npalliance.org**

¹⁷ Tamma PD, Wu H, Gerber JS, et al. Outcomes of children with enterobacteriaceae bacteremia with reduced susceptibility to ceftriaxone: do the revised breakpoints translate to improved patient outcomes? *Pediatr Infect Dis J.* 2013; 32: 965-9.

¹⁸ Finland. *The New Antibiotic Era.* Ibid.

Mr. PITTS. The chair thanks the gentleman, thanks to all of the presenters for their testimony. We will begin questioning, and I will recognize myself 5 minutes for that purpose.

Dr. Thomas, you mentioned in your testimony that a multi-pronged strategy is needed that includes both stewardship and antibiotic innovation incentives. If you think about the path to cures as being three phases, discovery, development, and delivery, do you believe that we need incentives in all three phases to have an effective incentive strategy?

Dr. THOMAS. Thank you for the question, Mr. Chairman. Yes, I do, because I think often the players or the stakeholders who are conducting that research at those different stages are different. And what incentivizes academic or biotech startup might be different from what incentivizes a multi-national corporation like Johnson & Johnson, might be different from organizations that are involved in healthcare delivery.

So one incentive is not going to—as we have seen, frankly, since we have had incentives introduced, we still have an empty pipeline of incentive is not going to solve this problem. It may well be that large grants or so-called prizes would attract academic researchers and startups. A very different incentive needs to encourage venture capitalism to go and back startup companies with a much higher level of risk. And for a company like Johnson & Johnson, we look at a portfolio of investment opportunities, need to understand which of those is both most important medically and to human impact but also which is most viably able to be conducted, and finally, which enables us to balance our risk and our return.

Mr. PITTS. All right. Let's look at each phase. First of all, what types of discovery or R&D incentives do you believe would encourage companies to develop new and novel antibiotics?

Dr. THOMAS. I think we need to look at the discovery incentives not just for antibiotics, but also for antibiotics in adjacent technologies. Here it is absolutely critical that we focus on point of care diagnostics, biomarkers, new capabilities of being able to diagnose, and also to advance clinical research in this field. For this sort of endeavor, this is where large grants, funding, prizes would make the most sense, tax credits, because they will encourage broad-based academic research as well as broad-based technology company research that is often shorter in duration and is able to be managed in a different way.

As we think about the incentives for development, development in the pharmaceutical process is the most expensive piece. We recently brought a new product called SIRTURO, which is indicated for multi-drug resistant tuberculosis. With 13 years of R&D and early development, we had proof of concept that was compelling, and through the leadership of agencies like the FDA and the European Medicines Agency and the World Health Organization had a conditional approval on early phase 2 results.

We still have more than 15 years of clinical trials evidence generation showing safety and effectiveness in children, showing safety and effectiveness versus other drugs in real-world use in the field and proving out the hope that we saw in the phase 2 studies. Having spent well over \$200 million to date with no commercial return foreseeable for this product, and nor necessarily should there be,

we are now looking at a further 15 years of investment and many hundreds of millions more.

Tax credits are not enough to spur that sort of effort on a broad base across the industry. And I think for drug developers, we need to make sure that there is a very definite incentive for 2 things: One is, how can they justify maintaining the infrastructure in-house, the competency to understand what is a good asset and how to develop it, whether or not they have one of those assets themselves, and that is critical because lightning doesn't always strike in New Brunswick where our headquarters is. Lightning for innovation strikes all over the world, and we have to be able to understand when it hits, what that technology is worth.

The second thing is we have to be able to encourage companies to actually invest in the long-range risks associated with the large dollars for drug development, and the way to do this is not to hope that they have a certain expertise in one drug. The way to do this is to say we want as many shots on goal as possible by as many large players as possible so that we can see a sustainable and continual pipeline to evolve, and for this activity, this is where the concept of tradeable vouchers or exclusivity additions comes in because what you are not doing is incentivizing people to go down a loss-making path. You are saying we understand that you have to go down a profit-making path in some of your business and we will trade off against these activities.

Finally in the area of the delivery side, this is really problematic. By the nature of the sort of research we conduct to get products approved for antimicrobial resistance, we are looking at non-inferiority studies. From a payment perspective, that usually means in most countries in the world that you get price parity. Despite the fact that your price parity with what is on the market was for costs that were achieved many, many years ago and may not no longer be relevant, and that is why the ENPVs you heard about before are usually negative, so the notion of a price premium or reimbursement incentives are certainly attractive in that area.

I would posit, however, and use as an example our own experience in multi-drug resistant tuberculosis, when you are talking about highly resistant bugs, highly transmissible bugs, you want the drugs used only in the people who need them, only for the bugs that need them, and by people who understand how to treat and use those products in an appropriate way. That is not really a very strong economic model for understanding how your product, even with a reimbursement incentive, is actually going to be successful. In fact, it is probably a negative commercial model in most areas.

Mr. PITTS. The chair thanks the gentleman. Now recognize the ranking member of the full committee, Mr. Waxman 5 minutes for questions.

Mr. WAXMAN. Thank you, Mr. Chairman. Last Congress we passed the GAIN Act to provide new incentives for the development of important antibiotics, and under that Act, antimicrobials and antifungals intended to treat serious or life-threatening infections can be designated as qualified infectious disease products, or QIDPs. We receive a priority review, that is helpful. If they are approved, they get an additional 5 years of protection from generic competition. That is a strong incentive. FDA has already granted

QIDP designations to almost three dozen different antibiotics, so companies clearly are interested in this program.

A major impetus for the GAIN Act and for today's hearing is a need for new antibiotics to treat the growing number of life-threatening pathogens that are resistant to all or virtually all antibiotics. However, in your testimony, Mr. Outtersen, you note that there is nothing in the law that requires QIDP designations be only given to antibiotics intended to treat resistant pathogens. As a result, you assert that essentially every antibiotic ever approved by the FDA would qualify as a QIDP.

Some of us, during the FDA Safety and Innovation Act negotiations tried to limit it, that designation to those antibiotics that would fulfill an unmet medical need. However, we were unsuccessful.

Can you tell us how many, or what percentage of the QIDPs are for antimicrobials intended to treat highly resistant pathogens, and are their public health impacts we should be concerned about as a result of the lost failure to prioritize drugs for resistant pathogens, and how could we better incentivize the development of the drugs we most need?

Mr. OUTTERSON. Thank you for your question. The definition of Qualified Infectious Disease Product is built on a previous definition of a qualified pathogen. And that list does not require any of the pathogens to be resistant. It includes most species known to cause any disease in humans. So, because it is difficult sometimes in these trials to run them where it historically hasn't been done, to run them on people only with resistant pathogens. So you are correct in saying that the qualified infectious disease product will apply probably to every antibiotic that will be approved in this next decade or two, which is a question about whether the incentives are properly targeted.

On the incentives themselves, when I talk to companies privately, large companies as well as small, they all say that the incentives in GAIN were in the correct direction, but there is a quiet walk when what we should be doing is running, that the economic value to them, of these incentives is really very small. They will take them and register, but it is 1 percent of the way to where we need to go to change the economic model. It is a small change, and we should be doing something else.

Mr. WAXMAN. So tell us how to change this economic model. You talked about that in your presentation. How much do we have to keep giving in order to give the right incentives? And we ought to know how much this is going to cost the American people and whether it going to be successful.

Mr. OUTTERSON. To use the three stages that the chairman mentioned. On the discover side, our NIH budgets need to be dramatically increased. We need basic science.

Mr. WAXMAN. Yes.

Mr. OUTTERSON. It was the PCAST report yesterday.

Mr. WAXMAN. And we have been cutting back on that.

Mr. OUTTERSON. It has been flatlined or slightly negative for the past half decade to the best of my knowledge on antibacterial research in the NIH. The second piece on developing, I think tax credits are a piece of that. I think BARDA is a huge piece of that.

Some of the best gram negative molecules in development now have a lot of money in them from BARDA.

Mr. WAXMAN. We have given tax credits. We want to shorten the time at FDA to get this review done as quickly as possible to get the drug out there. We want to help companies decide its in their economic interest to do this. What do we need to do?

Mr. OUTTERSON. The last piece is when it is delivered to the public, and I would agree with Dr. Thomas that there is a reimbursement problem, but I don't particularly like the solution. At the Chatham House work, we are looking at the linkage, which is just saying the companies will be generously rewarded but on something that has nothing to do with volume.

I think everyone here would agree we don't want to put \$100,000 price on a drug and give a company a reason to over-promote it. And so there needs to be significant price-type or BARDA grant-type rewards for companies, possibly based on an insurance model, which is what GlaxoSmithKline has suggested, to give significant rewards to the companies after they have delivered a drug to the market.

Mr. WAXMAN. Well, I would suggest that we may be better off putting much more money into biomedical research at NIH and throughout universities around the country because they don't have the profit motive and what they do helps the companies because that science is then used for these products.

But if the companies are having too difficult a time without enough incentives to make a lot of money, well, let's make sure that we get the work being done at the public expense because otherwise, we are going to pay a lot of money and we may not see the results that we need. You agree?

Mr. OUTTERSON. I completely agree. If we do not have enough basic science, the pipeline that flows to venture capital and then to the larger companies runs dry.

Mr. WAXMAN. Thank you. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman. Now recognizes the gentleman from Georgia, Dr. Gingrey, 5 minutes for questions.

Mr. GINGREY. That was a very interesting line of questioning from the distinguished ranking member of the committee, and Mr. Outtersen, your response was not unexpected. But there is something to say for the profit motive as well. You give more and more and more money, taxpayer money to NIH or wherever basic research is being done, and you don't have this profit motive that you are talking about and the wrong incentive, misguided incentive, but if you don't have somebody with the profit motive, a company, a pharmaceutical company, big or small, you can sit there doing basic research for 100 years, and maybe some brilliant scientist, many of them could be very comfortable in their labs and enjoy that to a fare thee well. I think I would. But you never really get to where you need to be in regard to drugs that treat patients that cure these terrible bugs that are killing them.

So I am going to shift my question to Dr. Murray as President of the American Society of Infectious Diseases to basically ask you the same question, Dr. Murray. The business model for antibiotics, diagnostics, and vaccines is broken. I think we will all sort of agree with that. That is what we have learned this morning in this rath-

er long two-panel hearing, but it has been good, but it a broken model. What specific steps, Dr. Murray, do you think Congress should take to address this crisis? Do you agree with Mr. Outtersen? Do you agree with Mr. Waxman? What do you think?

Dr. MURRAY. Well, I could take Dr. Woodcock's approach and say I am not an economist, but I will try to address it. I think basic research input is an important component. I am biased. I do basic research in my laboratory, but I agree also there has to be a reward at the end, and the suggestions I have heard from others, and they are not my own, include taking certain drugs out of the DRG so that they are not part of the total hospital budget, which means everybody is trying to attack on antibiotics as one place to decrease cost.

That or the other model is buying up a number of doses at the end of a product, so they are bought up. I think perhaps that is what you meant by the insurance model. So you hope you never have to use them. They would be there but it guarantees the industry some return on their dollar. So those are the two—in addition to, of course, in the development phase, the tax credits, but the end product, I have heard it for many years, there has to be—they answer to taxpayers. I mean, I am sorry, they answer to stockholders. They don't answer to taxpayers, and so the companies cannot just be motivated by the greater good.

Mr. GINGREY. It is kind of like when we talk on this committee about energy and the energy policy that we should have, and all of the above policy is the one that I like the best, and I think really in regard to this, too, because I mean, as Mr. Waxman said, you are talking about tax credits, you are talking about what you just said, Dr. Murray, of buying back a certain volume that is not used because you don't want to just incentivize based on sales, and more grants to the NIH. All of the above, really. I think that is the way we ought to look at it.

I have got a little less than a minute left, and I want to shift to Dr. Hillan. You mention in your testimony that half of the investment cost necessary to support your drug, SIRTURO; is that correct?

Dr. HILLAN. Plazomicin.

Mr. GINGREY. Yes.

Dr. HILLAN. Plazomicin.

Mr. GINGREY. Will be required. Half of the investment cost necessary to support it, that drug, will be required after the point of the United States regulatory approval. What drives the cost of these investments post-FDA approval? What is the big cost driver?

Dr. HILLAN. Sure. So I'm not sure if it was me, but I am certainly happy to answer that. There is an ongoing process after a drug is approved so that you actually understand the safety and effectiveness of the use of the product in the real world. There are additional pediatric studies which are very important. How do you—we believe our drug will be dosed in small—

Mr. GINGREY. Well, let me shift. Just I have got no time left, but Mr. Chairman, if you will bear with me because I really—and thank you, Dr. Hillan, and I really want to address this question to Dr. Thomas, so if you could quickly respond. Mr. Chairman, if you will bear with me.

Dr. THOMAS. Sure. And thank you for the question. Getting regulatory approval is really the start of a long process of paying for regulatory approval all over the world in a sequential basis for maybe over 100 countries. There is completion of commitments and unknown questions about safety. There is, as I said, 15 years of pediatric research, so with antibiotics that sometimes have toxicity starting at a 15-year-old and proving that, then a 10, a 12 and a 2 and so on. There is drug safety reporting requirements that when you have a commercial product, these are all costs of doing business, but when you have a product where the aim is not to use it unless you absolutely have to, it is just a tremendous overhead that you can't really discount any other way. It is the right thing to do and it is the way that we do it today, but it has caused a significant overhead.

Mr. GINGREY. And I thank both of you for your response to that question. Thank you very much. Mr. Chairman, I yield back.

Mr. PITTS. The chair thanks the gentleman. Now recognize the ranking member, Mr. Pallone, 5 minutes for questions.

Mr. WAXMAN. Mr. Pallone, would you yield to me 1 minute?

Mr. PALLONE. Yes, surely.

Mr. WAXMAN. I thank you for yielding. I don't think Mr. Outterson or I thought or would want anybody to believe that we thought you don't need a profit and you don't need the private enterprise, and I argue we need to put much more in the research side of it, but we do need a business model that says to a company if you do this work, you are going to make a profit. You have got to make a profit; otherwise, they are not going to do it, and to make a profit, we don't want to just sell more antibiotics. We want to make sure they get a profit so that we want to guarantee we could take their investment, guarantee a certain percentage, and say that is how much the government will pay you. That is one idea.

I don't know if it is the only idea, but it is obviously a different kind of incentive that we have in other areas. So I thought Dr. Gingrey was right when he said all of the above. We got to do whatever we can, and I believe a lot more in public investment because the pharmaceutical engineers are not going to make a lot of investment in this area when their research investments can result in a blockbuster drug, but this is a social need, and they have got to do what we need them to do, but they are not going to do it without making a profit. So thank you for giving me that chance—

Mr. PALLONE. Sure.

Mr. WAXMAN [continuing]. To add that additional thought.

Mr. PALLONE. Thank you. Thank you, Mr. Waxman. I wanted to ask Dr. Murray and Mr. Coukell. I know that IDSA and Pew have worked very closely with the sponsors of the ADAPT Act, and they are strong supporters of it, I would like to get your views on a few aspects of this legislation. First, I am concerned that as currently drafted, FDA may not have adequate authority to require that an ADAPT antibiotic be labeled in a way that calls attention to the fact that it is intended only for special populations. I don't think putting such a statement in the prescribing information is adequate, and I am concerned that if such drugs are used more widely

than appropriate, that we could end up both harming patients and losing the effectiveness of the drug to antibiotic resistance.

So what are your views about the adequacy of the current labeling language in the bill? Do you agree that it is critical that there be a strong and prominent labeling statement to signal to providers that they should use the drug only in circumscribed situations? And I guess we could start with Dr. Murray and then go to Mr. Coukell.

Dr. MURRAY. Well, I think it is important to have some label there. In a practical sense, what we do in the hospital to prevent overuse of certain drugs, is we already have stewardship in place in our county hospital, certain antibiotics, be they for cost, toxicity, or whatever reason, have to go through an infectious disease approval. That is already in place.

Another thing we sometimes do is we don't report on the chart of the report that goes to the patient's chart, the susceptibility to certain antibiotics. If you are in infectious diseases or smart enough to know what is going on, you know to call the laboratory and ask for that susceptibility so the doctors that are actually caring for these multi-drug resistant infections know to do that. Usually it is done because there are certain combinations that even though the antibiotic is susceptible, you wouldn't use it alone.

The third way with the electronic records that might be possible that I was thinking about last night is that when this drug is written for, there is an automatic pop-up. We have all sorts of automatic pop-ups now, and an automatic pop-up could say this has been approved in a limited population. I think in many ways—there may not be as much of a problem as people are imagining. These infections occur in certain settings, usually in intensive care units, they are complicated. Infectious disease physicians are usually involved in these patients.

For someone to try to use this drug or a special drug that has been approved in this fashion for an ordinary *E. coli* infection, there is not a need to do that. The companies are not going to be able to be out there marketing for that purpose. FDA will be overseeing what goes into the promotional materials, so I am not sure the ordinary physician—certainly the one out in the community is never going to even think about using it. These are IV drugs by and large. So I think there is some inherent safeguard.

Mr. PALLONE. OK. Mr. Coukell, do you want to respond?

Mr. COUKELL. Thank you for that question, and let me build on what Dr. Murray has said that we have worked very closely on this bill, and we think this is the one place that we really would like to see some improvements. And as I said in my testimony, it is so important that we convey to the provider community the special status and nature of these drugs, and let's recognize that the labeling is not just effective when somebody goes and looks at the fine print, but the labeling is the start of the process of how information about the drug is promulgated into the community through the medical record, through the marketing materials, and so on.

We have called for a logo to distinguish these drugs. There may be other ways, as long as it is communicated very clearly that these drugs are different, and that is part of what Congress is doing, too, by creating this designation.

Mr. PALLONE. All right. Thanks a lot.

Mr. COUKELL. One more point.

Mr. PALLONE. Sure.

Mr. COUKELL. The other thing that is in the bill that we think is important is the need to monitor how the drugs are used when they are out there so that we have some feedback and we know that the indication is working as intended.

Mr. PALLONE. All right. Thanks.

Mr. PITTS. The chair thanks the gentleman. Now recognize the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. This has been a tremendous hearing, and I am glad I stayed. I think you see the importance that this subcommittee puts on these issues. You-all on the panel, turn around and just turn around and see Dr. Woodcock is right there. Wave to her. And I want to make sure everyone knows she stayed, and I applaud her for doing that. So this is kind of a silly question but it is really, would you consider you-all Facebook friends with the FDA or in a relationship? Anyone want to answer? Are you friends or you not even—had a friend notification out there and they didn't even accept.

Dr. HILLAN. Maybe I could speak to that because obviously it is important that the pharmaceutical industry is regulated by the FDA both in terms of drugs and also in diagnostics, so I don't know we would call ourselves friends, but we are certainly, I would say, professional colleagues that work together.

Mr. SHIMKUS. Yes.

Dr. HILLAN. We have had—

Mr. SHIMKUS. Well, the point is this only gets solved with the people in this room. It gets solved with you at the panel, it gets solved with the FDA, and it gets solved with the public policy folks here, and so we have to have that communication. We have to be in a relationship, and that is what I am taking from this because a lot of ideas. And I couldn't believe it. I was also looking at stuff. The Pentagon was—the groundbreaking was September 11, 1941. The dedication was January 15, 1943. So in this issue, these are timelines. Thirteen years to get to one point; 15 years still down the road. We have got to switch those timelines, and there are people who are willing to accept some risk. And besides, we have heard numerous testimonies on this 21st Century Cures debate and how do we do that effectively.

The question I have by listening to the testimony is government is historically bureaucratic and not flexible and we are very rigid, but in this process, you are the experts, you are the doctors, you are the scientists and stuff, how do we write into legislation the flexibility to incentivize while protecting public health? And can we do that? And then that is what we are going to move on legislatively, but am I right in that analysis and do you think we can get there? And I only have 2 minutes left, so why don't we just go down and let everybody weigh into that if you would like.

Dr. HILLAN. So, it obviously has to be done appropriately, but much of this is about building trust. We are working towards the same goal of bringing forward new antibiotics to patients. We have interacted with the FDA, and I can tell you the FDA has really facilitated the development of plazomicin. They came up with really

good ideas, totally appropriate ideas actually the company hadn't thought about. BARDA has been incredibly supportive and brings technical expertise to the table as well, so we can work effectively together and we are all working towards the same goal. So I would hope that we can continue to do that in the future, and it does need to be flexible. We need to trust people to use good judgment so that we can all look after patients.

Dr. MURRAY. I think one of the benefits of the PCAST report and the new structure that there will be, will include external stakeholders, be included, and I certainly agree with that, and external to the government, and I think their input is needed, and that may help keep driving the process.

Dr. THOMAS. I think it is absolutely possible to write legislation that is flexible and also impactful. I also like to say that we want to be part of that discussion. We believe it does take a different way of thinking, and we have to be willing to test things that may not necessarily seem so palatable. I just want to finish with saying it is no accident that breast cancer is almost a curable disease today. It is no accident that many bone marrow tumors are curable of chronic diseases today. It is no accident that people can live with diabetes. It is because the incentives for everyone are to innovate in those areas. So if you don't want this to be an accident, we need to design the right incentives.

Mr. OUTTERSON. We need billion-dollar incentives hanging out there for companies, big incentives, not little. It is hard to write what you will need in 10 years, though, into legislation when we don't know what the diseases will exactly look like.

BARDA is a wonderful model. One of the most encouraging things I took from yesterday from PCAST was significant additional funding being proposed for BARDA because they can contract, given flexibility, based on what is happening now. The only other person who is not in this room are the pairs, so I would like to see Blue Cross and Blue Shield, insurance companies, Medicare, this is a pay-for-performance, pay-for-value issue. Let's pay more to keep it valuable.

Mr. COUKELL. There is no single solution here. There are things that Congress can do now and do quickly and should do. There are places where there needs to be continued collaboration. I think we have seen that with FDA and companies and stakeholders, and PCAST called for more of it. There are more important basic science questions that are not industry questions, are academic questions, but questions that will be solved when we have them effectively working together not just with more money but with smarter science, so there is no one-size solution here, but there are things we can do now quickly to move this along.

Dr. POWERS. I think we talked a lot today about the history of resistance and how we got to this point, and actually there is already tremendous flexibility built into FDA's regulations already. When FDA came out with the regulations in 1970 on what an adequate study was, the pharmaceutical companies immediately sued. And when it went to the courts, the courts actually found that the regulations allowed tremendous flexibility for FDA and how the studies can be designed.

I think what we were trying to say this morning, and Dr. Outterson brought this point up several times, is that these studies should actually show added value for patients, that really what we are trying to say is if we are going to give perks for companies, it ought to be perks for performance, not perks for potential, that the studies should actually show, as Dr. Hillan pointed out and how his study is designed, that the drugs actually save lives in the people that we need to use them in.

Mr. SHIMKUS. Thank you, Mr.—and thank you—a minute ago—I want to end on this or not—

Dr. MURRAY. Could I add one additional comment? Would that be—

Mr. PITTS. Yes, you may.

Dr. MURRAY. Thank you very much. I want to get back to the point of BARDA being a good model, and that is a wonderful model. NIAID could serve the parallel role of helping to develop drugs for—thanks. That BARDA is not directly applicable to, and they already do have an antibiotic resistance leadership group whose path is to help design trials for antibiotic resistance organisms, but I think the BARDA model is a good one. It does not necessarily have to be BARDA that would carry it out.

Mr. SHIMKUS. And I appreciate that. The last comment. I just will say that these companies, I really—and Mr. Waxman just raises my ire every now and then, too. Because it is not perks. These guys raise capital, assume risk to try to save lives, employ thousands of people, and pay taxes, so they are the ones who are raising the capital and assuming a risk. So, if we go down the route of trying to beat up corporate America in this process, we are not going to be friends. We will be defriended and we can't. We got to be all in this together, and with that, I yield back my time.

Mr. PITTS. The chair thanks the gentleman. The gentleman from Georgia wanted to make a point of clarification.

Mr. GINGREY. Mr. Chairman, thank you, and I don't disagree. In fact, I do agree with the comments from my colleague, the gentleman from Illinois, Mr. Shimkus, in what he just said. But I also want to, Dr. Powers, let you know that the concerns that you express in your testimony are not lost on me at all, and I don't think other members of the committee, and also, the ranking member of this health subcommittee, Mr. Pallone, and his concerns about labeling, and that is not lost on me either. And staff is working almost as we speak on that issue, Frank, to try to get that right and to lay those concerns.

Mr. Chairman, this has been fabulous. You-all are great, both panels. Dr. Woodcock, we are so grateful to you, and I, like the other members that stayed over, and didn't get an early flight back to Atlanta, I am grateful that I stayed because this has been most, most informative, and we are deeply appreciative. Thank you very much, and I yield back.

Mr. PITTS. The chair thanks the gentleman, and I would like to say it is good to hear of the collaboration that is occurring between the public and private sectors, and that is so important. And I might mention, Dr. Woodcock has been before this committee many times, and she is one administrator that always stays through the

whole hearing, and you should be commended for that, and we thank you for your responsiveness.

Now, other members will have questions, and we will have follow-up questions. We will send those to you. We ask that you please respond promptly. I remind members that they have 10 business days to submit questions for the record. That means they should submit their questions by the close of business on Friday, October 3rd. Very good hearing, exciting, very informative. Thank you very much for your participation. Without objection, this subcommittee is adjourned.

[Whereupon, at 11:35 a.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Today's hearing is an important opportunity to review the growing threat of antibiotic resistant infection—a global health crisis. To quote the CDC: “The loss of effective antibiotic treatments will not only cripple the ability to fight routine infectious diseases but will also undermine treatment of infectious complications in patients with other diseases.” This public health crisis is an important topic for us to explore as we continue our work on the bipartisan 21st Century Cures initiative and work to bring more effective treatments to patients more quickly.

Make no mistake: we are losing effective antibiotic treatments because the pace of new and novel drug development has not kept up with these organisms' ability to build resistance to the treatments available today.

Passage of the GAIN Act in the 112th Congress as part of our efforts to reauthorize the FDA User Fee legislation was an important step in incentivizing antibiotic drug development, but much work remains to be done.

Committee members Congressmen Gingrey and Green have put forward one such idea—the Adapt Act—and I want to commend them for their continued leadership in addressing these important issues.

The President's own Council on Science and Technology (or PCAST) just yesterday released a call to action on the issue of antibiotic resistance. This plan included a number of initiatives it intends to undertake over the next 5 years, including incentives for the development new drugs and diagnostic tests. We will continue to engage on this issue as part of our bipartisan 21st Century Cures agenda.

Today's witnesses will provide important perspectives on the types of incentives to help drive the types of new drug development necessary to meet this growing threat and whether such incentives might also address other areas of unmet need.

*For the Record by Rep.
Burgess
for 9/19/14 hearing on
antibiotic resistance*

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Andrew J. Moyer And Penicillin: Saving Lives on a Grand Scale

By BELLE KIM AND JENNIFER PARK

Posted August 25, 2010

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Soon after the discovery of penicillin, the number of wounded soldiers returning from WWII dying from infection mandated the antibiotic's mass production.

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Photo: [archive photo](#)

Star City, Indiana native and Wabash College graduate Andrew J. Moyer developed a method for the mass production of penicillin.

Discovered by Scottish bacteriologist Alexander Fleming in 1928, [penicillin](#) was found to be effective in treating serious bacterial diseases, from syphilis to staphylococcus infections.

Originally, penicillin was produced on a small scale. Within a decade, the number of wounded soldiers returning from World War II dying from infection mandated the mass production of penicillin.

Although a number of European scientists tackled the challenge, Indiana native and Wabash college graduate [Andrew J. Moyer](#) found the key to [mass-producing](#) the antibiotic while working as the director of the USDA's Northern Research Laboratory.

An expert on the nutrition of molds, Moyer found he was able to increase yields tenfold when penicillin mold was cultured in a broth of corn steep liquor and lactose.

The process known as industrial fermentation was the first use of corn steep liquor to grow microorganisms. Moyer also discovered that the production rate could be sped up when the improved medium underwent continuous shaking.

Moyer's innovation facilitated the mass production of penicillin, saving the lives of an estimated 12 to 15 per cent of Allied soldiers wounded in World War II. Mass production also led to greater supply of penicillin, subsequently lowering its cost from \$20 to 55 cents a dose in three years.

He was granted four patents for his work on penicillin, and continued to work for the Northern Research Laboratory until he retired in 1957. He died two years later on February 17, 1959, after a month-long illness.

In 1987, Moyer was posthumously invited into the National Inventors Hall of Fame; the first government researcher to be inducted.

Moyer's method of creating fermentation with corn steep liquor still serves as a model for the development of many other antibiotics.

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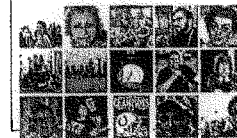
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TO: The Honorable Joe Pitts

The Honorable Frank Pallone

Re: 21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development

Dear Chairman Pitts and Ranking Member Pallone:

THE FLAG & GENERAL OFFICERS' NETWORK, Inc., an official 501.c.19 War Veterans Organization representing three quarters of all living U. S. Armed Forces Flag & General Officers (Guard, Reserve and Retired), now writes to thank you for your leadership in addressing the threat of antibiotic resistant bacteria by holding this hearing, entitled "Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development".

As the Administration recognized today in their report and announcement of executive action, the threat of antibiotic resistance is real and growing. It is clear that we need to act now. Drug resistant bacteria are infecting our military, veterans and fellow citizens at an alarming rate and, in far too many cases, we do not have the drugs to treat them. The Centers for Disease Control and Prevention estimates that 2,000,000 infections with antibiotic-resistant bacteria occur each year in the United States and 23,000 Americans die as a result.

The military is at particular threat from these infections. It is unconscionable that American military men and women are being saved from their combat wounds on the battlefield only to become the victims of untreatable superbugs. More than a third of wounded warriors injured in Iraq and Afghanistan developed a bacterial or fungal infection. And, according to Pentagon data, about one in 10 military recruits gets a skin infection, which are often caused by resistant bacteria.

We strongly support H.R. 3742, the Antibiotic Development to Advance Patient Treatment Act of 2013 (ADAPT). The ADAPT Act will be critical to getting new antibiotics to patients with severe infections. It will direct the Food and Drug Administration (FDA) to create a regulatory pathway for new antibiotics that treat serious and life threatening infections and are intended to be used in limited populations of people with few or no other treatment options. Because the drugs may be studied in smaller populations, clinical trials may be more feasible and development time may be shortened, potentially allowing patients faster access to these important treatments.

Too many of our shipmates and soldiers have died already because of untreatable superbugs. Without swift action more will meet the same fate.

We salute your efforts and leadership in addressing this important issue. We urge you to take action and to expedite the passage of H.R. 3742.

Please know you have our continued thanks for your efforts on behalf of America's veterans and their families.

Rear Admiral [Ret.] James J. Carey, National Chairman
THE FLAG & GENERAL OFFICERS' NETWORK
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Statement for the record from Cubist Pharmaceuticals

**Submitted to the
U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health**

**Hearing on
21st Century Cures: "Examining Ways to Combat Antibiotic Resistance and Foster New
Drug Development"
September 19, 2014**

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, Cubist Pharmaceuticals (Cubist) thanks you for convening today's hearing to address new ways to combat antibiotic resistance and foster new drug development. Also, we would like to thank Chairman Upton and Representative DeGette for the Committee's 21st Century Cures effort. In the last Congress, this Committee's leadership and the efforts of Dr. Gingrey and Representative Green, secured passage of the Generating Antibiotic Incentives Now (GAIN) Act—the single most important policy change to date for antibiotic innovation. While a number of approaches will be necessary to address the broken market for antibiotics, the most meaningful next step Congress can and should take is to ensure enhanced reimbursement for new drugs to treat patients with serious and life-threatening infections.

Cubist is a global biopharmaceutical company headquartered in Lexington, Massachusetts. Our company is focused on the research, development and commercialization of pharmaceutical products for use in the acute care environment. Cubist has a growing commitment to global public health through its leadership in the discovery, development and commercialization of novel antibiotics to treat serious and life-threatening infections caused by a broad range of increasingly drug-resistant bacteria. The company hopes to deliver at least four new antibiotics in support of the Infectious Diseases Society of America (IDSA) goal of 10 new antibiotics by 2020. Cubist also expects to invest approximately \$400M USD in 2014 on antibacterial R&D

and approximately 75 percent of its employee base is focused on the research, development, commercialization and support of antibiotics. Our deep experience in this therapeutic area makes us well positioned to comment on the types of incentives that could help companies deliver desperately-needed antibiotics to patients, and we welcome the opportunity to do so.

Opportunity to Build on Success of the GAIN Act to Enhance Antibiotic Innovation

Today's hearing builds on the Subcommittee's bipartisan contributions to what is arguably the most important federal policy adopted in recent history to incentivize antimicrobial innovation. In 2012, Congress took action to address the lack of innovation for antibiotics through enactment of the GAIN Act as part of the Food Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144. The GAIN Act established a new Qualified Infectious Disease Product (QIDP) designation for antibiotics that treat serious or life-threatening infections, fast tracking their development and regulatory review and allowing manufacturers to apply for extended market exclusivity upon approval. The Food and Drug Administration (FDA) recently approved the first drugs designated as QIDPs under the GAIN Act—including Cubist's SIVEXTRO® (tedizolid phosphate)—and others may reach patients later this year, if approved by the agency.

The Subcommittee should be aware that, in just over two years, the GAIN Act has proven to be an important foundation for renewed investment, research and development in the field of antibiotics. By relying upon its experience with the highly regarded Orphan Drug Act, Congress successfully crafted a set of proven incentives for QIDPs, a special designation for new antibiotics that address the most serious and life-threatening infections faced by patients. The FDA has already approved three new antibiotics as QIDPs, and as of late July, 35 drugs under development have received the designation, according to the agency.¹

Although the GAIN Act was a critical first step in revitalizing the antibiotic pipeline, it is widely recognized that more needs to be done. As supporters and beneficiaries of this important law, we

¹ Edward M. Cox, MD, Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research, FDA. "FDA's multi-pronged approach helps meet the challenge of bringing new and innovative antibiotics to patients who need them." July 28, 2014. <http://blogs.fda.gov/fdavoices/index.php/2014/07/fdas-multi-pronged-approach-helps-meet-the-challenge-of-bringing-new-and-innovative-antibiotics-to-patients-who-need-them/> (Accessed on 9/9/2014).

are grateful for the opportunity to contribute to the discussion and provide suggestions on other types of incentives that would build on the success of the GAIN Act to further encourage meaningful development in the antibiotic space.

Enhanced Reimbursement for QIDPs Would Expand Innovation

First and foremost, it is important to ensure that once manufacturers develop novel antibiotics, reimbursement barriers are not an obstacle to patients and providers having access to these important new treatments. Thus, enhanced reimbursement must be the next step to build on the incentives for development embodied in the GAIN Act.

We ask that you consider the following specific actions:

1. Increase reimbursement for antibiotics targeting serious or life-threatening infections by creating a Medicare DRG carve-out or new reimbursement mechanism for antibiotics designated as a QIDP under the GAIN Act.

Currently, unfavorable reimbursement by Medicare and other providers is a barrier to the development of innovative antibiotics.² A mechanism to offset the cost of novel antibiotics that provides an incentive for companies to develop them would be a vital next step in an effort to revive the broken marketplace. Reimbursement should better reflect the life-saving value of antibiotics and should remove the cost barrier to patients getting proper treatment for their specific condition.

Patients with the most serious infections are often treated in the hospital inpatient setting. Existing inpatient payment strategies available through the Centers for Medicare & Medicaid Services (CMS) to allow for adoption of new technology have proven unsuccessful for novel antibiotics. Due to the nature of antibiotic clinical trials that most developers must use for FDA

² Engelberg Center for Health Care Reform at Brookings, *Incentives for Change: Addressing the Challenges in Antibacterial Drug Development*, February 27, 2013.
<http://www.brookings.edu/~media/events/2013/2/27%20bcadd%20meeting/meeting%20summary%2020130925%20final.pdf> (Accessed 9/9/2014.)

approval, (data are typically collected in non-inferiority studies for ethical and other reasons)³ the New Technology Add on Payment (NTAP) program does not apply to most antibiotics. In addition, the short duration of the NTAP program is not well suited to appropriate antibiotic stewardship, and the coding limitations and partial reimbursement provided by NTAP do not effectively provide an enhanced payment system for drugs that reflects the true life-saving value of these medicines.

A carve-out from Medicare's Diagnostic Related Group (DRG) inpatient payment system or new reimbursement mechanism in the hospital (inpatient) setting, specifically for antibiotics designated as QIDPs under the GAIN Act, would alleviate some of the cost pressures that discourage the use of new treatments for serious or life-threatening infections. Removing QIDP reimbursement from the DRG bundle via an enhanced reimbursement mechanism would ensure providers are not adversely financially impacted when using an important new antibiotic and could employ appropriate stewardship without cost concerns. The cost to the government to apply this type of mechanism has been estimated to be very low, but the value as an incentive to antibiotic development would be extraordinarily significant. Reimbursement should be structured in such a way that it removes the financial barrier, allowing physicians to make their decisions based on clinical factors, including the needs of their specific patient and antibiotic stewardship.

Applying reimbursement incentives to antibiotics designated by FDA as QIDPs would ensure that coverage and payment is determined in a consistent manner. QIDP is a narrowly-tailored, carefully-crafted definition of the most critically-needed antibiotics—those targeting serious or life-threatening infections. The QIDP designation is limited in scope and provides the certainty companies must have in order to make business and investment decisions. An enhanced reimbursement should apply for the life cycle of a product and provide a consistent and well-defined pathway for innovators. Improved reimbursement will incentivize pharmaceutical companies to continue in, and even reenter, the antibiotic space to develop the new drugs we so desperately need to combat antibiotic resistant pathogens.⁴

³ S. Nambiar et al. *Antibacterial Drug Development: Challenges, Recent Developments, and Future Considerations*. *Clinical pharmacology & Therapeutics* (96): August 2014.

<http://www.nature.com/clpt/journal/v96/n2/pdf/clpt20141116a.pdf> (Accessed 9/15/2014.)

⁴ Matthew Herper, *How to Avert an Antibiotic Apocalypse*, *Forbes*. January 27, 2014.

2. Establish higher or multiple Medicare DRG rates for resistant infections

Patients in the acute-care setting with serious or life-threatening antibiotic-resistant infections often suffer from other (comorbid) conditions. The cost of managing these patients can be higher due to the serious infection, but current DRG payment rates may not cover the cost of treating these patients using novel new antibiotics. We urge Congress to establish higher or multiple Medicare DRG rates for resistant infections and/or support the use of major complication or comorbidity (MCC) classifications for such patients to alleviate the cost pressures hospitals face. Without higher DRG rates or MCC classifications, hospitals must utilize existing DRG codes that may or may not account for the higher costs associated with treating patients with resistant infections. Currently, novel treatments may increase treatment costs above the DRG reimbursement amount provided to the hospital, discouraging the use of new antibiotics. Reimbursement should not be a barrier to using the new antibiotics, when appropriate.

Modernizing Specific FDA Regulatory Procedures and Adopting Targeted Tax Credits for QIDPs Would Expand Innovation

It is likely that a variety of incentives will be necessary to jumpstart innovation and restock the antibiotic pipeline.⁵ In tandem with enhanced reimbursement, which we believe would provide the biggest incentive to antibiotic innovators, facilitating and lowering the costs of antibiotic development could also encourage more investment and innovation in the field. This aim can be accomplished through a number of means, including: streamlining and modernizing the regulatory process for antibiotics; FDA user fee exemptions; targeted tax credits; and increased investment in research networks to advance the development of antibiotics and rapid diagnostics. Cubist recommends the Subcommittee pursue the following reforms:

1. Modernize the regulatory approval process for establishing and updating susceptibility test interpretive criteria, also known as “breakpoints” for antibiotics and testing devices.

Cubist strongly supports the regulatory reforms for “breakpoints” proposed in HR 3742, the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, as introduced by

⁵ Aylin Sertkaya, et.al. *Analytical Framework for Examining the Value of Antibacterial Products*, April 2014. http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm. (Accessed 9/9/2014.)

Representatives Gingrey and Green last year and co-sponsored by a bipartisan group of over 20 Committee members. However, we recognize that a more comprehensive approach to improve the process for setting and updating antibiotic (and the associated automated testing devices that measure susceptibility) breakpoints would be valuable and understand that FDA has put forward some recommendations. We would support potential changes to the ADAPT Act, including a requirement that breakpoints be updated on an FDA website instead of the drug label and allowing the FDA to recognize breakpoints set by recognized standard setting organizations when appropriate.

2. Incorporate Elements of Newly Enacted Breakthrough Therapy Approval Pathway into the GAIN Act's QIDP Framework.

Cubist is aware that the ADAPT Act, the FDA, IDSA, The Pew Charitable Trusts and others have endorsed creation of a limited population approval pathway for use by antibiotic sponsors. To date, we have collaborated well with the FDA on robust but efficient clinical trials to support the approval and review of QIDPs. Cubist is confident that the FDA will continue to exercise their existing regulatory authority to expedite access of innovative antibiotics for patients. We also commend their efforts to streamline the clinical development of important treatments in order to address antibiotic resistance as described in recent regulatory guidance.⁶

If the Subcommittee elects to pursue a limited population approval pathway, we recommend that it be entirely voluntary and at the sponsor's discretion and that a designation be conferred in advance, much like the fast track and breakthrough drug designations, to allow sponsors to appropriately develop their clinical programs. Cubist also notes that, in addition to defining any pre- and post-market requirements, any proposal should provide for cross-disciplinary review by senior FDA staff (as with the breakthrough designation) and require that the FDA describe the types of clinical development programs that might be considered under this pathway. We believe the latter could be accomplished through regulatory guidance. Finally, the Subcommittee should

⁶ Food and Drug Administration, *Guidance for Industry Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases*. July, 2013.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf>
(Accessed 9/9/2014.)

consider inclusion of meaningful incentives, such as orphan drug based policies of exemption from requirements under the Pediatric Research Equity Act (PREA) (including Prescription Drug User Fee (PDUFA) fees, per below), research grants, tax credits or additional exclusivity protection.

Cubist also encourages the Subcommittee to consider an alternative approach of updating the GAIN Act to ensure QIDP sponsors have access to the new breakthrough drug approval pathway and its associated benefits under section 902 of FDASIA, in the same manner that Congress assured QIDP sponsors access to fast track under section 803 of FDASIA.

3. Provide transferable research and development and manufacturing tax credits to offset the costs of clinical testing for QIDPs.

While the GAIN Act provides valuable economic incentives, companies must fully develop a product before receiving the benefits from increased exclusivity. Financial support to help offset clinical development costs of QIDPs, including tax credits modeled after the Orphan Drug Tax Credit, would provide an attractive incentive to antibiotic developers. Such a credit should apply to expenses incurred during late-stage (phase 2 and 3) clinical testing. The credits should also be transferable to allow small, pre-revenue companies without tax liability to sell the credit and invest the sales income into additional research and development.

4. Exempt sponsors from FDA User Fees associated with approval of QIDPs.

As mentioned above, FDA user fees associated with the approval of QIDPs, including the Application, Product, and Establishment user fees, should be exempted in order to reduce the costs of development for these priority antibiotics.

5. Consider funding and or expanding existing clinical trials networks for the study of investigational antibiotics.

We encourage Congress to explore ways to improve clinical trial efficiency by developing a robust infrastructure to facilitate clinical trials for investigational antibiotics.

6. Invest in the development of rapid diagnostics.

Rapid diagnostics have the potential to streamline antibiotic development, improve antibiotic prescribing and drive innovation of targeted therapies, but technological and other challenges have slowed their availability. These significant barriers are unlikely to be overcome by any one entity and would benefit from public/private collaboration. Such efforts should aim to address not only the technological and scientific barriers to rapid diagnostic development, such as sample preparation and biomarker validation, but also must consider the significant economic and regulatory barriers to rapid diagnostic development, as well as barriers to uptake of diagnostics in various healthcare settings.

7. Expand tropical disease priority review vouchers, as established under FDAAA, to apply to QIDPs.

Section 1102 of the FDA Amendments Act of 2007 (FDAAA) authorizes the FDA to award priority review vouchers to sponsors of certain tropical disease product applications. A priority review voucher may be used by the sponsor who obtains it or may be transferred from the sponsor (including by sale) to another sponsor of a human drug application. This policy is intended to create a positive incentive (that can be monetized) to encourage companies to pursue drug development in neglected global diseases, but is easily extensible to the development of priority antibiotics.

Conclusion

Cubist thanks Chairman Pitts and the Subcommittee for holding today's hearing. We are eager to assist the Subcommittee in developing and promulgating new policies that build on the GAIN Act to further incentivize antibiotic research and development.

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**Statement of Todd E. Gillenwater
President & CEO, California Healthcare Institute (CHI)
Submitted to the House Committee on Energy & Commerce
Subcommittee on Health**

Hearing on “21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development”

September 19, 2014

CHI - California Healthcare Institute, the statewide public policy organization representing California's leading biomedical innovators – over 275 research universities and private, nonprofit institutes, venture capital firms, and medical device, diagnostic, biotechnology and pharmaceutical companies – appreciates the opportunity to present our views on the critical need for increased investment and incentives to spur the development of new antibiotics to combat drug-resistant pathogens.

Over the last century, the discovery, development and distribution of antibiotics ranks as one of the most transformative scientific achievements of man. In 1900, the three leading causes of death in the United States were pneumonia, tuberculosis, and enteritis – all infectious diseases. More than a hundred years later, these diseases have by and large been eradicated as a direct result of the anti-microbial drug development that led to therapeutics like penicillin.

Yet, those incredible achievements have led to a level of complacency in the United States and around the world with regard to the continued development of these life-saving treatments. Early victories in the antibacterial space led to an explosion of research and investment by government, universities and industry, producing effective antibiotics that were introduced against many different types of bacteria. The unprecedented successes in the treatment of a range of deadly infectious diseases caused industry and the government to turn its focus to other illnesses and away from the production of new antibiotics. However, many of these effective treatments experienced widespread and accelerated use, which over time weakened their ability to be effective in treating evolving pathogens. Simply put, as the rate of anti-microbial resistance grew, new research and drug development failed to keep pace with the incredible need for new medicines to treat these increasingly virulent strains.

Alarms were sounded this week when global health experts cautioned that more than 20,000 people worldwide may die from the ongoing Ebola outbreak. In formal statements, the President correctly noted that the time to act on an infectious disease is long before there is an outbreak, because by then, it is too late.

Hospitalizations related to Methicillin-resistant *Staphylococcus aureus* (MRSA) have increased 119 percent according to the Centers for Disease Control and Prevention (CDC) and the Infectious Disease Society of America (IDSA) estimates that 19,000 Americans died last year from MRSA alone – at least that many are expected to succumb to the infection again this year. The President's statements around the Ebola epidemic ring true for antibiotic-resistant pathogens as well: we cannot wait for MRSA infections to reach epidemic proportions – we must act now.

MRSA represents one of the most compelling case studies of antibiotic resistance in the past decade and clearly illustrates the incredible need for industry and government to work together to encourage the investment and development of new anti-microbial treatments *before there is an outbreak*. Beginning in the early 1990's the rates of MRSA, a gram positive bacterial infection that causes skin infections, began to rise. To treat MRSA infections throughout the 1990's, the antibiotic vancomycin began to be used frequently by physicians in hospitals. Like all antibiotics, when MRSA had been exposed to vancomycin on a widespread basis, the bacteria began to develop a resistance to the treatment. A previously effective drug like vancomycin had lost its ability to treat the MRSA infection, to dire consequences.

In 2012, Congress passed and President Obama signed into law the *Generate Antibiotic Incentives Now (GAIN) Act*. CHI was an early supporter of the GAIN Act, and launched an initiative in March 2012 focused on the growing need for antibiotic discovery and development to combat the emerging threat of antimicrobial resistance and pathogens that are highly resistant to known medicines. The GAIN Act has helped to spur research in the field of antibiotics, encourage investment in development of new antibiotics, and provide regulatory clarity for getting the antibiotics into the hands of physicians. CHI believes the GAIN Act will go down in history as a very important instrument of public policy in the battle against resistant bacteria.

But much more work remains to be done, and this Committee's 21st Century Cures initiative is an incredible opportunity in which to accomplish these goals. The U.S. Food and Drug Administration (FDA) plays a crucial role in turning the tide on antibiotic drug development. We strongly encourage the Committee to work together with FDA to implement a streamlined drug approval process that reduces regulatory barriers and provides the necessary incentives for academic and private research institutions as well as private industry to establish a sustainable R&D infrastructure. Additionally, the Committee must consider strategies to more appropriately reimburse for products targeting bacterial and fungal pathogens associated with high rates of mortality or serious morbidity, and for which we have limited or no alternative treatments. This modification is an important incentive to support enhanced research efforts and could provide sufficient encouragement for manufacturers to remain in or reconsider antimicrobial product development.

The growing epidemic of multidrug-resistant infections knows no borders and the re-establishment of antibiotic development as a viable investment for the biomedical industry is imperative to public health. Academia, industry and the federal government must work together to encourage investment in the development of these drugs.

We would be pleased to provide additional information on the important role Congress can play in creating incentives to spur the development of new antibiotics to combat drug-resistant pathogens, thus promoting venture investment in this field, and creating and retaining jobs in our state. Thank you again for the opportunity to present our views.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS
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Minority (200) 226-3641

October 15, 2014

Dr. Janet Woodcock
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

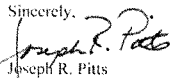
Dear Dr. Woodcock:

Thank you for appearing before the Subcommittee on Health on Friday, September 19, 2014, to testify at the hearing entitled "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, October 29, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUL 31 2015

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the September 19, 2014, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "21st Century Cures: Examining Ways to Combat Antibiotic Resistance." This letter is a response for the record to questions posed by certain Members of the Committee.

If you have further questions, please let us know.

Sincerely,

Thomas A. Kraus
Associate Commissioner
for Legislation

Enclosure

cc: The Honorable Frank Pallone, Jr.
Ranking Member

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1.1 When considering the importance of antibiotic breakpoints, what barriers do you face when attempting to keep them up to date?

The current system for updating breakpoint information in antimicrobial susceptibility testing (AST) devices is not getting up-to-date information regarding the susceptibility of bacteria and fungi to health care practitioners fast enough. Under the current regulatory system, AST device manufacturers initiate updating the breakpoint information used in the device labeling for a given drug after the manufacturer who produces that drug submits a labeling supplement to FDA, and FDA approves the supplement. The multiple steps to update the breakpoints adversely affect the public health by preventing AST device manufacturers from being able to update the breakpoint information in their devices promptly, and it utilizes resources that could otherwise be used for antibacterial and antifungal drug reviews, among other things.

Reviewing separate breakpoint labeling supplements for each individual drug product (even if they share the same active ingredients, and thus, generally have the same breakpoints) is no small task. There are approximately 200 reference-listed antibacterial drug products and more than 400 generic copies of those products. Moreover, the process begins with the submission of labeling supplements from the drug manufacturers, and although some drug manufacturers submit these promptly, the Agency needs to send others reminders. This approach to updating labeling is very resource-intensive from the FDA's perspective. The labeling of each reference listed drug (RLD) has to be addressed separately when, in fact, the breakpoints are often the same for all antibacterial drug products containing the same active ingredient, so there is a great deal of duplicate effort.

Many antibacterial drugs are very old, and they are now marketed only by generic firms. These companies often do not have staff with the technical expertise to evaluate and update the breakpoints. In addition to the 200 RLDs, there are approximately 400 additional generic systemic antibacterial drugs. It is expected that each generic firm will update their label when the RLD label for that generic antibacterial drug product is updated. The collective resources that are required of the pharmaceutical companies to update their drug product labeling and the associated FDA resources are/will be considerable, while most of this work will be to simply duplicate work previously performed to update the RLD label.

1.2 Does the FDA need new authority to ensure that antibiotic breakpoints are updated regularly?

FDA has begun to explore potential administrative options, at the same time as the Agency has been providing technical assistance to Congress on legislative options. Although we are

Page 3 - The Honorable Joseph R. Pitts

still working through the administrative options, there seem to be clear challenges associated with the ones we have identified.

- First, FDA Has Concerns that It Will Not be Able to Address this Issue Expeditiously – In order to address the issue comprehensively, FDA would likely have to take multiple administrative steps, including issuing several guidance documents and/or regulations to, among other things: (1) take the breakpoints out of the drug labeling, (2) recognize appropriate standard development organization standards, (3) explain the limited circumstances in which FDA may permit device labeling to contain information about bacteria that has not been identified in clinical trials, and (4) provide interested parties adequate notice about the new framework. The FDA Centers have been working together and are committed to addressing this issue, but each of these efforts could take 3-5 years due to the Good Guidance Practice processes and/or the notice-and-comment processes for issuing regulations.
- Second, FDA May Not Be Able To Execute Each Piece of the Administrative Strategy – If any one piece of the administrative strategy is delayed or stopped, the administrative approach would be less comprehensive, at best, and ineffective, at worst. FDA does not have complete control over whether and when documents are issued. Accordingly, if FDA began the process of executing an administrative strategy and developing a breakpoints website, neither FDA itself nor industry would have any certainty with regard to whether or when the new framework would be implemented.
- Third, Even If FDA Were Able to Issue an Entire Administrative Package, the Package Would Likely be Less Comprehensive than Legislation and Provide Less Certainty For Industry – Certain elements of the administrative strategy could require a fact-specific analysis, which would provide less certainty for industry than could legislation providing for an overarching framework.

Conclusion: FDA has determined that a legislative solution to the breakpoints issue is preferable to the potential administrative options that we have identified because it would: (1) address an increasing and significant public health issue much more expeditiously, (2) clarify FDA's authority to implement the program; (3) provide certainty to interested parties (and to FDA, before it invests resources in a new process) that a new framework will be put in place, and (4) address the problem more comprehensively.

1.3 Do the breakpoint provisions of H.R. 3742, the Antibiotic Development to Advance Patient Treatment Act of 2013 (ADAPT Act) address this matter sufficiently?

The breakpoint provisions of H.R. 3742 address a number of these issues; however, there are some modifications that could be made for the legislation to accomplish the bill's goal of enabling more timely updates of antibiotic breakpoints. We appreciate the Committee working with us to address these issues in H.R. 6. The modifications to H.R. 3742 include:

- Remove the breakpoint information from individual drug product labeling

altogether. This would allow AST device manufacturers to update their labeling, without waiting for the drug manufacturers to update their labeling first.

- Authorize FDA to: (a) recognize breakpoint standards, or portions thereof, established by Standard Development Organizations (SDOs), when the Agency agrees with the breakpoints, and (b) list other breakpoints on its website beyond what is in the drug labeling, when the Agency concludes such breakpoints are appropriate, along with appropriate language that can inform when such breakpoint information goes beyond the drug labeling. This would allow FDA to leverage its resources, while still ensuring that the Agency retains its authority to identify and update appropriate breakpoints.
 - Establish an FDA website where FDA-recognized breakpoint standards, as well as other appropriate breakpoints that are not covered by (or deviate from) FDA-recognized standards, would be posted. This website would: (a) allow FDA to update breakpoints for a drug, sold by multiple companies, at the same time, (b) make the latest breakpoint information instantly accessible to the health care community, (c) provide a centralized mechanism to help the health care communities track updates, and (d) make breakpoint information more transparent.
 - A device or drug manufacturer's use of breakpoints in FDA-recognized standards, or breakpoints otherwise listed on FDA's website, in submitting marketing applications is voluntary.
 - Individual drug and device manufacturers, including generic drug manufacturers, who disagree with FDA-recognized SDO breakpoint standards, or other breakpoints listed on the FDA website, may: (a) attend SDO meetings to weigh in on how SDOs should set breakpoints, (b) submit comments to FDA in response to the annual compilations of notices, in the *Federal Register*, which alert interested parties to breakpoint updates, and/or (c) submit marketing applications or supplements to FDA using different breakpoints.
2. **What are the challenges the FDA believe exist with regard to clinical studies for serious and life threatening antibiotics and how does this situation impact the setting of antibiotic breakpoints at the time of approval?**

Scientific Challenges Associated with Antibacterial Drug Development

There are several key scientific challenges associated with clinical trials of antibacterial drugs for serious and life-threatening infections:

Trial Enrollment: Patients with serious and life-threatening infections are very ill and may not be able to consent for themselves. Obtaining informed consent from such a patient or their family can be very difficult during this stressful time.

Prior Antibacterial Therapy: As patients with serious and life-threatening infections are very ill, antibacterial therapy needs to be started immediately as

any delay in therapy can have detrimental effects, including increasing mortality. These patients are often treated with non-study antibacterial drugs before they receive the new test drug, while the study enrollment procedures are underway. The antibiotics received before the trial may be the main reason the patient got better, not the test drug. This may make the trial results difficult to interpret as it may not be possible to determine the role of the new test drug in patient recovery.

Concomitant Antibacterial Therapy: At the time of enrollment, in most cases, the infecting microorganism is not identified. The infecting microorganism is definitively identified only when bacterial cultures are finalized about 48-72 hours later. During this early time period, non-study antibacterial drugs are administered empirically to provide coverage for likely potential causative microorganisms. Some of these non-study antibacterial drugs can have a spectrum of activity that overlaps with that of the test drug. This can confound assessment of the efficacy of the test drug.

Trial Conduct: As these types of studies are very difficult to conduct and enrollment at any one site is very slow, these studies are often conducted at multiple study sites (>100). In addition, to the difficulties with setting up several study sites, this can result in a significant increase in study costs.

Rapid Diagnostics: The lack of rapid diagnostic tests limits the ability to identify the infecting microorganism(s) within a few hours. It takes several days for the culture result to be available. Because of the delay in identifying the infecting microorganism(s), to ensure that a sufficient number of patients with the microorganism(s) of interest are included in the trial to allow for analysis, a larger number of patients have to be enrolled at the beginning of the trial.

Economic Challenges Associated with Antibacterial Drugs Development

We note that, in addition to the scientific challenges associated with studying a new antibacterial drug, the typical economic return on the marketing of antibacterial drugs is also an important factor that markedly limits what companies are willing to do (i.e., how much they are willing to invest) in order to properly study a new antibacterial drug.

Impact on Setting Breakpoints

The challenges with trials for serious and life-threatening infections do not impact the setting of susceptibility test interpretive criteria (breakpoints) per se. As these infections can be caused by a variety of microorganisms, often one may not identify any one particular microorganism in sufficient numbers to allow for setting of breakpoints based on this clinical trial data. Also, sufficient numbers of patients with microorganisms that are less susceptible are often not enrolled in clinical trials. This limits the amount of clinical data available regarding infections caused by these bacteria.

The Honorable Michael C. Burgess

- 1. You and the agency are leading champions of replenishing our antibiotic pipeline, but the economics are broken and HHS' own study on antibiotic incentives (*Incentives for the Development of New Drugs, Vaccines, and Rapid Diagnostics for Bacterial Diseases*) demonstrates that moving the needle in monetary terms for companies would take a reduction in clinical trials times by two to three years. Is that really possible? Can the ADAPT Act accomplish such? How else can FDA support bolstering the marketplace for antibiotics?**

The expected benefit of this legislation would be to encourage rapid development of antibacterial products to meet pressing unmet medical needs by conducting streamlined clinical trials enrolling fewer patients. Because approval in a smaller population with an unmet medical need could be based on limited data, drugs could be developed more quickly and less expensively than drugs undergoing typical antibacterial drug development. It is unlikely, however, that ADAPT's Limited Population Antibacterial Drug (LPAD) provisions would be able to reduce clinical trial times by two to three years. That does not mean that ADAPT would not help to bolster the marketplace.

In addition to providing a streamlined drug development process for addressing unmet medical needs, another positive outcome of the ADAPT legislation would be that it would likely contribute to an overall increase in the antibacterial armamentarium. More products representing different classes of drugs, many with different mechanisms of action, would make us better prepared to meet the unknown challenges of antibacterial resistance that lie ahead.

It is also critical that the ADAPT legislation that is eventually enacted require products approved via that pathway to have an LPAD pathway branding element, such as "LIMITED POPULATION" in close proximity to the brand name of the product. An LPAD branding element is critical to convey to all members of the health care community that the drug has been shown to be safe and effective for use only in a limited population. In order to make fully informed decisions, the health care community must understand that an LPAD drug was approved based on a unique benefit-risk profile in the indicated population and the safety and effectiveness of the product has not been demonstrated in broader populations. This is particularly important in the context of antibacterial drugs, which have historically been inappropriately overused.

Another way that FDA could support bolstering the marketplace for antibacterial drugs is to continue to work with companies to take advantage of existing expedited review pathways, such as fast track, qualified infectious disease product (QIDP) designation under GAIN, breakthrough therapy, priority review, and accelerated approval.

- 2. Even with accelerated approval, sponsors are still required to manufacture product batches on a large scale and perform long stability runs. To what extent has there**

been discussion at FDA to allow sponsors to build this over time, including after licensure, as this can be a rate limiting step to approval?

While there are general expectations related to the amount of stability data necessary to support approval of New Drug Applications, the Agency employs a risk-based approach in implementation of these expectations. In specific cases of clinical urgency and/or other types of public health impact, the Agency works collaboratively with Applicants to determine the most appropriate strategy for commercial scale manufacture and stability data submission. Alternate approaches include the submission of an abbreviated stability data package, adjustments to batch sizes used for primary stability data, and the use of supportive stability data in lieu of actual commercial scale primary data. These options are typically used for applications of high clinical urgency, including Breakthrough Therapies. The Agency has also found that a key part of successful collaboration with applicants, related to commercial scale manufacture and stability data submission, occurs when the applicant communicates challenges to the Agency as early in the process as possible. In the past, earlier communication with the applicant has enabled FDA to be a partner in solving some of these complex challenges and helped to bring these products to market in the shortest amount of possible time.

The Honorable Phil Gingrev

- 1. Congressman Green and I have been working on the ADAPT Act, which gives FDA greater flexibility to consider all forms of evidence, in addition to data from clinical trials, when setting breakpoints for new antibiotics at the time of approval. It is critical to ensure FDA has the tools required to incorporate the latest advances in science and modeling into its decision making process, especially when setting an antibiotic breakpoint at the time of approval. Does FDA agree with this statement?**

We already can use, and have been using, these types of information to make approval decisions. In addition to information from clinical trials, the Agency reviews data from studies conducted to understand the in vitro activity of the drug against large collections of bacteria of interest, studies to determine the efficacy of the drug in animal models of infection, and pharmacologic studies to predict the optimal dosing of the drug for greatest antibacterial effect. A thorough understanding of these types of data requires advanced analysis tools and familiarity with the best current thinking regarding the quality of the studies under review and the appropriate weighting of the various data types.

- 2. This Subcommittee has been a true leader in Congress to enact important reforms like the GAIN Act to stimulate development of important new antibiotics. We have also enacted mandates for FDA to update breakpoints for existing antibiotics in a timelier manner. For new antibiotics, the ADAPT Act would give FDA flexibility to consider all forms of evidence when setting their breakpoints – a parameter that guides the use of these drugs. Do you agree this would be an important reform to follow in the footsteps of what we have already done?**

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Thank you for your leadership in this area. While we agree that it would be important to clarify FDA's ability to rely on such information in setting breakpoints, we already can use these types of information and have been using these types of information. The challenges faced in updating breakpoints are largely related to the processes involved in first updating breakpoints in a drug company's label for each of the many antibacterial drugs, then the device companies follow by updating their testing devices. The current process is inefficient, duplicative and not a timely mechanism for updating breakpoints in diagnostic testing devices. New approaches, some of which ADAPT¹ contemplates, that leverage the work of standard development organizations (SDOs), take advantage of electronic means for updating (i.e., website), remove breakpoints from drug labeling, and affirm the Agency's recognition of interpretive criteria for bacteria not in the drug label could help to address the significant procedural challenges of updating breakpoints.

The Honorable Gus Bilirakis

1a. How many treatments were approved with novel biomarkers used for the first time within the last five years?

It is challenging to define biomarker novelty and to identify when such biomarkers were used for the first time. We are providing background information on biomarkers below and listings of a recent cohort of new drugs and accelerated approvals using biomarkers in Tables 1-3 in the enclosure to this response.

A biomarker is defined as:

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."¹

Biomarkers include laboratory tests (e.g., blood sugar or serum cholesterol), physical signs (e.g., blood pressure), and radiographic images, and are commonly used and relied upon throughout many phases of drug development from basic science, translational, and preclinical phases through to clinical testing. Biomarkers have many different uses. For example, they are used in pre-clinical animal toxicology testing to look for safety signals that indicate drug toxicity or target organ damage, in early phase clinical testing for pharmacokinetic and pharmacodynamic testing, such as to assess drug exposure and metabolism, guide dosing, assist with early safety evaluation, and to inform the design and conduct of later-phase trials, and in mid-to-later phase clinical testing, such as to assess early effects of intervention on biochemical pathways (such as LDL-cholesterol lowering). In pre-clinical and early clinical phase testing, these biomarkers may not directly factor into an approval decision for a marketing application, but the information gained from the use of biomarkers is usually critical to the development of drugs. In later-phase clinical testing

¹ Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89-95.

(e.g., Phase 3 efficacy or “pivotal” trials), in some circumstances a biomarker may be used as a surrogate endpoint.

Surrogate endpoints are a subset of biomarkers that are used as a substitute for a clinical endpoint in a clinical trial. A surrogate endpoint is defined as “a marker that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.”² Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may fall into one of three categories:³

- 1) The marker is *known* to predict clinical benefit; i.e., a validated surrogate endpoint that could be used as an endpoint in a clinical trial used to support a traditional approval. Some examples include HgA1C for diabetes medications and LDL-cholesterol (“bad” cholesterol) for statin medications used to treat hypercholesterolemia.
- 2) The marker is *reasonably likely to predict a drug’s intended clinical benefit*, and could be used as a basis for accelerated approval. An example includes tumor stabilization or shrinkage for some cancers, which is thought to be reasonably likely to predict an effect on overall patient survival.
- 3) A marker for which there is *insufficient evidence* to support reliance on the marker as either kind of surrogate endpoint, and that, therefore, cannot be used to support traditional or accelerated approval of a marketing application. An example includes HDL-cholesterol (“good” cholesterol) raising in clinical testing of a class of drugs (CETP inhibitors) intended to treat hypercholesterolemia and prevent cardiovascular disease. A trial for one such drug was halted when excessive mortality was seen in the treatment group despite the drug showing the intended pharmacologic effect of increasing HDL cholesterol levels in study subjects.⁴ A trial with another drug in this same class also raised HDL cholesterol but had a neutral outcome (neither harmful nor beneficial for the indication).⁵

Surrogate endpoints are most useful in settings where the disease course is long and an extended period of time is required to measure the intended clinical benefit of a drug. There may be many situations where the use of a clinical outcome assessment is more appropriate and where meaningful results can be more readily obtained.

For new drug development, many of the biomarkers, assays, tests, and measurements used during clinical development are product specific and need to be developed and tested during preclinical, early clinical, and later clinical phases of drug development. For example, markers of drug exposure (e.g., drug blood levels) or metabolism or, for biologic products, anti-drug antibodies, are commonly used in drug development and are likely to be product-

² Guidance for Industry, Expedited Programs for Serious Conditions –Drugs and Biologics at p. 17 (May 2014) <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

³ Ibid.

⁴ Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109-22.

⁵ Schwartz GC, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089-99.

specific (hence, novel). Thus, most new drug development programs will rely upon at least one (and often several) novel biomarker for product development and approval.

Novelty of a biomarker (or surrogate) can also include several different considerations:

- The biomarker may be entirely new and developed specifically for the drug development program.
- The biomarker (or surrogate) may have been available previously, but used for the first time for the disease or for the new drug (e.g., being adapted from a different disease or a different class of drugs).
- The biomarker (or surrogate) may have been available previously, but is now being used in a new way such as, as a surrogate endpoint when previously used as a pharmacodynamic measure.

There are thousands of drugs that have been approved over the course of FDA's extensive drug approval history. It would be extremely difficult to compile a comprehensive list of all drug and biological product ("drug") approvals for which a novel biomarker was used. Surrogate endpoints are commonly used to support both traditional and accelerated approvals for rare and common diseases, for new products (new molecular entity (NME)⁶ and original biologics) as well as for non-NME drugs and supplemental approvals (i.e., efficacy supplements).

We compiled the following list of primary endpoints used in clinical trials from a limited subset only of new product (NME and original biologic) approvals by FDA's Center for Drug Evaluation and Research (CDER) in a recent three-year period (January 1, 2010, through December 31, 2012 – please see Table 1, enclosed). These endpoints were classified as surrogates or clinical outcome assessments (COA) to illustrate the use of both these types of endpoints in product approvals. COAs are often defined as those endpoints that measure an effect upon how patients feel, function, or survive.⁷ Summary results are as follows:

- There were 85 new drugs approved in this time period: 29 for rare diseases (Orphan drugs) and 56 for common diseases.
- Of these 85 approvals, 40 relied upon a surrogate endpoint as the primary endpoint for the pivotal clinical trials, and 45 relied upon a COA:
 - For rare diseases, 20 of 29 (69%) approvals relied upon a surrogate endpoint.
 - For common diseases, 21 of 56 (38%) approvals relied upon a surrogate endpoint.

⁶ NMEs are defined as drugs for which the active pharmaceutical ingredient has not previously been approved by FDA.

⁷ Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, editors. *Clinical Measurement in Drug Evaluation* New York, NY: J. Wiley; 1995. Pp. 3-22.

- Seven drugs received accelerated approval, all of which were based on a surrogate endpoint reasonably likely to predict clinical benefit, and all of which were for rare disease indications.

Given these factors, it is challenging to define biomarker novelty, and we do not feel that providing a listing on our part would be useful. Please refer to Tables 1-3, enclosed, for listings of a recent cohort of new drugs and accelerated approvals.

1b. How many treatments approved with novel biomarkers used for the first time were for indications other than cancer and HIV?

For the 85 new drugs listed in Table 1:

- Twenty-three drugs were for cancer or cancer-related indications and four were for HIV or HIV-related indications.
- For the 58 non-cancer, non-HIV-indicated drugs:
 - 22 relied upon a surrogate endpoint as the primary endpoint for approval
 - 36 relied upon a COA as the primary endpoint for approval.
- Seven of the 85 drugs received accelerated approval, five of which were for cancer indications and two of which were for non-cancer, non-HIV indications. There were no accelerated approvals for HIV drugs in this time period. The two non-cancer, non-HIV drugs included:
 - Ferriprox (deferiprone) for transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.
 - Sirturo (bedaquiline), indicated as part of combination therapy in adults (≥18 years) with pulmonary multi-drug-resistant tuberculosis (MDR-TB).

The five cancer drugs included:

- Adcetris (brentuximab) for two indications: 1) systemic anaplastic large-cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen, and 2) Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.
- Xalkori (crizotinib) for locally advanced metastatic non-small-cell lung cancer that is anaplastic lymphoma kinase (ALK)-positive.
- Kyprolis (carfilzomib) for patients with multiple myeloma who have received at least two prior therapies, including Velcade (bortezomib) and an

immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

- Synribo (omacetaxine mepesuccinate) for adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI).
- Iclusig (ponatinib hydrochloride) for adult patients with chronic phase, accelerated phase, or blast phase CML that is resistant prior to TKI therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior TKI therapy.

1c. Have any accelerated approvals occurred with a novel marker and a never before treated disease?

Between October 1, 2007, and April 30, 2014, inclusive of NME and original biological products (NBE), supplemental approvals and non-NME NDAs, there were 40 Accelerated Approvals⁸ by CDER, including:

- Eighteen NME and original biologics Accelerated approvals (new drugs), and
- Twenty-two non-NME NDA or supplemental Accelerated approvals

The 18 novel product approvals are listed in the Appendix, Table 2. In summary, these include:

- Two Accelerated Approvals for HIV
- Twelve Accelerated Approvals for various Oncology indications
- Four non-HIV, non-Oncology Accelerated Approvals, which includes indications in the therapeutic areas of Hematology, Cardiovascular, and Infectious Diseases

The 22 non-NME NDA and supplemental Accelerated Approvals are listed in the enclosed, Table 3, including:

- One Accelerated Approval for HIV
- Sixteen Accelerated Approvals for various Oncology indications
- Five non-HIV, non-Oncology Accelerated Approvals, which includes indications in the therapeutic areas of Medical Countermeasures, Medical Genetics, and Obstetrics

Regarding novelty and disease indication, we note that the Accelerated Approval regulations require that drugs approved under this pathway generally provide meaningful advantage over available therapies. For example, many of the above disease indications are for refractory, resistant, or previously treated diseases where patients had previously failed one or several other available therapies, such as relapsed non-Hodgkin's lymphoma (NHL) and

⁸ CDER Accelerated Approval list updated through March 14, 2014 available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM404466.pdf>

tyrosine kinase-resistant chronic myelogenous leukemia (CML). While there are other drugs approved for these indications, refractory or relapsed NHL and CML are usually life-threatening diseases, and hence, these approvals were addressing unmet medical needs or providing patients with serious diseases and important additional treatment options.

1d. How many new biomarkers did the FDA accept for a first time use in the last five years?

Please see responses to Questions 1-3 above. Most drug development programs use biomarkers, and for new products, it would be expected that most (if not all) would use novel biomarkers. For descriptions of surrogate endpoints in a recent three-year period and accelerated approvals in a six-and-a-half year period, please see summaries above and Tables 1-3.

2. This committee led passage of the Pandemic and All-Hazards Preparedness Reauthorization Act last year. PAHPRA required FDA to establish a new process for frequent scientific feedback between the agency and developers of medical countermeasures under Project BioShield. These Regulatory Management Plans (RMPs) are critical to accelerating the review and approval of critical medical countermeasures against threats like anthrax, smallpox and Ebola. Will you describe FDA's efforts over the last year to implement RMPs with countermeasure developers?

Section 304 of PAHPRA amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to include a new mechanism—the Regulatory Management Plan (RMP)—whereby medical countermeasure (MCM) sponsors or applicants can interact with FDA regarding the development and regulatory requirements for eligible countermeasures. RMPs are agreed to by FDA and the product sponsor or applicant, and delineate developmental milestones that trigger meetings, written feedback, and decisions by FDA, or other activities (e.g., developing a plan to demonstrate safety and effectiveness in pediatric populations) conducted as part of the development and review process; associated performance targets and goals for such responses and activities; and how the plan will be modified if necessary. FDA has been coordinating with BARDA regarding the developmental stage of medical countermeasures that would most benefit from an RMP.

To date, FDA has not received any written requests for RMPs. This could be related to the proactive and flexible approach that FDA has employed to facilitate the product development of critical MCMs, as recently exemplified by those related to the prevention and treatment of Ebola Virus Disease (EVD), that provide heightened levels of interaction similar to those that might be expected under RMPs.

FDA provides MCM-focused regulatory advice and guidance through a variety of mechanisms, including direct engagement with sponsors and applicants, issuing guidance documents, and holding Advisory Committee meetings and public workshops. FDA medical product review centers have extensive interactions with MCM sponsors to discuss testing, data requirements, and scientific issues related to moving candidate MCMs into

clinical development and assessing progress as these specialized product candidates move through clinical development toward marketing application. FDA also provides technical assistance to minimize risk during MCM manufacturing, including pre-approval inspections or site visits to ensure that manufacturing establishments are capable of adequately manufacturing products, and that submitted application data are accurate.

FDA is fully engaged with our Federal partners to address MCM priorities and we continue to work with our Federal partners (e.g., HHS/ASPR/BARDA) to implement new authorities under PAPHRA. For a summary of these activities, please see our FY 2013 Annual Report at <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCM/tcm390308.htm>.

3. PAHPRA strengthened FDA's Emergency Use Authority (EUA), and provided the agency more flexibility to get products to the public in an emergency. I am glad to see that FDA recently issued an EUA for a diagnostic test related to the on-going Ebola epidemic. Will you provide more details on the agency's use of these new authorities for Ebola? Are there more tests or therapies that may become available soon to health care workers on the front lines of Ebola?

FDA is using all of its emergency use authorities to the fullest extent possible to fulfill its mission to protect and promote the public health. FDA is actively working with Federal colleagues, industry, and international organizations to facilitate development, including evaluation of safety and efficacy, of treatments, vaccines, and diagnostic devices with potential to help mitigate the Ebola epidemic. We are reaching out proactively to multiple medical product developers to clarify regulatory requirements, provide input on pre-clinical and clinical trial designs, and expedite review of data as they are received from product developers. These efforts should help advance the development and availability of investigational products as quickly as possible.

FDA has one of the most flexible regulatory frameworks in the world, which includes mechanisms to enable access to investigational medical products when appropriate, after the risks and benefits to the patient have been weighed. To date, FDA has issued EUAs to allow the use of nine diagnostic tests developed by the Department of Defense, the Centers for Disease Control and Prevention and commercial sponsors for use in certain laboratories during this Ebola epidemic. We were able to issue these EUAs, in part because of new authorities gained under PAHPRA, which provide greater flexibility in the issuance of EUAs. We are encouraging other product developers of investigational diagnostics to test for Ebola to submit data to FDA for EUA consideration.

While FDA is making every effort to encourage development, speed review, and use flexible approaches to authorize the use of potential medical products to address Ebola, investigational vaccines and treatments for Ebola are in the earliest stages of development for this purpose. Data on safety and/or effectiveness in humans are limited or lacking, and accurate assessment (especially of effectiveness) may be impossible if adequately designed clinical trials are not performed. Also, for most of the investigational drugs, only small amounts have been manufactured for early testing. This supply issue constrains the options

for properly assessing the safety and efficacy of these investigational products in clinical trials to respond to the epidemic, and also limits the possibilities for making investigational products available for therapeutic use outside of a clinical trial. Nonetheless, while investigational products are being developed, with the ultimate goal of product approval and manufacturing for wide-scale use, FDA is doing all it can to facilitate appropriate levels of access to these products when the clinical circumstances warrant. Access to investigational drugs used to treat Ebola outside of clinical trials has been effectively facilitated under FDA's expanded access mechanisms (e.g., emergency investigational new drug (eIND) requests). There has been no need to issue an EUA to facilitate broader access to these investigational drugs. That said, FDA is fully prepared to issue an EUA to enable broader access to investigational drugs for Ebola if the need arises and the scientific data warrants its issuance.

- 4. One of the challenges we have heard from countermeasure developers who are partnering with the federal government is that communication between FDA and the Biomedical Advanced Research and Development Authority (BARDA) has been severely lacking. This makes it difficult for developers to be confident that these high-risk projects, including drugs to combat antimicrobial resistance, can be ultimately be successful? What is FDA doing to improve communication with BARDA as it relates to countermeasure development?**

FDA's overarching objective with respect to MCMs is to facilitate the development of and access to safe and effective countermeasures to counter high-priority chemical, biological, radiological, and nuclear threats and emerging infectious disease threats. FDA works extensively with the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) partners led by the HHS Office of the Assistant Secretary for Preparedness and Response, and including BARDA, to pursue this objective and support MCM-related public health preparedness and response efforts.

FDA also provides subject matter expertise and technical assistance to numerous standing PHEMCE-specific committees and working groups that develop MCM requirements, plans, priorities, and policies and conduct program oversight and integration. These standing committees and working groups meet on a weekly, monthly, bimonthly, quarterly, semi-annually, or as-needed basis depending on the requirements of the issues at hand. These committees and working groups address a range of topics across the full spectrum of activities associated with MCMs from threat assessment to requirements setting to product development to procurement, stockpiling, and utilization. With regard to the example presented in the question, FDA is an active member of the standing PHEMCE working group that meets regularly to address the threat of antimicrobial resistance in addition to other government-wide working groups. In addition, FDA participates in BARDA's "In-Process Reviews" to evaluate the progress of medical countermeasures which BARDA has under contract with the sponsors of those medical countermeasures.

In addition, to ensure that the MCMi Regulatory Science Program is appropriately targeted and coordinated with U.S. government MCM priorities, FDA established a Steering Committee (which includes BARDA) to evaluate research proposals for scientific/technical merit and feasibility as well as for alignment with PHEMCE priorities. The goal of the

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MCMi Regulatory Science Program is to develop the tools, standards, and approaches to assess MCM safety, efficacy, quality, and performance and to help translate cutting-edge science and technology into innovative, safe, and effective MCMs—including for at-risk populations.

To facilitate this level of engagement, FDA and the PHEMCE, including BARDA, have a Memorandum of Understanding (MOU) in place to establish a framework to promote efficiency and collaboration between FDA and PHEMCE partners. Moreover, FDA and the ASPR/ BARDA have a separate MOU in place to explore ways to further enhance information sharing efforts through more efficient and robust interagency activities; promote efficient utilization of resources and expertise for development of safe and effective medical products regulated by FDA for use as MCMs; support development of collaborative processes that meet the common needs for supporting medical product development and innovation; and assist the industry so they may advance product development with core technical expertise and regulatory guidance, build manufacturing infrastructure, and surge capacity for medical products regulated by FDA for use as MCMs.

If you have more specific information about communication challenges between FDA and BARDA from countermeasure developers, we welcome follow-up to better understand the challenges identified.

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October 15, 2014

Dr. Kenneth J. Hillan
Chief Executive Officer
Achaogen, Inc.
7000 Shoreline Court, Suite 731
South San Francisco, CA 94080

Dear Dr. Hillan:

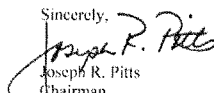
Thank you for appearing before the Subcommittee on Health on Friday, September 19, 2014, to testify at the hearing entitled "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, October 29, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,


Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

October 30, 2014

Achaogen's Responses to Followup Questions on Dr. Kenneth Hillan's Testimony to the House Energy and Commerce Committee Subcommittee on Health on "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development"

The Honorable Joseph R. Pitts

1. *What are other countries or the European Union doing to help spur research and development for anti-infectives? Which initiatives are working well and which will likely have the most significant impact to draw more companies to anti-infective product development moving forward?*

On the regulatory front, the EMA, similar to the FDA, has issued new guidance documents related to antibacterial drug development which describe streamlined pathogen-focused development pathways based on smaller clinical datasets. The feasibility of these approaches remains to be tested. The EMA is also piloting an adaptive licensing program (not specific to antibiotics) that will allow for early approval of drugs intended to treat conditions for which there is a high unmet medical need. Using existing EU regulatory mechanisms, an Initial approval would be granted for a limited patient population followed by subsequent approval(s) for a broader population based on postmarket trials and real-world data. We believe that an adaptive approval approach could have a positive impact on anti-infective product development. The passage of the ADAPT Act allowing a limited population approval would be an important step forward in facilitating this type of approach in the US.

On the research and development front, the EU and US independently have created excellent public-private partnerships that support antibacterial R&D, however the access to European R&D funding is restricted. The Innovative Medicines Initiative (IMI) funds antibacterial R&D and coordinates in-kind support from European pharmaceutical companies, but this funding may only be spent in EU member and designated associate countries. American researchers are not eligible for IMI funding. Conversely, in the US, the Biomedical Advanced Research and Development Authority (BARDA) generally has no such geographic restrictions. We support funding antibacterial R&D based on merit, regardless of where it is being performed.

Regardless of geographic location, any incentives that increase revenue potential, reduce product development costs, or ease regulatory requirements will stimulate R&D. We believe that the most effective incentives will be those which help manufacturers achieve sustainable commercial returns on new antibiotics. Examples of such incentives are noted in our answer to Ms. Blackburn's question below. Given the long development timelines for antibiotics, companies must know that these incentives are stable and not subject to decreases in funding. These incentives must have clearly defined budgets and protections to assure companies that they will be available tomorrow if companies choose to invest in antibiotic R&D today.

The Honorable Marsha Blackburn

1. *Our committee has enacted important reforms like the GAIN Act to stimulate development of new antibiotics, but realize more work needs to be done. It is my hope that as part of the 21st Century Cures effort we will put additional incentives in place for antibiotics that are designated as Qualified Infectious Disease Products (QIDPs). What other specific incentives do you recommend Congress consider for FDA designated QIDPs?*

We recommend that the Committee consider the following specific incentives for QIDPs:

1. Reimbursement reform to allow antibiotics to be priced at a level commensurate with their value to patients. The DISARM Act would reform reimbursement of qualifying antimicrobial products in the hospital setting for Medicare/Medicaid patients. We encourage the committee to also address reimbursement for patients covered by private insurance by authorizing a supplemental government payment to the hospital for certain QIDPs on top of the reimbursement payment made by the private insurer.
2. Transferrable market exclusivity vouchers. Companies that develop new antibiotics should be awarded a transferrable voucher for several years of market exclusivity. The antibiotic developer could either apply the voucher to one of its other products in a more commercially attractive therapeutic area such as diabetes, cardiology, or oncology, or in the case of a company like Achaogen whose sole focus is on antibiotics, could sell the voucher to another company that is interested in applying the voucher to another product.
3. New FDA approval pathways that allow for faster approval based on limited clinical data sets (e.g., the ADAPT Act).
4. Increased federal R&D funding, e.g. through BARDA and NIH, beginning with early research efforts to discover new antibiotics and continuing through late-stage clinical trials and FDA approval. The funding must be sustained throughout the entire development timeline for each new antibiotic.
5. Incentive payments (e.g., prizes and advance market commitments) that would be made as the QIDP meets certain development milestones. For example, payments of increasing dollar amounts would be awarded upon IND filing, completion of phase 1 clinical trials, evidence of efficacy clinical trials, FDA approval, etc.
6. Increased FDA flexibility and reimbursement reform for diagnostics intended for the safe and effective use of antibiotics. As technology evolves very rapidly, the FDA must take a nimble approach to approve new assays and instrumentation in a way that does not hold up the approval and use of new antibiotics. Diagnostics intended to be used in this manner should be approvable based on a dataset similar to that currently required for the existing 510(k) clearance pathway. Such diagnostics should also be considered in DISARM and other reimbursement reform measures.

We recognize that Congress faces pressure to limit the budget impact of new legislation, and that extending these incentive to all QIDPs may increase expenditures to a level that may reduce the

likelihood of passage. To control costs, QIDPs should be sub-categorized, with the highest incentives given to those that address the most serious unmet medical needs.

2. *Congress via the GAIN Act gave FDA a very important tool to designate certain anti-infectives as QIDPs; and the agency has made good progress on QIDP guidance, as well as designating over 30 developmental antibiotics as QIDPs. If we create other incentives as we should-- real incentives are needed --we must avoid a situation where there is confusion and differences over what qualifies for which type of incentive across different agencies of HHS. Will you respond to this statement?*

We agree that we must avoid confusion about which products qualify for various designations (e.g., QIDP, Fast-Track) and which incentives are associated with each designation. While it would be easiest if there were a single designation associated with all incentives, we believe that *further sub-categorization* may actually be necessary to ensure that the greatest incentives go towards antibiotics that address the most serious unmet medical needs. The specific incentives associated with each designation must be communicated very clearly to all stakeholders, including manufacturers, physicians, and pharmacy directors, so that we can understand and track the incentives.

The Honorable Michael C. Burgess

1. *When a small company considers early-clinical stage products, when does that company begin to weigh the cost of development, potential market size, and price point it would be able to achieve? I am presuming that many antibiotic products are left in the labs because there is limited ability to ever make the products profitable. How critical is product valuation to your investors?*

As small companies are for-profit entities whose operating capital ultimately depends on the proceeds from sales of products, the potential profit that a new antibiotic product could generate is critically important to company management and investors, and is considered at several stages of a company's life cycle. First, entrepreneurs seeking to form companies to address antibiotic resistance face a difficult challenge in raising funding from venture capitalists. According to a 2014 report "Trends in Healthcare Investments and Exits" from Silicon Valley Bank, from 2012-2013 at least 9 therapeutic areas attracted more new investment money from the 15 most active biopharmaceutical venture capital investors than anti-infectives. The therapeutic areas in which venture capitalists are investing, including oncology, cardiovascular diseases, and metabolism, all present greater potential return on investment than antibiotics, largely due to products in those therapeutic areas having greater commercial potential. Second, at the early research phase, small companies must devote their limited research dollars and human resources to the discovery programs most likely to generate product candidates that will provide a return on investment. This leads to management prioritizing research programs in other therapeutic areas over antibiotics, and in antibiotics that offer the best potential commercial returns over antibiotics where there may be an unmet medical need but no potential future profit. NIH budget constraints have led to a dearth in government funding for early stage antibiotic discovery research, leaving a critical funding gap for such early-stage discovery research. Finally, the cost of conducting clinical trials -- particularly Phase 2 and 3 trials -- is substantial, and products selected for clinical development must



generate a return on the upfront investment that companies must make to conduct clinical trials. Thus, profit potential is critical at every stage in the development of new antibiotics.

The Honorable Gene Green

1. *You mentioned in your testimony the importance of the innovative trial design for your CRE drug that was agreed upon with the FDA. How important is it for developers in your space to secure assurance from the FDA on trial design as early in the process as possible?*

FDA guidance relating to the development of new antibiotics has changed repeatedly over the past several years, and manufacturers have become concerned that their planned clinical trials will not meet the FDA's requirements for approval. A high-profile example where this has happened is that of the new antibiotic telavancin. Theravance was conducting Phase 3 clinical trials of telavancin in hospital acquired pneumonia (HAP) when FDA changed their guidance to require different endpoints than what were required when the clinical trials began, and FDA initially denied approval of telavancin for HAP on the basis that the trials did not meet the endpoints required under the new guidance. While we applaud the FDA for recognizing the need to assure developers that their clinical trial designs will eventually support regulatory approval, we believe that it is inefficient for the FDA to provide definitive assurance on a case-by-case basis. A better process would be for FDA to provide general guidance for developing new antibiotics that is unchanging, but that allows flexibility in application. Companies should be comfortable that clinical study designs that demonstrate the safety and effectiveness of new antibiotics will be accepted by the FDA without having to secure direct FDA assurance on the acceptability of the trial designs. Under this model, it would still be critical for FDA to be open and accessible to providing consultation to developers on areas where there may be flexibility within the guidance, especially in cases where the antibiotic is intended to fulfill a high unmet medical need.

2. *Is that an incentive that you believe would help support greater development in the antibiotic space? Why or why not?*

We believe that the lack of commercial viability for new antibiotics relative to other therapeutic areas such as oncology or endocrine diseases is currently the greatest barrier to the development of new antibiotics. As discussed in our responses herein, government incentives that increase revenue potential (DISARM Act, market exclusivity vouchers), reduce development costs (increased R&D funding, milestone-based "prizes"), or reduce regulatory requirements (ADAPT Act, greater FDA flexibility) will offer the greatest incentive for new antibiotic development.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

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October 15, 2014

Dr. Barbara E. Murray
President
Infectious Diseases Society of America
1300 Wilson Boulevard, Suite 300
Arlington, VA 22209

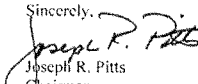
Dear Dr. Murray:

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Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

“21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development”

**Responses to Questions for the Record
Dr. Barbara Murray
Infectious Diseases Society of America (IDSA)**

The Honorable Joseph R. Pitts

I. What are other countries or the European Union doing to help spur research and development for anti-infectives? Which initiatives are working well and which will likely have the most significant impact to draw more companies to anti-infective product development moving forward?

In 2012, the European Medicines Agency (EMA), the European Union’s (EU) equivalent to our Food and Drug Administration (FDA), released a guidance document¹ on antibiotic development that included a focus on the development of new antibiotics to treat serious or life-threatening infections that occur in small numbers of patients and for which there is an unmet medical need. It is important to develop drugs to treat these infections before they sicken larger numbers of people yet development is challenging because when a resistant pathogen infects only a small number of people, it is not feasible to conduct a large clinical trial. The EMA addressed this regulatory barrier by permitting companies to study new antibiotics to treat such infections in smaller clinical trials. The limited population approach makes it possible for companies to study and bring to market some of the most urgently needed new antibiotics for patients who currently have few or no safe and effective treatment options.

The bipartisan Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, would establish a similar limited population antibiotic development approval pathway in the U.S. in which companies could study in smaller clinical trials new antibacterial or antifungal drugs to treat serious or life-threatening infections for which there is an unmet medical need. ADAPT drugs would receive approval just for the limited population in most need of the therapy, as opposed to all patients. Smaller clinical trials are also less costly, which is an important consideration given the economic hurdles still facing antibiotic research and development (R&D). Enacting ADAPT will enable urgently needed antibiotic development more rapidly than is now possible through existing FDA regulations. Further, the ADAPT Act also includes several provisions to help guide the appropriate use of these drugs. One half of Energy and Commerce Committee members have cosponsored the ADAPT Act, and the legislation enjoys broad

¹ European Medicines Agency, “Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 REV 2) to address indication-specific clinical data,” June, 2012, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129443.pdf

support among medical societies, public health organizations and industry.² The President's Council of Advisors on Science and Technology (PCAST) has also endorsed this approach in its 2014 Report to the President on Combating Antibiotic Resistance.³

Also in 2012, the European Commission (EC) launched their ground-breaking New Drugs For Bad Bugs (ND4BB) public private partnership (PPP). PPPs are essential to furthering the discovery process for new antibiotics because they convene the required diverse stakeholders to tackle the complex scientific and economic challenges facing antibiotic R&D. For example, ND4BB brings together government leaders, academia, industry and other experts for an unprecedented sharing of information and multi-disciplinary collaboration. The focus of this program is to develop strong networks of researchers, create fluid and innovative clinical trial designs and provide incentives for companies to meet the challenges of antibiotic resistance quickly and efficiently. Initial support for ND4BB (approximately \$300 million for the first phase) was nearly equally split from government and industry sources.

IDSA recommends that the US establish a similar, complementary PPP, using the ND4BB model. We are encouraged by the recent National Strategy for Combating Antibiotic Resistant Bacteria (CARB), released by the White House on September 18, 2014, which lists as an objective the creation of a biopharmaceutical incubator.⁴ The incubator is described as a consortium of academic, biotechnology and pharmaceutical industry partners to promote innovation and increase the number of antibiotics in the drug-development pipeline. While we have not yet seen any details about how the incubator would be established or operated, we believe this proposal holds significant promise. It should help incentivize research among industry and academic laboratories. Our understanding is that the key limitation for moving forward with this incubator proposal is the need for increased appropriations for the Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health (NIH). Thus, while it is not within this Committee's jurisdiction per se, we hope that you would be willing to weigh in with your colleagues regarding its importance.

In July 2014, United Kingdom (UK) Prime Minister David Cameron announced the establishment of a high level international assessment committee (headed by Jim O'Neill, the former chief economist at Goldman Sachs) to consider how governments can effectively incentivize industry to develop new antibiotics and how to best encourage the appropriate use of antibiotics, especially in poorer countries. IDSA recommends that the US support these global activities. But we also recognize that many thoughtful expert reports have already made recommendations regarding the variety of economic and

² Infectious Diseases Society of America, "ADAPT support letter," February, 2014, http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10x20/Letters/To_Congress/ADAPT%20group%20sign%20on%20letter%20FINAL.pdf

³ Executive Office of the President, President's Council of Advisors on Science and Technology, "Report to the President on Combating Antibiotic Resistance," September, 2014, http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf

⁴ The White House, "National Strategy for Combating Antibiotic-Resistant Bacteria," September, 2014, http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf

regulatory incentives needed to spur antibiotic development; including the ADAPT Act, tax credits, reimbursement reform, and additional funding for key federal agencies; and we urge Congress to quickly advance these policies and not wait for additional reports.

The Honorable Marsha Blackburn

1. **Our committee has enacted important reforms like the GAIN Act to stimulate development of new antibiotics, but realize more work needs to be done. It is my hope that as part of the 21st Century Cures effort we'll put additional incentives in place for antibiotics that are designated as Qualified Infectious Disease Products (or QIDPs). What other specific incentives do you recommend Congress consider for FDA designated QIDPs?**

IDSA appreciates the strides in antibiotic development made possible by the GAIN Act and wholeheartedly agrees that additional incentives are urgently needed. The antibiotic pipeline remains quite tenuous and patients are continuing to die from antibiotic resistant infections because we lack the new antibiotics needed to safely and effectively treat them. To enact the array of incentives that we believe are necessary, multiple Congressional committees will need to act, beyond just the informed health experts of the Energy and Commerce Committee.

Strengthen the Mission of the Biomedical Advanced Research and Development Authority (BARDA)

In December 2006, the Energy and Commerce Committee and others worked to ensure enactment of the Pandemic and All-Hazards Preparedness Act (PAHPA), Public Law No. 109-417, which has broad implications for the Department of Health and Human Services' (HHS) preparedness and response activities. Among other things, the Act amended the Public Health Service Act to provide new authorities for a number of programs, including the advanced development and acquisitions of medical countermeasures or the Biomedical Advanced Research and Development Authority (BARDA).

In 2010, BARDA established a Broad Spectrum Antimicrobials (BSA) Program to focus on developing novel antibiotics to address biological threats as well as the public health threat of antibiotic resistance. In four years, the BARDA program has grown from supporting one industry partnership with an antibiotic candidate in Phase 2 development to six partnerships with three industry partners in Phase 3 clinical development. Since 2010, BARDA has awarded over \$550 million to companies for antibiotic development.

In its September 2014 Report to the President on Combating Antibiotic Resistance, the President's Council of Advisors on Science and Technology (PCAST) strongly recommended that BARDA's antibiotic development program be expanded beyond projects justified by security/bioterrorism considerations to include antibiotics that meet urgent public health priorities that are not traditionally defined as material threat agents. **It would be helpful for the Energy and Commerce Committee to clarify BARDA's**

mission to make explicitly clear that the agency should support the development of antibiotics that meet urgent public health priorities.

Federal Funding

IDSA agrees with the PCAST report's assertion that significant new federal funding will be needed to support antibiotic research and development (R&D). Specifically PCAST recommended:

- An additional \$150 million per year for the National Institutes of Health (NIH), the Defense Advanced Research Projects Agency (DARPA), and the Defense Threat Reduction Agency (DTRA) to support antibiotic resistance research. Federal agencies are important sources of funding for academic researchers in this space. IDSA urges that some of this funding be directed to the Antibacterial Resistance Leadership Group (ARLG), which was founded by the National Institute of Allergy and Infectious Diseases (NIAID) to develop, design, implement, and manage a clinical research agenda to increase knowledge of antibacterial resistance. The ARLG is focusing on antibacterial drug and diagnostic development, optimal usage strategies, infection control and other activities to limit the development of resistance.
- \$25 million per year to begin, with additional funds in the future, to establish the necessary infrastructure for a public private partnership (to be jointly administered by BARDA and NIH) and to pursue the development of a master clinical trials protocol (to be led by the NIH and the Food and Drug Administration or FDA).
- \$400 million for BARDA to support antibiotic development and \$400 million for BARDA to provide advance market commitments (AMC) and milestone payments as incentives for bringing a new antibiotic to market.

Tax Credits to Promote Antibiotic R&D

Economic experts agree that a combination of “push” and “pull” incentives are needed to effectively stimulate antibiotic R&D. The GAIN Act provides a valuable “pull” incentive (additional exclusivity). Improving reimbursement for the most urgently needed new antibiotics would be another important pull incentive. While not within the Energy and Commerce Committee's jurisdiction, we hope that Congress will also provide targeted tax credits for antibiotic R&D. Tax credits would provide an extremely valuable “push” incentive and would be a very important complement to other efforts undertaken by this Subcommittee. IDSA has developed a proposal to provide a credit of 50 percent of the qualified clinical testing expenses (which we would define as expenses incurred in phase 2 and 3 clinical trials) for new antibiotics and antifungal drugs to treat serious or life-threatening infections—the very same drugs eligible for the additional 5 years of exclusivity under the GAIN Act (life-saving new drugs that this Subcommittee deemed worthy of federal investment). Economic modeling has indicated that financial support during expensive clinical trials, as provided through tax credits, would be a powerful incentive to complement enhanced exclusivity and reimbursement. In fact, Ernst & Young analysis estimated that our tax credit proposal would result in an additional 5-7 new antibiotics or antifungal drugs to treat serious or life-threatening infections in the pipeline every year.

Reimbursement Reform

Reimbursement mechanisms can be used to help stimulate antibiotic R&D, such as through the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act, H.R. 4187. This bill, which has been jointly referred to the House Ways and Means Committee and the House Energy and Commerce Committee, would provide Medicare add-on payments for antibiotics used in inpatient settings to treat infections associated with high rates of mortality. Strong communication between the Centers for Medicare and Medicaid Services (CMS) and FDA is critical for the success of such efforts, to help ensure that criteria to determine a drug's coverage and payment are applied in a scientifically and medically appropriate and consistent manner that provides companies with the certainty and predictability they need in order to develop life-saving new antibiotics or other novel life-saving therapies to treat serious or life-threatening infections. It is also very important to monitor the use of antibiotics that receive this increased reimbursement.

Congress may also wish to consider new policies that would significantly alter the way in which we pay for antibiotics, such as "delinkage" models that would de-link antibiotic reimbursement from antibiotic use by engaging in advance purchase contracts or by offering a prize or similar lump sum payment for licensing rights once the product is brought to market. Delinkage policies would clearly define the economic reward for antibiotic developers and help ensure good stewardship. The above mentioned PCAST report on antibiotic resistance discusses two potential approaches to delinkage for policymakers' consideration, summarized below:

Complete Delinkage

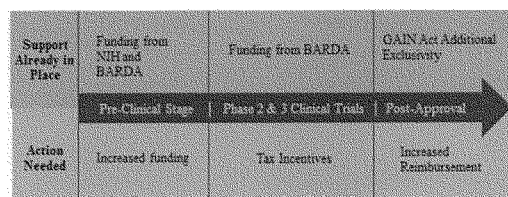
In this model, a drug developer might receive from the federal government (possibly through BARDA) a one-time lump sum payment that serves as a patent buyout and reward for bringing a new antibiotic to market. BARDA, or another appropriate federal agency, could contract with the drug company to produce the antibiotic as needed, and limit clinical use to specific circumstances and certain pre-defined conditions. Under complete delinkage, PCAST estimates that buyouts in the range of \$1 billion might be required.

Partial Delinkage

Under this model, a drug developer would receive a reward for developing the drug and would sell the drug, but would agree to certain stewardship requirements. BARDA has used such rewards successfully to incentivize the development of medical countermeasures to bioterrorism threats. An Antibiotic Incentive Fund (AIF) could be established under BARDA to provide advance market commitments and milestone payments as incentives for bringing a new antibiotic to market. The advance market commitment could be structured to secure the market availability of a given number of doses per year, determined by projected demand, over a given number of years, at a specified price. As a condition of receiving a payment from the AIF, industry partners could be required to develop and implement stewardship plans and apply other considerations (e.g., patent buyouts, restricted marketing, royalty payments, pricing

discounts, etc.). According to PCAST's analyses, incentive payments in the range of \$400 million per drug would likely be required.

The chart below helps demonstrate the types of financial support needed throughout the antibiotic R&D process.



2. Congress via GAIN gave FDA a very important tool, to designate certain anti-infectives as Qualified Infectious Disease Products (QIDP); and the agency has made good progress on QIDP guidance, as well as designating over 30 developmental antibiotics as QIDPs. If we create other incentives as we should—real incentives are needed—we must avoid a situation where there's confusion and differences over what qualifies for which type of incentive across different agencies of HHS. Will you respond to this statement?

IDSA completely agrees that additional incentives are needed for antibiotic R&D. While GAIN has helped generate important progress, experts agree that the antibiotic pipeline remains fragile. As Congress creates incentives, it is also very important that the government effectively communicates to companies what incentives are available for particular products. For the sake of simplicity, when appropriate, Congress should apply new incentives to products that receive the Qualified Infectious Diseases Products (QIDP) status. For example, IDSA proposes providing a new tax credit for QIDPs. Because the proposed tax credit could be utilized during costly phase 2 and 3 clinical trials, it would be a strong complement to the increased exclusivity provided through the GAIN Act, from which companies derive a benefit after the drug has been brought to market.

However, there are instances in which it is in the best interest of patients to apply a new incentive to a narrower category of new antibiotics than QIDPs. The first example would be the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, which would establish a limited population antibiotic approval pathway. IDSA is very grateful that you are an original cosponsor of this important bill. As you know, the ADAPT Act would address a key regulatory barrier to the development of certain new antibiotics — the inability to populate a traditional, large scale clinical trial because the targeted infection is currently occurring in too few patients. Under ADAPT, companies could study these new antibiotics in smaller, less costly clinical trials, and must still demonstrate the drugs' safety and effectiveness under FDA's current evidentiary

standards. ADAPT drugs would be approved for a limited population. ADAPT includes several provisions to help guide the appropriate use of these drugs. Because ADAPT drugs would be studied in smaller trials, a greater amount of uncertainty regarding these drugs' risks would exist, as compared to antibiotics studied and approved through a more traditional pathway. Instead, Representatives Gingrey and Green, the authors of both GAIN and ADAPT, appropriately crafted ADAPT to apply only to drugs meeting an unmet medical need for a limited population of patients—i.e. those patients who could tolerate a greater amount of uncertainty because they do not have other viable treatment options and for whom drugs could not be developed using a traditional approval pathway.

IDSA believes that improving reimbursement for the most urgently needed new antibiotics would be another important pull incentive. In order to best meet the most urgent needs of patients, it may be most appropriate to target increased reimbursement for antibiotics to treat serious or life-threatening infections for which we have few or no safe or effective treatments. Only some QIDPs and Qualifying Pathogens under GAIN would meet this additional criterion. For example, Carbapenem-resistant *Enterobacteriaceae* (CRE) is a type of gram-negative bacteria — a category of highly resistant pathogens that cause deadly infections. It is resistant to all or nearly all existing antibiotics, and half of patients who contract a bloodstream infection from this germ die. Of the four new antibiotics that received FDA approval this year, none target gram-negative bacteria. It is extremely difficult and costly to develop antibiotics effective against gram-negative bacteria, in part because the outer layers of their cells (including cell walls and membranes) block drugs from getting into the cell. For antibiotics that address unmet medical needs, such as those to treat gram-negative infections or other gram-positive infections identified as urgent or serious threats, it is clear that additional incentives beyond those applied to all QIDPs, such as increased reimbursement, are needed to help overcome the particularly challenging barriers to the development of these drugs. IDSA agrees that it is important to ensure strong communication between FDA, CMS and any other agencies involved in incentivizing antibiotic R&D to ensure that companies are provided with consistent and predictable information regarding available antibiotic incentives.

As Congress continues its important work to provide additional incentives for antibiotic development, IDSA underscores the equally critical need to monitor the use of new and existing antibiotics, such as through the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN). Data on antibiotic use is critical to understanding and reducing the overuse of and misuse of these drugs, which puts patients at risk for adverse events and suboptimal outcomes and fuels the development of resistance. Usage monitoring is important for all antibiotics, and particularly for ADAPT or limited population antibiotics and antibiotics that receive increased reimbursement to protect patients and to protect the federal investment in these drugs by maintaining their utility. One way to increase data reporting on antibiotic use would be to connect reporting with increased reimbursement for certain antibiotics. This approach is similar to those used in other CMS programs.

Due to the different functions and legal authorities of the FDA, CMS, and CDC, Congress may opt to tailor antibiotic incentives to best achieve the ultimate goals of improving patient outcomes and saving lives. Thus, while the definitions and programs may differ, ultimately, the goal is streamlined coordination between all Federal health programs (including approval to reimbursement) to ensure that urgently needed new antibiotics are available and appropriately utilized.

FRED UPTON, MICHIGAN
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October 15, 2014

Dr. Adrian Thomas
Vice President
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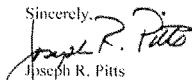
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Thank you for appearing before the Subcommittee on Health on Friday, September 19, 2014, to testify at the hearing entitled "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development."

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To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, October 29, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment



November 5, 2014

The Honorable Joseph R. Pitts
Chairman, Subcommittee on Health
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515-6115

Re: "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development," September 19, 2014

Dear Chairman Pitts:

Thank you again for the opportunity to testify on the important topic of antibiotic resistance and policy options for fostering new drug development. Below please find my responses to questions posed in writing by Subcommittee Members in follow-up to the hearing.

The Honorable Joseph R. Pitts

1. What are the other countries or the European Union doing to help spur research and development for anti-infectives? Which initiatives are working well and which will likely have the most significant impact to draw more companies to anti-infective product development moving forward?

In recent years, a number of countries have acknowledged and begun to respond to the need to foster research and development (R&D) for areas of high unmet medical need, including drug-resistant infectious diseases. In the European Union (EU), at least several policy initiatives to this end have been substantial. The EU's primary model for spurring R&D for anti-infectives has centered on public-private partnerships (PPPs).

The EU launched its "Priority Medicines for Europe and the World Project" in collaboration with the World Health Organization in 2004. The Project's stated goal was and remains "to help bridge the gap between public health needs and the development priorities of the pharmaceutical industry."¹ The Project aims to bridge these gaps through a large-scale PPP launched in 2008, known as the Innovative Medicines Initiative (IMI). With a budget of €2 billion in its initial phase, the IMI embraced a novel funding model in which public funds are targeted toward Product Development Partnerships (PDPs). These PDPs aim to

¹ Kaplan, Warren, Veronika J. Wirtz, Aukje Mantel-Teeuwisse, Pieter Stolk, Beatrice Duthey, & Richard Liang. *Priority Medicines for Europe and the World 2013 Update*. Geneva: WHO Publications, 2013.



stimulate "open innovation" between pharmaceutical companies and other key actors in the healthcare system, including academic institutions, small- and medium-sized enterprises (SMEs), patients, and regulatory authorities. The current IMI budget is €3.3 billion for the period 2014-2024 (€1.638 billion from the EU, and €1.425 billion committed by participating innovator pharmaceutical companies).² Important to note is that the largest portion of that funding is dedicated to projects related to chronic disease research for which markets of significant size exist.

For anti-infectives, available IMI funding is disproportionately smaller, though not insignificant: The IMI has reportedly set aside €700 million for a PPP to boost innovation under the "New Drugs for Bad Bugs" (ND4BB) program.³ An ultimate aim of this program is the clinical development of antibiotics to treat resistant Gram-negative pathogens. Research programs to date have focused on basic antimicrobial resistance (AMR) research.

Outside of AMR, IMI-funded research activities have yielded some notable successes. However, due in part to the disconnect between available short-term funding commitments (3 to 5 years) and necessarily long-term development periods, PDPs have not yet produced hoped-for medical breakthroughs in antibiotics. PPPs for R&D as structured in the EU system are subject to a number of additional limitations. These include, for example, the following:

- The EU has settled on a "consortium management" model, which attempts to integrate academic institutions and SMEs with large pharmaceutical companies through PPPs. While this mechanism is intended to create internal synergies in innovation, conflicts can arise in consortium leadership and project management given the disparate set of competencies and skills represented.
- The intellectual property structure for consortium participation is not fully defined. To date, the EU has not developed specific intellectual property protocols that can be readily allocated against the contributions made by each of the public and private partners participating in the consortium.

At present, with these and other operational questions still outstanding, the ability of the consortium management model to successfully drive the development of new therapies, including new antibiotics, remains uncertain.

² IMI. *Innovative Medicines Initiative 2 Joint Undertaking Budget Plan 2014, Including Staff Establishment Plan 2014*. IMI. 2014.

³ IMI. "New Drugs 4 Bad Bugs." IMI.europa.eu. IMI, n.d. Web. 23 Oct. 2014.



Those uncertainties notwithstanding, the EU has clearly demonstrated global leadership in the fight against drug-resistant infectious disease. We applaud efforts undertaken in the EU to date, which include but also go beyond PDPs.⁴

Among EU member states, at least several have demonstrated leadership in their own capacities on matters pertaining to antibiotic resistance. The United Kingdom (UK), for example, has created an independent review commission on the economic impediments to antibiotic drug development, the results of which will likely support new legislation to help mitigate current hurdles. Additionally, a high-level working group established in the UK is actively exploring new business models for antibiotics (an initiative known as “Chatham House”). The output of the Chatham House efforts will support the newly launched DRIVE-AB⁵ initiative, a multi-year IMI-funded program that will further assess the economics of antibiotic drug development.

At Janssen, we believe the U.S. has a special opportunity to complement the PDP and other programs advanced by the EU and EU Member States, and to demonstrate its own global leadership with a set of fresh, bold policy incentives capable of surmounting current barriers and sparking a new era of antibiotics innovation.

The Honorable Marsha Blackburn

- 1. Our committee has enacted important reforms like the GAIN Act to stimulate development of new antibiotics, but realize more work needs to be done. It is my hope that as part of the 21st Century Cures effort we will put additional incentives in place for antibiotics that are designated as Qualified Infectious Disease Products (QIDPs). What other specific incentives do you recommend Congress considers for FDA designated QIDPs?**

Looking ahead to “GAIN II”-related efforts, we recommend that Congress advance a “menu” or “basket” of incentives capable of attracting a larger number and wider range of innovators to the field of antibiotics R&D. At Janssen, our analysis of various incentive

⁴ Beyond IMI, its PDPs and ND4BB program, the EU has initiated a number of other efforts that educate Member States and their citizens with regard to the need to stimulate R&D for anti-infectives in the EU. These additional efforts include the following initiatives:

- In 2009, during its tenure in the EU presidency, Sweden advanced antimicrobial resistance as an EU-wide priority.
- In 2011, the EC issued a five-year “Action Plan against the Rising Threats from Antimicrobial Resistance (AMR).” The EC added additional research funding through the IMI 6th Call on AMR, which supported a part of the Action Plan.
- The European Parliament approved a Resolution in 2012 to address the “Rising Threats of Antimicrobial Resistance.”

⁵ DRIVE-AB stands for Driving Reinvestment in R&D and Responsible Antibiotic Use.



models suggests that three in particular merit inclusion among those contemplated for GAIN II legislation.⁶ They are as follows, listed here in order of anticipated effectiveness:

1. A Transferable Regulatory Exclusivity Incentive (TREI) program;
2. Public-sector underwriting of both early- and late-stage development;
3. Prize models.

As underscored in my testimony, the creation of a special incentives framework for antibiotics innovation, sufficient to attract the world's best and brightest to this great challenge, must be a primary point of focus as Congress examines solutions to the current crisis. Combinations of these and other incentives would, in our view, substantially expand the pool of innovators participating in antibiotics R&D.

2. **Congress via the GAIN Act gave the FDA a very important tool, to designate certain anti-infectives such as QIDPs; and the agency is made good progress on QIDP guidance, as well as designating over 30 developmental antibiotics as QIDPs. If we create other incentives as we should -- real incentives are needed -- we must avoid a situation where there is confusion and differences over what qualifies for which type of incentive across different agencies of HHS. Will you respond to this statement?**

At Janssen, we agree that definitions should be simple and focused. The GAIN Act included such a designation when it was crafted, targeting its incentives to areas of the greatest and most urgent unmet medical need. For new reforms, we suggest maintaining this narrow focus, even limiting eligible products further to those that both meet an unmet medical need and address infections associated with high mortality rates or significant patient morbidity.

The Honorable Gene Green

1. **We have heard a lot of talk about the inherent lack of incentives for drug companies to develop new and novel antibiotic medicines. Why is it that the package of current incentives is not enough to stimulate new drug development? And from your perspective, what is required to solve this problem?**

⁶ Of note, per our internal analysis, less effective incentive models include reimbursement adjustments and tax credits.



The package of current incentives for antibiotics R&D in the U.S. is insufficient because it fails to overcome a major challenge facing antibiotics developers today: no clear commercial viability, no clear return-on-investment potential. While current incentives have streamlined the regulatory pathway for new antibiotics, and provided some modest financial incentives for their development, the overall costs and risks of antibiotics R&D remain disproportionately high relative to the potential for financial reward. This area of research is unique for many reasons,⁷ and thus requires a unique and uniquely robust set of incentives to drive progress.

While the GAIN Act certainly recognized the uniqueness of antibiotics, and while it marked an important first step toward spurring greater investment in antibiotics R&D, the need for bolder action remains.⁸

As a next step, to help create the potential for innovator rewards while promoting antibiotic stewardship principles that do not tie financial rewards to the overuse of novel antibiotics, we recommend the establishment of a new package of policy incentives that include, for example,

1. A Transferable Regulatory Exclusivity Incentive (TREI) program;
2. Public-sector underwriting of both early- and late-stage development; and
3. Prize models.

From our company's perspective, no proposed U.S. legislation in view at present offers incentives sufficient to turn the tide against drug-resistant bacteria. Though laudable in their intent, proposals such as those included in the current DISARM⁹ Act lack the potency to support meaningful progress. Incentive models such as TREI, by contrast, offer a viable pathway forward for investment in this and other categories of medical products marked by high social value but limited to no commercial value.

2. **We have heard from witnesses on the issue of antibiotic incentives also discussed the importance of stewardship, and you brought up the importance of appropriate use in your testimony. When we are thinking about strategies to combat antibiotic drug resistance, how should incentives for innovation be considered in relationship to stewardship strategies?**

⁷On this point, it is reasonable to suggest that some new antibiotics developed against drug-resistant bacteria may have different revenue profiles entirely, in some cases developed "in trust," to be placed under the stewardship of others such as public-sector disease control agencies. This scenario is particularly out of concert with standing business models for pharmaceutical R&D.

⁸Tellingly, the CBO Score for the GAIN Act was zero.

⁹DISARM stands for *Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms*.



At Janssen, we support vigorous antibiotics stewardship policies such as those proposed by the U.S. Centers for Disease Control and Prevention (CDC)¹⁰ and others discussed at the hearing on September 19. Stewardship programs play a vital role in managing the overuse of antibiotics and preserving their effectiveness over time. Such programs should be pursued in parallel with, and should be seen as on par with, programs to stimulate R&D toward new antibiotic medicines. Some programs can achieve both innovation and stewardship aims simultaneously: The Transferable Regulatory Exclusivity Incentive (TREI), for example, furthers stewardship aims by de-linking the financial return for a new antibiotic from its use.

3. You mentioned Transferable Market Exclusivity (TME) as a pull-based incentive that could encourage innovation by affording companies a defined risk period of market exclusivity that can be applied to any compound. Will you elaborate on how you believe TME could be structured to maximize its advantages and minimize downside risks? What guardrails you see necessary to incorporate in any such program?

As described in my testimony, one of the main barriers to industry investment in antimicrobial drug development is the fact that the expected revenues for such drugs are uncertain and significantly lower, and the risks of research higher, than for drugs in other therapeutic areas. Transferable Market Exclusivity—referred to here as the Transferable Regulatory Exclusivity Incentive (TREI)—can help to address this imbalance by enhancing the expected returns from approval of a qualifying antimicrobial drug. This improved equilibrium is accomplished by permitting the company responsible for the antimicrobial drug to transfer a portion of that drug's regulatory exclusivity to another drug (the "recipient drug"). The increased revenues from the recipient drug partially compensate for the lower revenues from the antimicrobial drug, thereby increasing incentives for companies to invest in research and development activities for antimicrobial drugs.

TREI can be structured in a variety of ways. The TREI proposal outlined below includes a number of "guardrail" provisions designed to protect potentially impacted stakeholders, such as generic drug manufacturers, while stimulating new and sustained investments in antibiotics R&D. These proposed provisions are as follows:

- Limitation to qualifying antimicrobial drugs. By passing the GAIN Act, Congress recognized that the failure of antimicrobial product development to keep pace with the evolution of pathogens constitutes a public health crisis. Like the GAIN Act, the TREI proposal is limited to antimicrobial drugs intended for serious or life-

¹⁰ CDC. "Core Elements of Hospital Antibiotic Stewardship Programs." Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, 04 Mar. 2014. Web. 23 Oct. 2014.



threatening infections. The TREI proposal is further limited, however, to drugs that meet an unmet medical need and address infections associated with high mortality rates or significant patient morbidity.

- Maximum transfer of 12 months. Although qualifying antimicrobial drugs are granted a number of years of regulatory exclusivity upon approval, the 12-month maximum for transfers of exclusivity reduces the potential that a company will receive a windfall for its development of a qualifying antimicrobial drug.
- Minimal disruption of generic development. A recipient drug must have at least four years left of its own regulatory exclusivity or at least four years of patent life remaining on a patent covering the drug. Because generics of the recipient drug generally cannot be approved by FDA until expiration of the recipient drug's regulatory exclusivity and patents, this provision gives generic companies significant notice of the additional exclusivity and allows generic companies to make informed decisions about product development.
- Private sector donations to NIH. The owner of a recipient drug must make donations to NIH, not to exceed 5 percent of TREI-derived sales, for purposes of funding grants for basic antimicrobial research. Such donations would provide a stream of new funds for infectious disease research.
- Patient assistance programs. The owner of the recipient drug must make donations to patient assistance programs that are designed to help financially needy patients obtain access to FDA-approved drugs in the therapeutic area the recipient drug is intended to treat. These donations would provide important safety-net assistance for patients who cannot afford their cost-sharing obligations for prescription drugs.

The ways in which this TREI proposal is structured helps to maximize its public health advantages and minimize downside risks, including risks to generic manufacturers. We believe this TREI model is an especially strong option for reinvigorating development of antimicrobial drugs and getting more innovative therapeutic options to patients, sooner.



It is my hope that the written responses provided here have proven helpful to Members of the Subcommittee. Please feel free to contact me should you or your colleagues wish to discuss these topics in greater detail.

Sincerely,

A handwritten signature in black ink, appearing to read "Adrian Thomas".

Adrian Thomas

Vice President, Global Market Access & Global Public Health

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS
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October 15, 2014

Mr. Kevin Outterson
Professor of Law
Boston University School of Law
765 Commonwealth Avenue
Boston, MA 02215

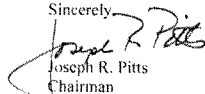
Dear Mr. Outterson:

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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

Boston University School of Law

765 Commonwealth Avenue
Boston, Massachusetts 02215
www.bu.edu/law



October 28, 2014

The Honorable Joseph R. Pitts
Chairman, Subcommittee on Health
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515-6115

Re: "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development," September 19, 2014

Dear Chairman Pitts,

Thank you for the opportunity to testify on this important matter. We cannot allow the most important drug class in human history to be lost. Today we face Ebola; next time it could be drug-resistant bacteria originating in our hometowns. We need urgent action that is much bolder.

You asked me to respond to written questions from Members. The questions and my responses are as follows:

The Honorable Joseph R. Pitts

- 1. What are other countries or the European Union doing to help spur research and development for anti-infectives? Which initiatives are working well and which will likely have the most significant impact to draw more companies to anti-infective product development moving forward?**

My response:

The most advanced efforts abroad are in Europe, particularly in England, Sweden and the European Union. Current antibacterial R&D initiatives in Europe are larger than in the US, and include significant studies on the economics of antibacterial drug development.

In England, the Chief Medical Officer, Dame Sally Davies has long championed the issues of antibiotic resistance. Earlier this year, the Prime Minister, David Cameron, created an independent review commission to study the economic problems relating to antibiotic drug development. An interim report is due next year and the UK government is expected to take up legislation in response to this report. Over the past two years, I have led a high-level Working Group on New Business Models

for Antibiotics for the Royal Institute of International Affairs (Chatham House). England is making significant strides to building a better business model for antibiotics.

England is also home to the Longitude Prize, which has announced a £10 prize for a rapid point of care diagnostic that would help reduce unnecessary antibiotic use globally. Most antibiotics are prescribed without diagnostic certainty and in many cases the antibiotic is entirely unnecessary.

Sweden held the Presidency of the EU in 2009 and focused on antibiotic resistance. These efforts raised the profile of resistance across Europe, leading to the €700 million New Drugs for Bad Bugs ("ND4BB") program in the Innovative Medicines Initiative. The first three ND4BB projects focused on basic antibacterial research. The fourth project, DRIVE-AB examines economic problems with antibacterial drug development. I serve as a consultant on DRIVE-AB, which has a funded budget exceeding €9 million. Three additional projects will focus on bringing Gram-negative drugs through the development pipeline to market. ND4BB is an impressive program.

Several things are notable about the European efforts.

First, the magnitude is very large, more than ten times the unofficial cost estimate of DISARM. Every expert agrees that the European efforts are still too small for the problems we face, but their efforts dwarf ours.

Second, every European initiative includes industry, government, academics and civil society working together.

Third, much of the European focus is on the economics, trying to build a new business model for antibiotics. Prominent among these is a concept called "delinkage." For antibiotics, we do not want to drive sales inappropriately. Volume-based sales lead to resistance. Delinkage provides generous rewards for innovative R&D, paying for value rather than volume.

Fourth, stakeholders in the EU are very impressed with BARDA and hold it up as a model for their efforts as well.

In conclusion, several valuable initiatives are underway on both sides of the Atlantic that may be opportunities for the US to coordinate a global response to resistance.

The Honorable Marsha Blackburn

1. Our committee has enacted important reforms like the GAIN Act to stimulate development of new antibiotics, but realize more work needs to be done. It is my hope that as part of the 21st Century Cures effort we will put additional incentives in place for antibiotics that are designated as Qualified Infectious Disease Products (QIDPs). What other specific incentives do you recommend Congress consider for FDA designated QIDPs.

My response:

The ERG Report described in my written testimony lays bare the economic problems facing antibacterial drug development. We require economic incentives that change company investment decisions. I suggest five actions:

- Invest in surveillance, infection control and public health. The easiest way to address resistant pathogens is to prevent infection.
- Double NIAID funds for antibacterial R&D over the next decade, without reducing funding for important work on viruses, AIDS, TB or malaria. We need research to feed ideas to industry;
- Expand BARDA's funding and mandates on a stable basis, at a funding level larger than Europe's NB4BB program. BARDA has carried several important Gram-negative antibiotics across the "valley of death;"
- Give refundable tax credits for qualified infectious disease clinical trial expenses; and
- Significantly increase reimbursement for antibiotics, increasing US spending by more than \$1 billion per year, approximately 100 times larger than the unofficial annual cost estimate for DISARM. That bill correctly focuses on reimbursement, but it is far too small in size to have an appreciable effect.

Every industry and academic leader that I have spoken with agrees with the basic thrust of these five actions, even if they might be unwilling to be so plain spoken about the limits of DISARM.

In conclusion, act boldly to significantly improve economic incentives for antibiotics.

2. Congress via the GAIN Act gave FDA a very important tool, to designate certain anti-infectives as QIDPs; and the agency has made good progress on QIDP guidance, as well as designating over 30 developmental antibiotics as QIDPs. If we create other incentives as we should – real incentives are needed – we must avoid a situation where there is confusion and differences over what qualifies for which type of incentive across different agencies of HHS. Will you respond to this statement?

My response:

QIDP was appropriate for GAIN because the incentive -- 5 years of additional exclusivity -- had a zero CBO score. But when we start spending real money, as I suggest is imperative, then we need to be more carefully tailored across the life cycle of drug development:

- For the doubling of NIAID funds, QIDP is not needed. Let NIH/NIAID manage the grants, looking for both basic research and major breakthroughs;
- BARDA already demands a much higher standard than QIDP. This model works very well and deserves additional funding that is stable over time. BARDA is a truly innovative and important program to carry antibiotics across the “valley of death;”
- Limit tax credits to qualified infectious disease clinical trial expenses, perhaps built on QIDP; and
- For reimbursement after approval, QIDP is far too broad for DISARM or any more powerful version of DISARM. To be blunt: every new molecular entity (NME) antibiotic will probably qualify for QIDP. Probably every NME antibiotic from the past several decades would have qualified. The standard is too easy to meet if we have limited funds and have to prioritize. We should pay for value, not just FDA approval.

In conclusion, business realities are different at various stages of the antibiotic product life cycle. We need carefully designed incentives at each stage. QIDP is not a “one size fits all” solution.

The Honorable Michael C. Burgess

1. Some in Europe are debating a new system that would change the traditional drug commercialization model, whereby an antibiotic company would receive payment from some third-party for developing a valuable product but then would not handle the sales/distribution of that product. That is, the company would not need to deploy sales teams and whose profit would not be tied to volume sales – they call it “delinkage.” What kind of promise does a system like this have? The closest U.S. analog seems to be BARDA. Can we improve the BARDA model to work specifically in this context?

My response:

Antibiotic delinkage is simply paying for value rather than volume. Paying for volume drives resistance.

I lead the Working Group at Chatham House on antibiotic delinkage. Delinkage will also be a major part of the European Union's DRIVE-AB research project over the next three years and will feature prominently in the UK Independent Commission appointed by the Prime Minister. Delinkage is indeed an important effort to stimulate new antibiotics without boosting resistance. Supporters include governments, universities, and several of the global companies, most notably GlaxoSmithKline and AstraZeneca.

But I must emphasize that many of the details of delinkage will require some additional time to work out. The Chatham House Report from our Working Group will be published in December 2014; the UK Commission will issue a preliminary report in 2015; DRIVE-AB is a three-year project, ending in 2017.

My suggestion is for the US to closely collaborate with this process in Europe and to adapt these ideas to the US context. Our health care system is different from those in Europe and the precise contours of delinkage might well differ here. A study provision should be attached to DISARM to evaluate delinkage in the US context.

In any event, US and European efforts should be coordinated at the highest levels, together with any other nation willing to work together to ensure that antibiotics are not destroyed. That coordination might require some significant diplomatic work around a framework that moves every country in the correct direction.

You also mentioned BARDA. I strongly support BARDA; it is a very effective program, acting like a venture capital fund providing non-dilutive capital. Expanding BARDA to include delinkage will require significantly larger funding that must be stable over a number of years. Companies need to be able to count on those funds being available when their drug is ready. My suggestions for BARDA:

- Expand the Congressional mandate beyond biodefense to include all resistant pathogens that threaten US health;
- Replenish funding on a stable, long-term basis;
- The funding amount should be larger than the European Union's ND4BB program; and
- Also emphasize vaccines, diagnostics and other technologies that blunt resistance as well.

In conclusion, deepen our commitment to BARDA, evaluate delinkage, and coordinate with other countries to counter the threat of resistance.

Thank you for this opportunity. I will send you a copy of the Chatham House report when it is finalized in December.

Sincerely,

A handwritten signature in black ink, appearing to read "Kevin Outterson", with a stylized flourish extending from the end.

Kevin Outterson
Professor of Law and N. Neal Pike Scholar in Health and Disability Law
Boston University

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS
Congress of the United States
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COMMITTEE ON ENERGY AND COMMERCE
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WASHINGTON, DC 20515-6115
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Minority (202) 225-3641

October 15, 2014

Mr. Allan Coukell
Senior Director
Drugs and Medical Devices
The Pew Charitable Trusts
901 E Street, N.W.
Washington, D.C. 20004

Dear Mr. Coukell:

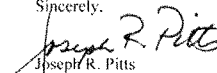
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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,


Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

Allan Coukell, Senior Director, Drugs, Medical Devices, and Food Safety, Pew Charitable Trusts

Questions for the record for September 19 hearing “Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development”

The Honorable Joseph R. Pitts

- 1. What are other countries or the European Union doing to help spur research and development for anti-infectives? Which initiatives are working well and which will likely have the most significant impact to draw more companies to anti-infective product development moving forward?**

To support antibiotic development, the European Union established the Innovative Medicines Initiative (IMI), a partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations trade group. IMI includes a program called New Drugs for Bad Bugs (ND4BB), which is funding projects to develop guidelines for designing and developing new drugs to target resistant pathogens, establish a pan-European network of clinical trials sites, facilitate information sharing, and provide concrete recommendations for new commercial models that provide industry with investment incentives while ensuring that new antibiotics are used wisely. Four of these projects are ongoing while another three projects are still in development. While it is too soon to assess the impact of the ND4BB program, companies have welcomed the EU’s public-private partnership approach to tackle antibiotic resistance and address some of the key barriers to the development of effective antibiotics.

The Honorable Marsha Blackburn

- 1. Our committee has enacted important reforms like the GAIN Act to stimulate development of new antibiotics, but realize more work needs to be done. It is my hope that as part of the 21st Century Cures effort we'll put additional incentives in place for antibiotics that are designed as Qualified Infectious Disease Products (or QIDPs). What other specific incentives do you recommend Congress consider for FDA designated QIDPs?**

Pew supported the GAIN Act as an important first step to addressing some of the economic challenges to antibiotic development and we appreciate the Committee’s leadership on this issue. To date, 39 antibiotics in development have received qualified infectious disease product (QIDP) status under GAIN. Of these, three have recently received FDA approval, with a fourth decision expected by the end of this year. But more needs to be done to encourage drug companies to enter and stay in antibiotic development, particularly for drugs to treat multidrug resistant infections. For this reason, Pew supports the creation of a new regulatory pathway for antibiotics that meet an unmet medical need and are intended to treat serious and life-threatening

infections in a limited population of patients. Any drug approved under this pathway would also qualify as a QIDP and therefore be eligible for additional exclusivity, as well as fast track and priority review, as authorized under GAIN.

Representatives Gingrey and Green and their bipartisan colleagues have introduced the Antibiotic Development to Advance Patient Treatment (ADAPT) Act to create a limited population antibacterial drug (or LPAD) pathway. ADAPT would allow drug developers to bring drugs through the approval process for narrow indications, which would make these clinical trials more feasible than the larger clinical trials that companies now have to conduct in order to get a broader indication.

2. **Congress via GAIN gave FDA a very important tool, to designate certain anti-infectives as Qualified Infectious Disease Products (QIDP); and the agency has made good progress on QIDP guidance, as well as designating over 30 developmental antibiotics as QIDPs. If we create other incentives as we should – real incentives are needed – we must avoid a situation where there's confusion and differences over what qualifies for which type of incentives across different agencies of HHS. Will you respond to this statement?**

The National Institutes of Health, the Biomedical Advanced Research and Development Authority, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services, as well as agencies outside of HHS and academic and industry partners, can all play roles in addressing the economic, regulatory, and scientific challenges that stymie antibiotic drug development

It is certainly important that leaders in Congress and the Administration ensure that federally funded research and incentives are transparent and coordinated, but differences in incentive programs are not inherently problematic. Different agencies at HHS can influence drug development at different stages in the process, and the barriers at each of those stages are different, and thus we would expect responsive policy solutions to also be different. For example, if NIH were to only fund research anticipated to lead to the development of QIDPs, or, more narrowly, drugs that would qualify for an LPAD pathway, significant advancements in basic science that could lead to new classes of broad-spectrum antibiotics could be missed. But later in the development process – e.g. as product sponsors are seeking FDA approval -- barriers may be more significant for drugs targeting narrow populations where clinical trials are more difficult and thus policy solutions targeting that smaller subset of drugs, such as the ADAPT Act, are more appropriate.

Given the urgent need for new antibiotics, it is important that everyone involved in the drug discovery process understand what programs exist within the federal government to facilitate antibiotic development. We believe that effective outreach to the research community, including

academic and industry researchers, is an essential component of any meaningful national strategy to address antibiotic resistance.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

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October 15, 2014

Dr. John H. Powers
Associate Clinical Professor of Medicine
George Washington University
2300 Eye Street, N.W.
Washington, D.C. 20037

Dear Dr. Powers:

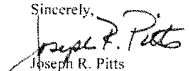
Thank you for appearing before the Subcommittee on Health on Friday, September 19, 2014, to testify at the hearing entitled "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, October 29, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,


Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment