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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, D.C.

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.

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 "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, Congressman 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 phase.

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.

Dr. Burgess. Thank you, Mr. Chairman, and 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 popular 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 taking 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 is only -- he couldn't produce a lot of penicillin, and it was Andrew Moyer, a -- 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 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 follows:]

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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.

Mr. Pallone. Thank you, Chairman Pitts. And 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 resistance bacteria or super bugs is growing, yet the supply of new antibiotic drugs is dwindling due to drug manufacturers' declining interests 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 infection. Additionally, 5 to 7 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 cost on patients and the healthcare system.

And due to the current state of the market, manufacturers are incentivized to focus their efforts elsewhere at the expense of R&D with new antibiotics to combat these rapidly evolving strains of bacteria. And this reason is why Congress included many of the provisions of the GAIN Act in 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 exclusivity. 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, and 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 market and regulatory exclusivity, 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.

But there are some ideas that are worth further examination, such as the ADAPT Act introduced by Congressman 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, and I think we all agree this is an issue which warrants further action, and I welcome the opportunity to hear from our witnesses today, and 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 in the national Combating Antibiotic Resistance Bacteria, CARB strategy. We need to control bacteria and carbs, I guess.

Recently, both the World Health Organization, 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 the 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 new novel antibiotic drugs. Antibiotics have saved millions of lives by treating infections caused by bacteria 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 by 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.

Dr. 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, 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, and they 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, and in July of 2012. As many of the witnesses' testimony 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 is the 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.

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 in -- 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 a better data -- 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:]

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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 51(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 follows:]

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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 is -- we have been implementing. In Europe, the Innovative Medicines Initiative, which is a public/private partnership, has 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, and 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 tests -- testing methods.

Despite all this progress, we must recognize that a robust pipeline of new investigational antimicrobials does not currently exist, nor are there 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 right now, which we do need urgently, new treatments for resistant organisms, although we need that urgently, we need to keep introducing additional treatments against common conditions as well, since our existing armamentarium is inevitably going to weaken over time; so 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:]

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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 the -- I think the threat here to public health is that we can have emerging epidemics of these organism that they will spread. Right now they are fairly limited and sporadic, but they 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 used 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. Okay. 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 when we develop an antimicrobial, 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 under many different mechanisms of 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 we -- 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, you know, 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 -- 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, I -- 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, I am not the most qualified person to make those tradeoffs. I think Congress is really -- has to weigh those.

I can tell you that the urgency, 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. And 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 stewardships, including the Get Smart Campaign, and 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 use 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 that -- but it is CDC primary the lead on improving better use in health care, and that is a multi-facetted 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 -- discontinue use of important human antimicrobials for growth promotion in food animals, and we -- they have secured the cooperation of the -- 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 for -- 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's 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, and 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 the -- 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 the 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 them in broad populations is difficult, and 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, worry that they 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 the -- what the study was done on the drug and so forth. It often may be the only drug ever studied for that condition.

So our thoughts, and we have -- 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, you know, some kind of signal, some kind of message that this is special. There is more uncertainty and also really good -- use good stewardship about 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 recognize the gentleman from Georgia, Dr. Gingrey, 5 minutes for questions.

Dr. Gingrey. Mr. Chairman, thank you for recognizing me. I know that 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, just -- 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 know, 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 they are going to hang some antibiotic, even if it is wrong, they are going to start treating them, and then, all of a sudden, you know, 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, right. 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, right, and that is true for many. But for these very rare, fortunately, resistant organisms that are multi-drug resistant and 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 -- and if we enrolled thousands of people, it will have been too late, because 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, and 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 have -- we accept more uncertainty, and that means novel trials that we might do.

Dr. 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.

Dr. 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.

Dr. 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 -- 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 conversation --

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 Technology, 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, like, 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 cold -- colds or something, upper respiratory infections of one sort of 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.

Dr. Burgess. Thank you, Mr. Chairman. And Dr. Woodcock, again, welcome to our humble little subcommittee. Your last statement, diagnostics are the key, now, it is not really -- 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 is, I mean, 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, we have -- 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 actually, there are 150 different mutations in that chain, each of which may translate to a slightly different phenotype in prognosis, and so we need ways to rapidly -- that goes with cancer and many other diseases, and so 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.

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

Dr. Woodcock. Uh-huh, yes.

Dr. Burgess. Is it really possible to move the needle on that?

Dr. Woodcock. Well, I believe for the, say, 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 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, okay. No, that this didn't have a huge development program. We are offering you a tool, but you ought to be aware that -- and have 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.

Dr. Burgess. You know, on the issue of judicious use and stewardship, and I hear the birds that are set on that, but you know, 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.

Dr. Burgess. -- 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. Totally agree. It is not -- I mean, 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.

Dr. Burgess. And it concerns me that we are -- you know, 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. You know, it has to be suspected. You know, 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 what -- how much information pertains to the drug and what kind of drug it is.

Dr. Burgess. Thank you, Mr. Chairman. I will yield back.

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DCMN HUMKE

[10:00 a.m.]

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 cosponsored 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 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 you are trying to do 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 they are pretreated with different things until they get into the clinical trial, and then you have all the heterogeneity, and so -- and then you have existing therapies. It is not ethical to treat -- to have the comparison group have no treatment usually -- all right? 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. Okay.

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 trade off like 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 about another drug for pneumonia, we are not talking about that. We are talking about resistant organisms where there is really very little. 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, you know, 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, you know, 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, you know, those tradeoffs, those economic tradeoffs and I am not qualified to say what is the right course. I think that is the position 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 many, many are not being developed.

We are doing some things such as working with the National Organization for Rare Diseases and so -- 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 is 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, which is, you know, primarily CDC lead, but FDA, for example, the NARMS system, 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 a better -- doubling our efforts to incentivize antimicrobial development, and obviously there is interest in better diagnostics which is put forth in that report.

So we have a 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.

Know 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 all -- 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 Worldwide 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 we can -- 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 know, 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, and you know, 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, to where they see a business model 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 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 is some additional things we can do to incentivize, like the ADAPT -- 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 is government awards. Those are usually under contract. They are for certain entities -- molecular entities.

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

And I didn't know that until I talked to them, that they have screened like, you know, large numbers of molecules and pathways and so forth, and it is harder, it is hard to find in new generation, 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. Okay? And they don't have that faith right now, I can tell you.

So I don't think whatever has been done is enough 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 us -- 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 both -- a lot of ears on it.

And I am going end just with this, this labeling debate, the way I understand it. I also -- we went through this debate with the paper labelings and the information on pill bottles that -- and no one reads these things. 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?

I mean --

Mr. Shimkus. Please do.

Dr. Woodcock. --I think the FDA -- the Center for Drugs 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. Okay? 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 a electronic physician label which is that thing that is folded up inside the pill bottle. 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 at FDA, at 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, but we asked some questions -- we submitted some questions for the record in November, and to my knowledge, we haven't -- 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 never been before, treated before within the last 5 years? How many new

biomarkers did the FDA accept for the first time used in the last 5 years? If you can provide that answer.

Dr. Woodcock. Yes. We will -- 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 have approved -- 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 on 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. Okay. 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 the 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.

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

Mr. Bilirakis. Okay. 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 World Health, and I think the executive order yesterday and the strategy conceives of much tighter collaboration with WHO in a very concerted way.

Mr. Bilirakis. Okay. 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. Outterson 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 resistant, you know, drugs for antimicrobial resistance. I do agree that -- I think the streamlining of clinical trials for resistant organism will stimulate development

in that area. Why? Partly because developers have told me that.

Part two, because we know from experience that if we have a clear path to market and people understand that, they are willing to put their money down on a, you know, on a kind of bet that they will have a molecule that can get through.

But this is clearly not sufficient. Number one, we are only talking about the most resistant organisms here and a 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 idea and the streamlining of clinical trials, which wouldn't just decrease the time frame, it would also the decrease the cost and the, you know, 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 respond.

[The information follows:]

******** COMMITTEE INSERT ********

Mr. Pitts. 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 chairman -- or vice president of the Global Market Access and Global Public Health, Janssen Global Services; and then Mr. Kevin Outterson, professor of law, Boston University School of Law; Mr. Allan Coukell, senior director Drugs and Medical Devices of the Pew Charitable Trust; and Doctor 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 OUTTERSON, 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 being 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 lead 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 belive 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:]

******** INSERT 2-1 ********

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 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 researched; 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:]

******** INSERT 2-2 ********

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, biotechs 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:]

******** INSERT 2-3 ********

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 this is based on -- 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 we don't really -- 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 this is a -- 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 Astrizinica 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. You know, 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. You know, 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 HABP/VABP. Okay? 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, you know, 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 a 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 has a, you know, it doesn't have that sort of effect. What the companies need is money, not the promises of earlier approval.

Thank you.

Mr. Pitts. Chair thanks the gentleman.

[The prepared statement of Mr. Outterson follows:]

******** INSERT 2-4 ********

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 Limit 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:]

******** INSERT 2-5 ********

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 cochair 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, quote "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 focusses 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 continue 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:]

******** INSERT 2-6 ********

RPTS KERR

DCMN ROSEN

[11:00 a.m.]

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 conducted, and finally, which enables us to balance our risk and our return.

Mr. Pitts. All right. Let's -- 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 for -- 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, you know, lightning doesn't always strike in New Brunswick where our headquarters is. Lightening 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 and gold 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, that -- 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 QDIPs -- 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. Outterson, 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, you know, pathogen. And that -- that list does not require any of the pathogens to be resistant. It includes most species known to cause any disease in humans. So the -- and that was done for -- 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 steps that -- 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 flat-lined 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, you know. All of the -- some of

the best gram negative molecules in development now have a lot of money in them from BARDA, and BARDA has --

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 -- 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.

Dr. Gingrey. That was a very interesting line of questioning from the distinguished ranking member of the committee, and Mr. Outterson, your response was not unexpected. But, you know, there is something to say for the profit motive as well. I mean, you know, 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, you know, 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 want -- 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 this -- what we have learned this morning in this rather 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. Outterson? 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 certain -- a number of doses at the end of a product, so that it is -- they are bought up. I think perhaps that is what you meant by the insurance model. So you never -- 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 mean I have heard it many -- 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 they are not -- the companies cannot just be notified by -- motivated by the greater good.

Dr. Gingrey. You know, 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 mean, 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 Hillan. You mention in your testimony that half of the investment cost necessary to support your drug, SIRTURO; is that correct?

Dr. Hillan. Plazomicin.

Dr. Gingrey. Yes.

Dr. Hillan. Plazomicin.

Dr. 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 -- or 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 --

Dr. Gingrey. Well, let me -- 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 -- 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 is -- it has caused a significant overhead.

Dr. 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 be -- 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. -- 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 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 -- 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, because 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 infection know to do that. Usually it is done because we -- 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. Okay. 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 the 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 we -- 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 -- I don't know we would call ourselves friends, but we are certainly, I would say, professional colleagues that work together.

Mr. Shimkus. Yeah.

Dr. Hillan. We have had --

Mr. Shimkus. Well, you know, the point -- I mean, 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 policy -- public policy folks here, and so we have to have that communication. We have to be in a relationship, and that is -- that is what I am taking from this because a lot of ideas. And you know, I took that -- 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 -- we have got to switch those timelines, and there is 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, my -- you are the experts, you are the doctors, you are the scientists and stuff, can there

be -- how do we write into legislation the flexibility to incentivize while protecting public health? And can we do that? And then that is the -- 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. Shimkus. 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, you know, if we go down the route of trying to beat up corporate America in this process, we are not going to be friends. You know, 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.

Dr. 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.

This has been -- 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.]