REVIVING THE PIPELINE OF LIFE-SAVING ANTIBIOTICS:
EXPLORING SOLUTIONS TO SPUR INNOVATION

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REVIVING THE PIPELINE OF LIFE-SAVING ANTIBIOTICS: EXPLORING SOLUTIONS TO SPUR INNOVATION

TABLE OF CONTENTS

NEED NEW ANTIBIOTICS

INTRODUCTION

Antibiotic-resistant infections are a growing public health threat. At the same time, antibiotic innovation is waning. Howard Florey, the co-discoverer of penicillin, lived to see 13 new classes of these drugs make it through the pipeline. Since his death in 1968, however, there have been just two.

The Pew Health Group (Pew), the Infectious Diseases Society of America (IDSA), and the Pharmaceutical Research and Manufacturers of America (PhRMA) hosted a one-day conference, *Reviving the Pipeline of Life-Saving Antibiotics: Exploring Solutions to Spur Innovation,* at the offices of The Pew Charitable Trusts in Washington, DC, on September 22, 2011. About 100 attendees, including infectious diseases physicians, pharmacists, economists, pharmaceutical industry representatives, and government officials, explored ways to overcome the challenges that hinder the development of new antibiotics (drugs designed specifically to kill disease-causing bacteria, as opposed to viruses, fungi, and other pathogens).

The conference, moderated by Allan Coukell, director of medical programs at Pew, was divided into three sessions. During the first session, panelists identified the greatest unmet health needs requiring new antibiotics. The second session was aimed at addressing the current regulatory and scientific challenges that hinder antibiotic development. Throughout the third session, speakers and panelists examined economic incentives that could spur greater innovation.

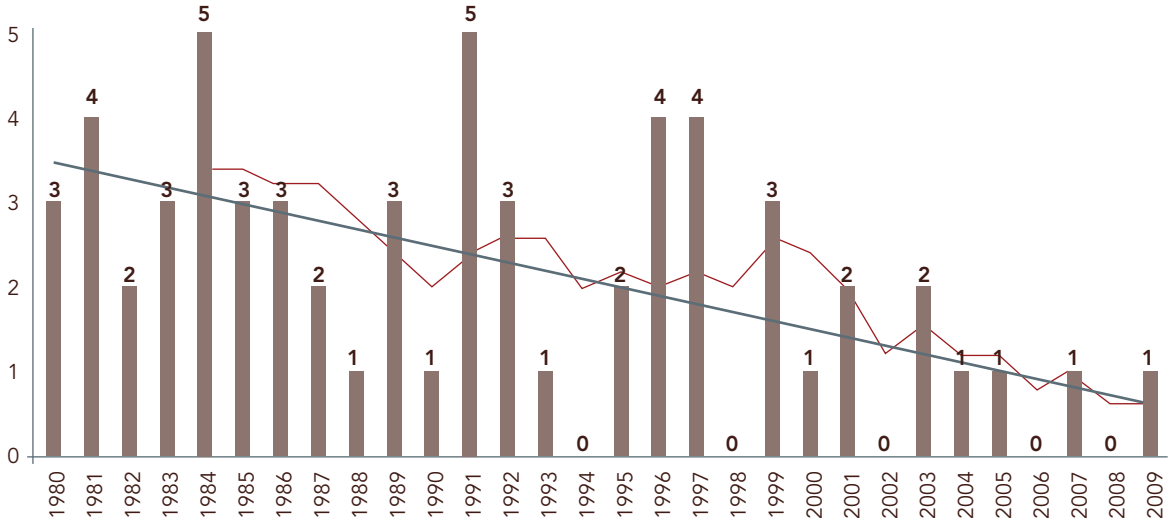
Although the conference was not designed to generate consensus, some common themes emerged:

- Several factors make antibiotic research and development challenging, including drug resistance and the low return on investment compared with other therapeutic areas.
- The greatest immediate public health need is for antibiotics designed to treat infections caused by multidrug-resistant,

Gram-negative bacteria, such as *Escherichia coli, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae.*

- The U.S. Food and Drug Administration (FDA) should provide clearer guidance to industry about conducting antibiotic clinical trials (i.e., testing in humans), including feasible study designs.
- Faster diagnostic tests are needed to identify suitable patients for enrollment in antibiotic trials. New diagnostics can also guide proper usage of these drugs in clinical practice.
- Drug companies require better financial incentives to develop antibiotics, and a variety of potential policy solutions exist. Panelists emphasized that no single incentive is sufficient to address the multiple challenges impeding research and development.

Figure 1. Systemic Antibiotics Approved by FDA (1980–2009)
Total Approvals, Linear Trend, and Five-Year Moving Average



FDA approved 29 systemic antibiotics (those that fight infection throughout the body) in the 1980s, 23 in the 1990s, and only nine in the 2000s.

Source: Adapted from presentation by John Powers

THE ANTIBIOTICS WE NEED MOST

I. THE ANTIBIOTICS WE NEED MOST: CURRENT AND ANTICIPATED MEDICAL NEEDS

The purpose of the first session was to pinpoint the most urgently needed antibiotics, including those for vulnerable patient populations.

Officials from the Centers for Disease Control and Prevention (CDC) and FDA each affirmed that antibiotic-resistant infections and the lack of new drugs to treat them pose a significant public health threat. Steven Solomon, director of CDC's Office of Antimicrobial Resistance, said that infections contracted in health care and community settings, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae,* are a major worry. To illustrate his concern, Solomon noted that bacteria isolated from patients with *Streptococcus pneumoniae* infections, which were once easily treated with antibiotics such as penicillin and erythromycin, are now demonstrating resistance or decreased susceptibility to those drugs in 10 to 25 percent of cases. He also said that the emergence of resistance to the cephalosporin class of antibiotics in bacteria causing gonorrhea was a "particularly alarming threat." Whereas about one in 1,000 gonorrhea infections were cephalosporin-resistant in 2000, that rate jumped to one in 100 by 2010.[1]

Edward Cox, director of FDA's Office of Antimicrobial Products, said, "We know we need additional antibacterial drugs to treat patients' infections today. We know, given the biology of resistance, that's going to continue on into the future." Cox noted that while there has been an encouraging uptick in the number of new antibiotics in development, many of these drugs are still in the early and volatile stage of the process. "There can be shifts that occur from year to year as compounds enter and exit development," he said. "I think it is very fragile in the field." He also acknowledged challenges regarding the regulatory pathway for developing new antibiotics, telling the audience that FDA is "committed to try and work to solve these problems."

Heightened Concern over Gram-Negative Bacterial Infections

While panelists expressed concern about overall antibiotic resistance, they were particularly alarmed by the growing drug resistance of Gram-negative bacteria and said there was an urgent need for additional medications to fight these pathogens. These microbes can cause serious diseases, including meningitis, pneumonia, gonorrhea, and infections of the blood, urinary tract, and intestines. They are distinguished from Gram-positive bacteria, in part, by an extra outer membrane that makes them more difficult to attack with antibiotics.

David Gilbert, chief of infectious diseases at the Providence Portland Medical Center and chair of the IDSA Antimicrobial Availability Taskforce, presented preliminary findings from a September 2011 survey of nearly 400 infectious diseases physicians across the United States. When asked what kind of infection represented the greatest unmet treatment need, 74 percent of respondents cited those caused by Gram-negative bacteria. Drug-resistant tuberculosis (13 percent) and MRSA (9 percent) ranked a distant second and third.

A RECENT SURVEY OF NEARLY 400 INFECTIOUS DISEASES PHYSICIANS FOUND THAT 62 PERCENT HAD SEEN AT LEAST ONE PATIENT INFECTED BY BACTERIA RESISTANT TO ALL AVAILABLE ANTIBIOTICS.

The survey also asked doctors if they had ever seen an infection caused by an organism that was resistant to all available antibiotics. Gilbert reported that "a striking" 62 percent of respondents indicated they had encountered at least one such case. More than half of the physicians who had seen such pan-resistant infections—55 percent—reported that the number of these cases increased over the last two years.

Gilbert also presented survey data detailing resistant infections in four hospitals in New York and New Jersey. The "scary data" accounted for the Gram-negative organisms, he reported, specifically *Acinetobacter,* which exhibited resistance to commonly used antibiotics in most

instances. Of particular concern, up to 78 percent of *Acinetobacter* infections were resistant to imipenem, a drug that Gilbert called "our big gun."

Solomon pointed to resistance-conferring genes as a special concern. Gram-negative bacteria are particularly adept at acquiring and sharing genetic information with each other, which can accelerate the spread of pathogens that, in some cases, are essentially untreatable, said Solomon.

At the end of the session, Coukell posed a question to members of the panel: if you could choose only one drug to be approved in the next five years, what would it be? The panel largely agreed that new medications to treat Gram-negative infections were the most urgently needed. Solomon called the increasing rates of resistant, Gram-negative bacteria an "impending crisis." Cox emphasized that a broad approach was warranted since the biology of resistance is unpredictable and treatment needs may shift over time.

Gram-Positive Bacterial Infections Still a Threat

Several panelists asserted that new drugs were also needed to treat infections caused by Gram-positive pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus* (including MRSA).

Paul Ambrose, director of the Institute for Clinical Pharmacodynamics, said: "I think even though we have a lot of drugs, or we appear to have a fairly robust pipeline for Gram-positive drugs right now, let's not be so complacent about that." Ambrose elaborated that many of these medications "die in late-stage development." Problems can also develop after they reach the market. Several antibiotics in the fluoroquinolone family that were approved in the 1990s are no longer in use, not because they failed as therapies but "because when they got on the market, we realized that they had toxicities that we weren't willing to accept," said Ambrose. "We need to be very vigilant."

Patient Populations in Special Need of Antibiotics

A series of anecdotes illustrated how antibiotics were particularly vital treatments for children, military personnel, and those whose immune systems are being taxed by other conditions.

CHILDREN

Sheldon Kaplan, chief of infectious disease services at Texas Children's Hospital in Houston, noted that infections in children with cystic fibrosis, a genetic disease that causes mucus to build up in the lungs, presented a growing challenge. In one child he had treated recently, Kaplan identified an *Achromobacter* infection that proved resistant to "every single antibiotic" except one, piperacillin, to which it was partially resistant. In addition, Kaplan said that in a growing number of cases clinicians were forced to administer antibiotics intravenously, which can require longer hospital stays and cause complications.

Kaplan noted that medications were especially needed to treat children with Gram-positive infections. He noted that ear infections due to *Streptococcus pneumoniae* in patients at Texas Children's Hospital have shown resistance to multiple antibiotics. For the most part, only two classes of oral drugs remain potent, but, he said, doctors often avoid giving children one of them—fluoroquinolones—because of concerns about toxicity.

Kaplan also called attention to the lack of antibiotic testing in children and said pediatric studies should be launched as medications get closer to market, as opposed to several years later: "We need to have these drugs come into pediatric trials much earlier."

ANTIBIOTICS ARE PARTICULARLY VITAL TREATMENTS FOR CHILDREN, MILITARY PERSONNEL, AND THOSE WHOSE IMMUNE SYSTEMS ARE BEING TAXED BY OTHER CONDITIONS.

MILITARY

Gram-negative infections pose a particular threat to the military population, according to Duane Hospenthal, infectious diseases physician in the U.S. Army. Military patients face many of the same resistance issues as civilians, but there is the added problem of infections associated with traumatic bone, tissue, and burn injuries that soldiers sustain in combat. These are chiefly multidrug-resistant, Gram-negative infections, and patients often endure long-term therapy

to treat them. Military doctors are trying to preempt problems by preventing infections at the site of injury. "But certainly it makes us very nervous if we have no specific antimicrobial that we can add to the good surgical care," Hospenthal said.

IMMUNOCOMPROMISED PATIENTS

By treating infections, antibiotics have become critical in helping patients with suppressed immune systems survive procedures like bone marrow transplants and chemotherapy. Gilbert called this "one of the miracles" of antibiotics, but added that, due to drug resistance, some of these patients will make it through treatment only to die from an incurable infection.

Gilbert spoke of a 51-year-old female patient who received a bone marrow transplant for lymphoma and then developed pneumonia. She was immediately given several antibiotics, including vancomycin, meropenem, and tobramycin, but died 16 hours later. Cultures later showed she was infected by a strain of the bacterium *Klebsiella pneumoniae* that was resistant to every drug she was given.

Helen Boucher, director of the Infectious Diseases Fellowship Program at Tufts Medical Center in Boston, and a member of IDSA's Antimicrobial Availability Task Force, described a similar case: a young cancer patient underwent a successful bone marrow transplant, but then developed an infection in her lung that was proving resistant to every antibiotic available. The patient would likely die from her infection, not her cancer, said Boucher.

Identifying Urgently Needed Antibiotics

Throughout the day, panelists discussed how best to identify priorities for antibiotic development. Speaking during the second session, John Powers, associate clinical professor of medicine at The George Washington University School of Medicine and the University of Maryland School of Medicine and former lead medical officer for antimicrobial drug development and resistance initiatives at FDA, stressed the need to develop drugs that address public health concerns. In an analysis he and colleagues conducted, Powers found that many of the antibiotics approved in the 1980s and 1990s are no

longer available. In fact, 50 percent of the antibiotics approved since 1980 are no longer on the market, compared with 3 percent of cancer drugs, Powers said.

Antibiotics were twice as likely to be discontinued as other drugs, not because of safety concerns or because bacteria developed resistance to them, but solely because they were not being used. Drugs should be developed to meet a need, said Powers: "We don't want to put all this effort into it and, 10 years down the line, have them disappear because they really didn't address the problems we were interested in."

During the third session, Brad Spellberg of the Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles Medical Center, referenced IDSA's proposal to establish a board that would provide expertise to help pinpoint the most urgent needs and priorities now and over the next five to 10 years. This information would be reevaluated annually.

John Hollway, vice president of business development at Achaogen, a California-based company focused on developing antibiotics for Gram-negative infections with several products in development, countered that plenty of knowledge about priorities already exists. He pointed to the agreement among the first session's panelists that therapies for Gram-negative infections are most critical.

NEARLY ALL OF THE PANELISTS EMPHASIZED THAT ALONG WITH NEW DRUG DEVELOPMENT THERE MUST BE APPROPRIATE USE OF CURRENT MEDICATIONS.

John Rex, vice president of clinical infection at AstraZeneca, a large pharmaceutical company headquartered in London with an active antibiotic clinical development program and several antibiotics on the market, noted that industry has been predicting the medications most likely to meet future needs for years, and yet the products that turn out to be most valuable are often least expected. "So the idea that this board is going to know which ones to do and not and to be able to pick and choose can be tricky," he said.

Solomon pointed to the bacteria that cause gonorrhea as a good example of how resistance evolves over time and how we can use early warning signs to predict imminent medical needs and, ultimately, direct new drug development. For over a decade, Solomon said, the bacterium *Neisseria gonorrhoeae* grew significantly resistant to fluoroquinolones, a class of antibiotics that served as a primary treatment for these infections. He observed that the bacteria now appear to be developing resistance—slowly and steadily—to the next line of defense against gonorrhea, cephalosporins. Even though there "is still not a full-blown resistance [to cephalosporins] on a national scale," he said, global trends indicate that the problem will get worse. "If you look to the western U.S., you've got about double [the national rate of drug-resistant gonorrhea] because of the association with people coming back from Asia," he said. It is "absolutely critical" to learn from these emerging trends and "pivot from a research point of view as well as a development point of view on fairly short notice."

A Call for Both Conservation and Innovation

Nearly all the panelists emphasized that along with new drug development there must be judicious use of current medications. Studies have shown that up to 50 percent of antimicrobials are not used appropriately and may not even be needed in some cases, Solomon said. Clinicians must boost the lifespan of available antibiotics by using them properly and with care every time they are given to a patient.

We will always need a "pipeline of a significant number of new drugs coming down the road to rescue us," Solomon said. However, he also pointed out that because using antibiotics judiciously can slow the evolution of resistance, "we're actually going to get further behind" if we focus exclusively on innovation.

Ambrose came to a similar conclusion. "Even appropriate use of antibiotics drives resistance," he said, "so appropriate use is great . . . but it sure doesn't solve the problem."

SCIENTIFIC AND REGULATORY CHALLENGES

II. OVERCOMING ANTIBIOTICS' UNIQUE SCIENTIFIC AND REGULATORY CHALLENGES

The panelists held a broad and wide-ranging conversation on the slew of scientific and regulatory challenges facing antibiotic development. Two issues that came up repeatedly were how to design clinical trials that adequately assess both a new antibiotic's safety and efficacy and how FDA can grant timely approval to deliver that new drug to patients who need it. A related question also arose frequently: Can FDA be more flexible in setting requirements for these trials?

Mark Goldberger is divisional vice president for regulatory policy and intelligence at Abbott Pharmaceuticals, an Illinois-based pharmaceutical company with several antibiotics on the market but none in development, and the former director of FDA's Office of Antimicrobial Products. He explained, "FDA regulations as they currently exist are extraordinarily flexible." For the last "quarter of a century," he continued, FDA has used "a benefit-risk assessment that takes into account the seriousness of the disease and the availability of alternatives."

Cox, who holds the position at FDA that Goldberger once occupied, also made this point. FDA considers "the degree of unmet need, the degree of benefit that the product can bring forth," and whether the antibiotic "does something that other products can't do, provides better efficacy or better safety." These factors contribute to a greater tolerance for risk or uncertainty, he said.

Many panelists said FDA was not clear enough in its guidance and, in some cases, had not made guidance documents available. Cox noted that the agency was working to develop guidance documents that represent FDA's current thinking and are intended to help manufacturers design optimal clinical trials. As of September 2011, FDA was updating guidance documents on community-acquired and hospital-acquired

bacterial pneumonia and on complicated urinary tract and intra-abdominal infections. Cox said all of these documents would be issued in 2012. "There's a lot of work still to be done, but it's certainly something that we're committed to doing," he said.

Some panelists also noted that for several infections for which FDA has issued draft guidances the agency's requirements were too stringent and difficult—even impossible—to meet. For example, the requirement that large numbers of patients be enrolled in antibiotic trials is unrealistic, said Boucher. "For these newly emergent, super-resistant pathogens we've been talking about, this type of study often just can't feasibly be done."

As a clinician, Boucher said she is particularly worried that trial restrictions have led to a dearth of studies for the most life-threatening, Gram-negative infections, especially hospital-acquired pneumonia, which kills more than 20 percent of the patients it infects. "That's really concerning, because if no studies are going on, that really doesn't even portend hope in the next five years." She noted that IDSA has proposed the possibility of having smaller but very well conducted studies to allow conditional approval of antibiotics that are desperately needed now, with follow-up studies built in.

SOME PANELISTS NOTED THAT FOR SEVERAL INFECTIONS WHERE THE FDA HAS ISSUED DRAFT GUIDANCES, THE AGENCY'S REQUIREMENTS WERE TOO STRINGENT AND DIFFICULT—EVEN IMPOSSIBLE—TO MEET.

Cox noted that his agency has been reassessing its clinical trial requirements. "The goal is to get to scientifically sound, feasible, and ethical clinical trials," he said. "Obviously we're not trying to make the trials more difficult, but as we get to scientifically sound studies or try and learn things from what we've seen in the past, sometimes it doesn't take us in the direction of a trial that's necessarily easier to do." He added later that the agency is thinking carefully about "the balance of precision versus that of feasibility, recognizing that the ultimate goal here is public health."

Barry Eisenstein, senior vice president for scientific affairs at Cubist Pharmaceuticals, a midsized Massachusetts-based company with multiple antibiotics in clinical development and one on the market, offered a counterpoint later on: "If we try to drive the scientific perfection too hard, we'll end up with no antibiotics, and I would argue from a public policy standpoint, that would be an absolute disaster." He and other panelists stressed the need for a regulatory pathway based on more feasible trials and greater reliance on post-approval studies to monitor safety and efficacy of new antibiotics.

Powers placed antibiotic issues in a broader context, pointing out that the approval process is difficult for all kinds of medications. He pointed to a 2001 study showing that antibiotics have "the highest approval rate, the shortest development time, and the lowest development costs compared to other drugs since 1962."[2] Twenty-eight percent of antibiotics that have been submitted to FDA have been approved, he said, compared with 15 percent of drugs for cancer and 12 percent to treat pulmonary diseases. "What's that message tell you? It's hard to develop drugs everywhere."

Updating Trial Requirements to Spur Antibiotic Innovation

SETTING APPROPRIATE ENDPOINTS

Another question that arose was how best to measure the success of antibiotic clinical trials—e.g., by the number of patients who survive their infections, by measuring the size of a skin infection, or by assessing other symptoms. Such metrics are called endpoints, and many panelists asked whether those for antibiotic trials should be rethought and revised in light of new scientific developments and understanding. During the first session, Cox affirmed FDA's interest in both microbiology endpoints (the drug's effect on the bacteria) and clinical endpoints (the drug's effect on the patient). "Usually these two things are going hand in hand," he said. On the clinical side, Cox said the agency recognizes the need to consider additional endpoints other than mortality, including whether or not the drug improved the patient's overall condition.

Some panelists questioned endpoints measured soon after treatment begins because they may not always predict a clinical outcome such as

a cure. The job of the drug is to kill the bacteria, Ambrose said in the first session, but even if that happens very quickly, it does not mean the patient will actually look or feel better immediately. Symptom resolution can take as long as seven days, so forcing an endpoint at 48 hours may make it impossible to distinguish a good antibiotic from a bad one. "My fear is we're forcing these endpoints very early based on sometimes very little data, and I worry . . . that we are tossing out flawed but useful endpoints for nondiscriminatory endpoints, and we do ourselves a disservice."

Later, Boucher discussed work that IDSA, industry, academia, and the Foundation for the National Institutes of Health (FNIH) had done to assess the value of early endpoints. Industry voluntarily shared data from its trials for antibiotics used to treat skin infections and community-acquired pneumonia, she said, and researchers compared the endpoints they used with the ultimate patient outcomes—i.e., whether or not they survived their infections—and found that some early endpoints were good predictors of outcome. Recommendations were filed with FDA in August 2011. Now, five companies are using these endpoints to study antibiotics that may benefit patients. This "wasn't without controversy," she said, but "the new ideas of the early endpoint measures offered a lot of insight scientifically into how to do trials and, I think, do serve as a way forward for clinical trials."

> "THE GOAL IS TO GET TO SCIENTIFICALLY-SOUND, FEASIBLE, AND ETHICAL CLINICAL TRIALS."
>
> **— Ed Cox, Director, Office of Antimicrobial Products, FDA**

Powers said it was important to weigh the benefits of a drug based on how individual patients assess their own responses to the medicine —i.e., patient-centered outcomes—in addition to measuring how the treatment affects the pathogens, since the ultimate goal of medicine is to improve the quality of people's lives. He pointed to recent trials in urinary tract and ear infections, which showed little correlation between what the infections looked like and how the patients actually felt. "If we measure things like whether the bacteria is dead or not," he said, "we still need to know how does that translate into [whether it makes] the person feel better, function better, or live longer."

ENROLLING PATIENTS WITH PRIOR ANTIBIOTIC EXPOSURE

Panelists challenged the provision in 2009 and 2010 FDA draft guidance documents that restricted the enrollment of patients into antibiotic clinical trials who have received prior antibiotic treatment.[3, 4] It can be difficult to determine the safety and efficacy of one drug when patients have recently taken another medication designed to treat the same illness. The question arises: are the patients responding to the new drug being tested or to the initial treatment they received, or some combination of the two? Yet withholding medications from sick patients so they can later enroll in a clinical trial can endanger those patients' lives.

Eisenstein said that patients with serious infections must receive treatment right away, and every hour that doctors wait before prescribing antibiotics to patients with pneumonia, for example, increases their mortality rate. Boucher added that clinicians must also follow ethical practice guidelines that often mandate immediate therapy and, thus, may disqualify patients under treatment for serious conditions from enrolling in a trial.

Cox acknowledged that patients with acute bacterial infections are often gravely ill and require immediate treatment to survive, making enrollment in controlled clinical trials challenging. Study results can be difficult to decipher if patients have been exposed to different antibiotics prior to participating in a clinical trial. He contrasted the differences between enrolling patients in antibiotic versus antiviral clinical trials. Patients with chronic hepatitis C—a long-term, viral disease—can be screened and enrolled in a clinical trial before being treated with any existing therapies without jeopardizing their health.

Steven Barriere, vice president of clinical and medical affairs for Theravance, a California-based company with antibiotics on the market and in development, suggested that prior drug treatment may not always be as much of a problem in antibiotic trials as it is perceived to be. In a Theravance study of patients with skin and soft-tissue infections, the company compared early endpoints in patients who received prior antibiotic therapy to those who did not.[5] "There was no difference in terms of the outcome at the early endpoint," he said.

Powers noted that it was possible to enroll very sick patients in clinical trials quickly, pointing out that his hospital participated in studies for coronary heart disease where patients were enrolled within four hours of admittance to the emergency room. "It can be done," he said, "if you have the infrastructure."

Cox suggested that clinical trials consortia might help. In addition, emergency room doctors could aid in finding patients who have not received prior therapy, he said, and there might also be a role for intensive-care-unit clinicians.

PATHOGEN VERSUS INDICATION-BASED APPROVAL

FDA traditionally approves drugs based on the disease they are designed to treat. Antibiotics are unique in that they are used to fight both diseases (e.g., pneumonia) and pathogens (e.g., MRSA). Several panelists suggested that FDA should allow antibiotics to be approved based on tests against specific infectious organisms rather than against a particular syndrome (e.g., approval for MRSA rather than pneumonia). Patients infected with the same strain of bacteria but in different tissues or organs could then be enrolled in a single clinical trial. This suggestion also came up in the first session. During that discussion, Hospenthal said that clinicians usually select therapies according to the type of organism a patient is battling, so "it really comes down to bugs and not actually the infection in most cases." Gilbert said FDA would have to provide "clear guidance" on how to conduct organism-specific trials.

ALTERNATIVES TO MULTIPLE, PLACEBO-CONTROLLED CLINICAL TRIALS

One key hurdle in designing clinical trials for most antibiotics is that it is not ethical to conduct placebo-controlled studies wherein half of the infected patients are receiving no treatment at all. Eisenstein offered an IDSA-proposed idea that the National Institutes of Health (NIH) support studies to better understand the natural history of infectious diseases. If researchers knew the mortality rate for a particular untreatable, highly resistant, Gram-negative infection in the lung, for example, they could use that as a standard for assessing the effectiveness of a drug. "It's ethical, and if you can show a mortality improvement, it then makes an extremely compelling story."

A related question arose: how much data should be necessary for antibiotic approval? Rex suggested that the estimated efficacy of an antibiotic could be well established in animal tests that are conducted before moving on to human trials: "There is no other disease setting where these tools are so consistently accurate and predictive." He outlined a proposal calling for approval of a drug based on one, well-controlled clinical trial along with good supporting data. In this one-trial scenario, he proposed, drug labels would make it clear that the data were limited, and would help guide physicians on use of the medication and whether it might be helpful against other kinds of pathogens. "Physicians often are forced to make guesses," said Rex. "Let's actually make the label be as informative as possible, so they make the best guesses possible."

The Need for Diagnostics

Another major theme was the urgent need for rapid and accurate diagnostic tests not only to improve patient care but also to make clinical trials more feasible and informative.

Better diagnostics would allow doctors to tailor treatments more precisely, rather than making educated guesses and finding the most effective therapy through trial and error. During the first session, Gilbert said that without diagnostics clinicians might treat patients with five or six antibiotics before they are able to determine what kind of pathogen they are up against.

Doctors need "rapid, sensitive, specific tests" that can be used wherever the patient is—in a hospital bed, in the emergency room, in a doctor's office—so they can choose the most appropriate medication possible, said Boucher.

More germane to the theme of the second session, panelists discussed the impact that rapid diagnostics would have on clinical trials. Quick and accurate identification of infections "can help to enroll patients who actually have the disease of interest," which would reduce the number of patients needed for a trial, said Cox. "I think it's absolutely true that it would accelerate and facilitate the enrollment of patients in

clinical trials," added Barriere. Designing a test that could be done within an hour, ideally, would make trials "much easier, more efficient, [and] less expensive," said Gilbert.

WE URGENTLY NEED RAPID AND ACCURATE DIAGNOSTIC TESTS NOT ONLY TO IMPROVE PATIENT CARE BUT ALSO TO MAKE CLINICAL TRIALS MORE FEASIBLE AND INFORMATIVE.

However, development of diagnostics presents both scientific and economic challenges. Several panelists noted that aiming too high and trying to create the perfect test—both fast and accurate—could distract from the urgent care sick patients need. "It doesn't have to be a bull's-eye to be useful," said Rex. A test that could help confirm whether or not patients have the disease being studied would greatly improve clinical trial efficiency, he noted. Currently only about 30 percent of patients enrolled for a study of community-acquired bacterial pneumonia turn out to actually have the disease. So a test that "only nudged us up from 30 percent to 50 percent" would represent a great step forward by reducing costs and time. Eisenstein cautioned that calling for a perfect diagnostic might turn innovators away. Spellberg added that a test that produced an accurate answer in 24 hours would still be revolutionary.

To support the development of new diagnostics, IDSA is calling for the creation of a centralized clinical specimen repository for blood, urine, and sputum samples, which researchers could use to test new diagnostics much more quickly than currently possible.

Regulation in a Global Context

The level of concern about the current U.S. regulatory system became clear when audience member David Shlaes, founder of Connecticut-based Anti-Infectives Consulting and a consultant to the pharmaceutical industry, suggested that, because of the slow pace of new drug

development in the United States, emerging Asian economies and perhaps Russia will begin to dominate the antibiotic marketplace. When Coukell asked the pharmaceutical representatives present at the conference if they were considering developing drugs exclusively outside the United States, several participants answered affirmatively.

Cox responded that "we want drugs developed here in the U.S. We want drugs available for people here that have been studied here in clinical trials. . . . It's just going to take more work, more time, and we'll try and get [clinical trial guidelines] there as fast as we can."

UNIQUE ECONOMIC CHALLENGES

III. OVERCOMING ANTIBIOTICS' UNIQUE ECONOMIC CHALLENGES

In the third session, participants discussed the economic hurdles facing drug manufacturers as well as incentives that could spur antibiotic development and get new medicines to market. Coukell began by noting that one of the world's best-selling antibiotics earns about $1 billion a year globally. "That's not bad, but it doesn't compare to revenues from many other products, and most antibiotics don't get anywhere close to that."

Limited Return on Investment

Several panelists described the limited potential for return on investment that pharmaceutical makers see in antibiotics. Economic challenges cited by panelists included the typically short duration of therapy and the low prices of antibiotics compared with many other types of medications.

The first two speakers were Chantal Morel, research officer in health policy and economics at the London School of Economics, and David Payne, vice president of the Antibacterial Discovery Performance Unit at London-based GlaxoSmithKline (GSK), a large pharmaceutical company with antibiotics on the market and in development.

Morel and Payne each presented data from a 2003 paper to illustrate the limited return on investment for new antibiotics using a common financial measurement called net present value (NPV).[6] Pharmaceutical companies use NPV to predict the profit potential of individual medicines and to compare the benefits of investing in different types of drugs. A cancer drug, for example, has an NPV of around $300 million, and a musculoskeletal drug's NPV is about $1.1 billion. An antibiotic, by contrast, has an NPV of only $100 million. "So you can see that compared to drugs in other therapeutic categories," said Morel, "it doesn't look very profitable to invest in creating new antibiotics."

Payne said pharmaceutical companies have to make difficult choices about how to spend research and development money. In the past, antibiotics looked more financially attractive than they do now because they could be developed quickly and were less expensive to produce compared with other drugs. However, he said, today's regulations require longer trials and the inherent economic challenges of new antibiotics—low pricing, short-term therapy, and a relatively small population of patients—are all disincentives for drug makers. The likelihood that the new medication will be put in reserve immediately only makes matters worse. "So the weird thing about antibacterials as a therapeutic area is that we will spend 10 years and a lot of money creating this wonderful . . . new antibiotic," said Payne. "I think the world will say 'thank you, this is really going to make a difference,' and then they're going to put it on the shelf and only use it when they need to use it, and that is a very challenging commercial model."

Payne also talked about the failures that drug companies encounter throughout development. "This is the piece that keeps me awake at night," he said, pointing to a study published in the journal

Figure 2. Antibacterials Have Lower Net Present Value Compared with Other Therapeutic Areas

THERAPY AREA	NPV*	DEVELOPMENT COSTS	DEVELOPMENT TIME	PRICE	USE	PATIENT POPULATION
Musculo–skeletal	$1,150m	$$$$	+++	⬆⬆⬆	Chronic	Large
Neurology	$720m	$$$$	++++	⬆⬆	Chronic	Large
Oncology	$300m	$$$	++	⬆⬆⬆	Acute/ Chronic	Medium
Antibacterials	$100m	$$$	+++	⬆	Acute	Small (specialist hospital antibiotics)

*Projan 2003

Source: Adapted from presentation by David Payne; based on data from S.J. Projan, "Why is big Pharma getting out of antibacterial drug discovery?," *Curr Opin Microbiol.* no. 5 (2003): 427-30.

Nature Reviews Drug Discovery that showed the probability of success across therapeutic areas. On average, manufacturers must pursue roughly 15 leads, or drug development candidates, to ensure one successful approved drug.[7] However, an analysis of a GSK program showed that the development of one successful antibiotic required 72 promising compounds. It "doesn't look very attractive for any company to move back into this area or to expand their effort."

During the second session, Robert Meyer, head of global regulatory strategy for Merck Sharp & Dohme Corporation, a subsidiary of New Jersey-based Merck and Co. with antibiotics in development and on the market, asserted that economic and regulatory issues were intertwined and that it was necessary to overcome challenges in both areas. Meyer explained his company's formula for valuing a potential new drug: "you take what the likely revenue of the drug is after it's approved and you multiply that up front by the likelihood of its success. At Merck, we call [that likelihood] the technical and regulatory chance of success. If that [chance of] success is close to zero, it doesn't really matter what the long-term revenues will be." A medicine with the potential to generate significant revenues but little chance of regulatory approval will not rank high on a company's list of priorities, he said.

> "WE WILL SPEND 10 YEARS AND A LOT OF MONEY CREATING THIS WONDERFUL … NEW ANTIBIOTIC. … AND THEN THEY'RE GOING TO PUT IT ON THE SHELF. … AND THAT IS A VERY CHALLENGING COMMERCIAL MODEL."
>
> **— David Payne, Vice President, GlaxoSmithKline**

Push and Pull Incentives

Panelists agreed that drug makers need financial incentives to spur the development of antibiotics. Morel outlined the two main approaches to economic support: push and pull incentives. Push incentives provide research subsidies, tax credits, or other supports for developers up front. These programs can be especially attractive to small- and medium-size companies that need cash to proceed. Pull incentives,

by contrast, reward developers once the drug makes it to market. The reward might be a set amount of money at completion, agreement on higher drug pricing, or an extension of intellectual property protection.

Push and pull incentives both have problems, said Morel. A concern about push incentives is that developers may perceive them as "easy money," which could make companies less motivated to work as hard or as quickly as they should. Push incentives may also spur programs that do not pan out, leaving funders in the lurch with no return on their investment. Pull incentives, by contrast, shift the responsibility to the manufacturer. But because the cost is so high and the risk is so steep, many companies will decide not to take part. Pull incentives "may lack credibility," Morel added, because drug development takes years and the possibility of changes in the political or budgetary arenas makes it hard to ensure that the pull will still be in place.

A Pull Incentive: The GAIN Act

One example of a pull incentive is the exclusivity provision found within the Generating Antibiotic Incentives Now (GAIN) Act, which was introduced in the House of Representatives by Congressman

Figure 3. Patents and Exclusivity: IP Protection for Drug Makers

Drug makers typically enjoy two kinds of intellectual property protection for their FDA-approved products—patents and non-patent exclusivity—both of which can delay the entry of generic competitors into the market.

	PATENTS	EXCLUSIVITY
How many years of protection does it offer?	20 years from the time of filing, with up to a five-year extension under certain circumstances	Five years from the time of FDA approval for most new drugs
Which federal agency grants it?	U.S. Patent and Trademark Office	U.S. Food and Drug Administration
Can it be challenged?	Yes, judicially and administratively	Not under most circumstances
What changes under the GAIN Act?	No changes to patent protection	An additional five years for a new qualified infectious disease product

Phil Gingrey, M.D. (R-GA),[8] and in the Senate by Senator Richard Blumenthal (D-CT).[9] The GAIN Act would provide manufacturers of a qualified infectious disease product an additional five years of FDA-granted exclusivity.

The GAIN Act also contains a provision granting access to early FDA advice on approval requirements and expedited review for companies seeking to bring a qualifying antibiotic to market. It also would mandate a review of current clinical trial guidelines.

Robert Horne, Congressman Gingrey's senior health policy advisor, said he was realistic about how much the GAIN Act could accomplish. It will not solve the entire problem of antibiotic development, he said, but even if the GAIN Act got just three new drugs approved over the next 10 years, "we've done something good" by creating a precedent of success, and "the one thing I do know is that Congress likes precedent."

MANY PANELISTS MADE IT CLEAR THAT DRUG DEVELOPERS NEED MORE THAN ONE KIND OF FINANCIAL INCENTIVE TO SPUR ANTIBIOTIC INNOVATION.

Some panelists raised concerns about the overall benefit of an exclusivity extension as a financial incentive. Spellberg pointed out that it would provide limited financial rewards because of the economic principle of discounting, which says that money delivered in the future is worth less than the same amount of money today. Payne added that GSK's own economic analysis showed that up-front funding (e.g., through funding partnerships and tax credits) is more attractive than getting an additional five years of exclusivity. He also pointed out that the GAIN Act will not help with new classes of antibacterials, which start out with a substantial patent life at the time of market entry. GSK has two such drugs in phase two trials. Still, Payne acknowledged that the GAIN Act is critical to advancing the field: "I can tell you that this Act is the first time it's actually got industry together to . . . seriously think about what incentives are important. This is a very important first step."

During the discussion following the third panel, audience member Timothy Douros, Cubist Pharmaceuticals' chief intellectual property counsel, noted that the extended exclusivity would have value for his company. Even if the exclusivity and patent periods overlapped, he said, the greater certainty that comes with exclusivity compared with patents makes "a difference for smaller companies." Douros stated that 30 percent of pharmaceutical patents are invalidated, whereas "exactly 0 percent" of exclusivity terms are invalidated.

Expanding on Push Incentives

Spellberg outlined several examples of push incentives. Tax credits for research and development are one possibility. Public-private partnerships (PPPs) are another. Government-funded PPPs include programs managed by the Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA). As a nongovernmental approach, Spellberg suggested tax-exempt 501(c)(3) entities could be developed to encourage private investment, for example, by supporting research on antibiotics that have a small market potential.

> "WE'RE WILLING TO PAY $50,000 FOR A COURSE OF CANCER CHEMOTHERAPY THAT PROLONGS LIFE AN AVERAGE OF FOUR WEEKS, BUT WE DON'T LIKE TO PAY MORE THAN $50 FOR A SEVEN-DAY COURSE OF ANTIBIOTICS THAT CURES THE DISEASE AND HAS THE POTENTIAL TO ADD DECADES OF LIFE."
>
> **— Brad Spellberg, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center**

So far, BARDA has awarded two contracts for antibiotics, both between $50 million and $100 million, for about four to five years of development work, said Joseph Larsen, chief of BARDA's Broad Spectrum Antimicrobials Program. BARDA was established in 2006 to provide incentives for the development of countermeasures against bioterrorism and pandemics, but it also has a growing focus on emerging infections, including antimicrobial-resistant diseases that

pose a public health threat. BARDA is seeking to create a publicly funded "strategic investor" program, which would exist independent of government. Larsen stressed that companies that pursue BARDA funding must allow access to their records and progress during drug development. "We're marching down the path with you every step of the way."

One company that has received BARDA funds is Achaogen, which was founded in 2004 to develop antibiotics to treat Gram-negative bacterial infections. Achaogen has three drugs in development—one in phase two and two products nearing the clinic, said Hollway. The company raised $100 million in venture capital, but each of its programs have also been supported by substantial government commitments, including funding from BARDA, NIH, and the Department of Defense. Without these federal push incentives, Hollway said, the company's products would have been shelved in 2008 when the economy collapsed and "would not exist" today. "I think these drugs will be successful, and all of humanity will be indebted to what the federal government has done here."

Payne, whose company has also received BARDA funding, said the money was critical to increasing GSK's probability of success in antibiotic development. The funding has also reassured the company that the cost of antibiotic development can be offset.

Many panelists made it clear that drug developers need more than one kind of financial incentive to spur antibiotic innovation. Morel called for a two-pronged approach, using both pushes and pulls. "We need to have a strong, traditional, market-driven mechanism that's going to pull from the market what we can get . . . complemented by some push to level the playing field." Paul Miller, vice president of AstraZeneca Pharmaceuticals' iScience group, agreed that there needs to be a combination of incentives because of the variety of challenges antibiotic discovery presents.

The current economic climate, however, may limit the likelihood that Congress will pass a bill that includes push incentives and affects the federal budget. Horne emphasized this point, saying that "any legislation that passes the House floor must have an offset. It must be paid for." He reiterated that we must consider goals "within the framework of the political process we have."

Alternative Pricing Models

There was considerable discussion about pricing and its effect on the economic landscape for antibiotics. Spellberg argued that these medications are undervalued: "We're willing to pay $50,000 for a course of cancer chemotherapy that prolongs life an average of four weeks, but we don't like to pay more than $50 for a seven-day course of antibiotics that cures the disease and has the potential to add decades of life."

At the same time, he acknowledged his own reluctance to use a recently approved antibiotic due to its high cost compared with a generic drug that, in his experience, has worked well for patients. This prompted a response from Hollway, who said he believed that the price tag of the newer drug was justified because clinical trials showed that it was "demonstrably better" than the present standard of care.

During the question and answer period, Rex posed the question: what would it take to turn Spellberg's thinking around? Spellberg reiterated his point that pricing concerns have little to do with economic modeling. "It's cultural. We fear cancer. We're deathly afraid of cancer and will pay any price," he said. "We don't have the same fear of infections, and we don't have the same willingness to accept cost."

As a long-term goal, Payne raised the prospect of changing how companies are compensated for their products and suggested separating the volume of antibiotics sold from the revenue the drugs generate. He proposed advance market commitments, wherein pharmaceutical developers obtain agreements from large buyers up front to purchase a certain amount of a drug once it is approved. He also proposed that hospitals could agree to pay for licenses to use antibiotics, rather than paying for individual doses. If a company knew there was a guaranteed market for one of its products (either in the form of a set level of sales or a license agreement), it could invest more confidently in that medicine's development. He acknowledged, however, that this could be difficult: "I think to get that advance market commitment, it requires probably new legislation, new law, and that's going to be a tough thing to put in place."

NEED NEW ANTIBIOTICS

CONCLUSION

Following the final session, Allan Coukell provided an overview of the day's conversation.

- There is, and will continue to be, a need for new antibiotics, yet market dynamics and the regulatory structure have created an environment in which manufacturers are discouraged from developing the drugs that are urgently needed.
- FDA and drug developers are committed to working together to strike the right balance between assessing the safety and efficacy of new drugs thoroughly and in a timely manner. Industry would like greater flexibility when it comes to approval requirements, and better diagnostics may help by reducing the cost of clinical trials.
- Industry would benefit from a mix of push and pull incentives, but the political and economic environments likely will impede efforts to encourage antibiotic innovation by means that require increased federal spending.

In closing, Coukell reminded attendees what this issue is ultimately about: the people suffering from drug-resistant infections who desperately need new antibiotics now.

PRESENTERS AND PANELISTS

APPENDIX A— PRESENTERS' AND PANELISTS' BIOGRAPHIES

Paul Ambrose

Pharm.D., FIDSA, Director, Institute for Clinical Pharmacodynamics, Ordway Research Institute

Dr. Paul Ambrose's areas of scientific inquiry involve anti-infective translational science, with the goal of improving patient care through the application of pharmacokinetic-pharmacodynamic (PK-PD) principles. Ambrose's expertise ranges from the microbiology laboratory, with *in-vitro* PK-PD infection models, to the animal laboratory for PK-PD studies, through the phase one stage of clinical trials for healthy-volunteer and patient studies, into phase two through four of clinical trial design, to pharmacokinetic and PK-PD mathematical analyses to support regulatory and commercial efforts. He is interested in novel PK-PD–based clinical trial design, which serves to better describe the time course of drug effect. Ambrose has written more than 90 peer-reviewed scientific publications and approximately 150 scientific abstracts. He has served as an editor for four textbooks, including the first and second editions of *Antimicrobial Pharmacodynamics in Theory and Clinical Practice.*

Steven L. Barriere

Pharm.D., FIDSA, Vice President, Clinical and Medical Affairs, Theravance

Dr. Steven L. Barriere received his Doctor of Pharmacy degree from the University of California, San Francisco. He directs anti-infective clinical research and medical affairs functions at Theravance. In that role, he led the clinical development of telavancin (VIBATIV®), now approved in the United States and Canada for the treatment of complicated skin and skin-structure infections and in Europe for the treatment of hospital-acquired pneumonia, including ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus*.

Barriere has more than 18 years of experience in the pharmaceutical industry, largely in anti-infective development. Prior to joining the pharmaceutical industry, he spent 17 years in infectious diseases practice, teaching, and research at the University of California, San Francisco, the University of Michigan, and, until 1993, at the University of California, Los Angeles Center for the Health Sciences. He has authored or co-authored more than 150 publications and book chapters in the area of infectious diseases therapeutics and is an editor of the first edition of the textbook *Antimicrobial Therapy and Vaccines.*

Helen Boucher

M.D., FIDSA, FACP, Director, Infectious Diseases Fellowship Program, Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center; Associate Professor of Medicine, Tufts University School of Medicine; Member, Infectious Diseases Society of America's Antimicrobial Availability Task Force

Dr. Helen Boucher received her medical degree from the University of Texas Medical School at Houston. She completed her internship, residency, and chief residency in internal medicine at the New England Deaconess Hospital and her clinical and research fellowships in infectious diseases at the Beth Israel Deaconess Medical Center. She is board certified in internal medicine and infectious diseases. She is the author or co-author of numerous abstracts, chapters, and peer-reviewed articles, which have been published in such journals as the *New England Journal of Medicine, Antimicrobial Agents and Chemotherapy, Clinical Infectious Diseases* and *Drugs.* In 2006, she was elected to IDSA's Antimicrobial Availability Task Force, and in 2007, she was elected to the organization's Research Committee. She was elected a fellow in the American College of Physicians in 2008. In 2009, she was appointed to the steering committee of the Mycoses Study Group and was selected in *Best Doctors in America.*

Allan Coukell

Director, Medical Programs, Pew Health Group

Allan Coukell oversees Pew Health Group's medical programs, including the Antibiotics and Innovation Project. Coukell practiced as a clinical pharmacist in oncology and bone-marrow transplant at the Victoria Hospital and London Regional Cancer Center in London, Ontario, and was subsequently a senior medical writer and editor with Adis

International, publisher of the peer-reviewed journals *Drugs, Drugs & Aging,* and *PharmacoEconomics,* among others. He also spent a decade in journalism, including as a health and science reporter for WBUR, Boston's NPR news station. He was the founding producer and host of the weekly Eureka! science program on Radio New Zealand, and he has written for the *Economist,* the *New York Times, New Scientist, Discover,* and other publications. He is the recipient of the Edward R. Murrow award for hard news reporting. He serves on FDA's Cardiovascular and Renal Drugs Advisory Committee as the consumer representative.

Edward Cox

M.D., M.P.H., Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Dr. Edward Cox received his medical degree from the University of North Carolina School of Medicine. He completed an internship and residency in internal medicine at the Hospital of the University of Pennsylvania in Philadelphia, and went on to complete a fellowship in infectious diseases at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Bethesda, MD. Cox is board certified in internal medicine and infectious diseases.

Barry I. Eisenstein

M.D., FIDSA, FACP, Senior Vice President, Scientific Affairs, Cubist Pharmaceuticals

Dr. Barry I. Eisenstein received his medical degree from Columbia University College of Physicians and Surgeons. He has served as chief of the Infectious Diseases Division at the University of Texas Health Sciences Center, San Antonio; professor and chair of the Department of Microbiology and Immunology and professor of internal medicine at the University of Michigan Medical School; vice president of science and technology at Beth Israel Deaconess Medical Center; and a professor of medicine at Harvard Medical School, where he established a technology-transfer office and clinical trials program. Since early 2003, he has worked at Cubist Pharmaceuticals, where he helped lead the FDA approval process for daptomycin (Cubicin®) and is now senior vice president of scientific affairs. He continues teaching at Harvard Medical School as clinical professor of medicine. Eisenstein has authored more than 100 original papers, book chapters, and editorials. He currently serves as an editor of *Antimicrobial Agents and*

Chemotherapy. He is a member of the Research on Resistance Working Group of IDSA and of the Foundation of the NIH Biomarkers Consortium for clinical indications in bacterial infections, and he chairs the PhRMA Key Issue Team on emerging pathogens.

David N. Gilbert

M.D., FIDSA, Chief of Infectious Diseases, Providence Portland Medical Center; Professor of Medicine, Oregon Health & Science University; Chair, Infectious Diseases Society of America Antimicrobial Availability Task Force

Dr. David N. Gilbert served as the Garnjobst Chair of graduate medical education at Providence Portland Medical Center for 35 years before stepping down in 2006. His work with the infectious diseases program encompasses clinical consultation, clinical microbiology, hospital epidemiology, collaboration with the infectious diseases' regional viral molecular diagnostic referral laboratory, advising on the antimicrobial portion of system drug formulary, and medical student/resident infectious diseases training. Gilbert has long been involved with IDSA and was its president in 2001–2002; he is currently chairman of its Antimicrobial Availability Task Force. He is also a principal co-investigator for IDSA's Emerging Infections Network. He is senior editor of the *Sanford Guide to Antimicrobial Therapy* and the *Sanford Guide to HIV/AIDS Therapy,* both of which are updated annually and distributed worldwide. Gilbert is a master of the American College of Physicians. He has published more than 130 articles in peer-reviewed journals, 200 abstracts, and several books, and is a reviewer for the *Journal of Infectious Diseases, Clinical Infectious Diseases, Annals of Internal Medicine,* the *New England Journal of Medicine,* the *Journal of the American Medical Association* and *Proceedings of the National Academy of Sciences.*

Mark J. Goldberger

M.D., M.P.H., FIDSA, Divisional Vice President, Regulatory Policy and Intelligence, Abbot Pharmaceuticals

Dr. Mark J. Goldberger received his medical degree from Columbia University College of Physicians and Surgeons in New York and his Master of Public Health degree from The George Washington University in Washington, DC. He completed his postgraduate training at Presbyterian Hospital in New York and the Centers for Disease

Control and Prevention in Atlanta, GA. While working for the CDC, he participated in the investigation of the outbreak of Legionnaires' disease in Philadelphia, PA, in 1976 and the swine flu immunization program and subsequent outbreak of Guillain-Barré syndrome in 1976–1977. He is board certified in internal medicine and infectious diseases and is a fellow of IDSA. He was also on the faculty of Columbia University for nine years. Goldberger joined FDA in 1989 and served as primary reviewer, medical team leader, director of the Division of Special Pathogen and Immunologic Drug Products, and director of the Office of Antimicrobial Products within the Center for Drug Evaluation and Research. In 2006, he became medical director for Emerging and Pandemic Threat Preparedness within FDA's Center for Biologics Evaluation and Research. In 2007, he joined Abbott Pharmaceuticals as divisional vice president in regulatory policy and intelligence.

John Hollway

J.D., Vice President, Business Development, Achaogen

John Hollway manages Achaogen's business development, strategic marketing, and legal activities, including its non-dilutive financing strategies and its relationships with government agencies. Prior to joining Achaogen, he was the vice president of operations, strategy, and corporate development and chief privacy officer for Acurian, Inc., a clinical services company. He built Acurian's clinical data services, in addition to being responsible for the overall management of client projects and the establishment and maintenance of data management standards and procedures. Hollway was the general manager in charge of wireless strategy and product development for Shared Medical Systems Corporation, now Siemens Medical Systems. Prior to his business career, he was an attorney at Morgan, Lewis & Bockius LLP. He holds a J.D. with honors from The George Washington University Law School.

Robert Horne

Senior Health Policy Advisor, Representative Phil Gingrey (R-GA)

After graduating from The Ohio State University, Robert Horne worked for Ohio Representative Greg Jolivette, then chairman of the Ohio House Health Committee, eventually serving as the committee's staff director. He left in 2003 to work for a health care consulting firm with offices in Ohio and Washington, DC. In his capacity as director of federal affairs for the firm, Horne worked with medical providers and physician-driven health plans across the country. In 2007, he went to work for U.S. Rep. Jeff Fortenberry (R-NE), and in March 2009, at the beginning of the health-reform debate, he went to work for U.S. Rep. Phil Gingrey (R-GA), an obstetrician/gynecologist physician and member of the Energy and Commerce Committee's Subcommittee on Health. Today, he supports Rep. Gingrey's work in the U.S. Congress and on the committee as his senior health policy advisor.

Duane R. Hospenthal

M.D., Ph.D., FACP, FIDSA, Infectious Diseases Physician, U.S. Army, Brooke Army Medical Center, Fort Sam Houston, Texas

Dr. Duane R. Hospenthal earned his graduate and medical degrees from Michigan State University and completed his postgraduate training at Walter Reed Army Medical Center in Washington, DC. He is a professor of medicine at the Uniformed Services University of the Health Sciences in Bethesda, MD, and a clinical professor of medicine at the University of Texas Health Science Center at San Antonio. He has served in the U.S. Army since 1984, attaining the rank of colonel. He served as the infectious diseases consultant to the U.S. Army surgeon general (2005–2011), as the clinical champion for the Infectious Disease Deployment Teleconsultation Service, and the Department of Defense representative to the CDC's Office of Infectious Diseases Board of Scientific Counselors. Dr. Hospenthal was a member of the IDSA State and Regional Societies Board (2004–2007) and Standards and Practice Guidelines Committee (2007–2010). Hospenthal was secretary-treasurer, vice president, and president of the Armed Forces Infectious Diseases Society and is a past president of the Texas Infectious Diseases Society. He has authored more than 200 publications and has served as editor of his own textbook, *Diagnosis and Treatment of Human Mycoses.* His recent work has focused on

response to multidrug-resistant bacteria and invasive fungal infections of combat-injured U.S. military personnel. He has also worked to improve infection prevention and control in combat zones.

Sheldon L. Kaplan

M.D., FIDSA, Chief, Infectious Disease Service, Texas Children's Hospital; Professor and Vice Chair for Clinical Affairs, Department of Pediatrics, Baylor College of Medicine

Dr. Sheldon L. Kaplan graduated from the University of Missouri, Columbia, and the University of Missouri, Columbia, School of Medicine. He was a resident in pediatrics and a fellow in pediatric infectious diseases at St. Louis Children's Hospital and Washington University School of Medicine, St. Louis. Kaplan is now professor and vice chairman for clinical affairs and head of the Section of Pediatric Infectious Diseases in the department of pediatrics at the Baylor College of Medicine. He is also chief of the Infectious Disease Service as well as head of the department of pediatrics at Texas Children's Hospital in Houston, TX. He has published more than 190 peer-reviewed articles and 125 invited articles or chapters and is a co-editor of the sixth edition of *Feigin and Cherry's Textbook of Pediatric Infectious Diseases.* He is editor-in-chief of *Pediatrics* as well as the co-editor of the pediatric infectious diseases section of the electronic textbook *UpToDate.* His current research interests include infections in children caused by *Staphylococcus aureus, Streptococcus pneumoniae,* and *Neisseria meningitidis.* He currently serves on the Anti-Infective Drugs Advisory Committee of FDA as well as on the sub-board of Pediatric Infectious Diseases of the American Board of Pediatrics.

Joseph Larsen

Ph.D., Chief, Broad Spectrum Antimicrobials Program, Division of Chemical, Biological, Radiological and Nuclear Countermeasures, Biomedical Advanced Research and Development Authority, U.S. Department of Health and Human Services

Dr. Joseph Larsen received his Ph.D. in microbiology from the Uniformed Services University of the Health Sciences. He is chief of the Broad Spectrum Antimicrobials Program at the Biomedical Advanced Research and Development Authority. The goals of BARDA's Broad Spectrum Antimicrobials Program are to enable the U.S. government to acquire medical countermeasures to protect the American public

against bioterrorist threats and to develop additional antimicrobial treatment options needed to counter the growing threat of antimicrobial resistance in clinically prevalent bacterial pathogens. Larsen previously served as a senior science and technology manager at the Joint Science and Technology Office for Chemical and Biological Defense within the Defense Threat Reduction Agency. From 2005 to 2006, he was an American Association for the Advancement of Science fellow at the Department of Homeland Security, where he managed university-based research programs aimed at the development of enhanced food safety detection systems and medical countermeasures for agricultural threat agents. He was a 2005 National Academy of Science Christine Mirzayan Fellow with the Board of Life Sciences.

Robert Meyer

M.D., Head, Global Regulatory Strategy, Policy, and Safety, Merck Sharp & Dohme Corporation

Dr. Robert Meyer received his medical degree from the University of Connecticut School of Medicine. He is vice president and head of Global Regulatory Strategy, Policy, and Safety at Merck Research Laboratories. He is responsible for oversight of all regulatory strategy and operations, regulatory policy and intelligence, and global product safety. He joined Merck in 2007 after several years at FDA, where he served most recently as director for the Office of Drug Evaluation II within the Center for Drug Evaluation and Research (CDER). He was involved in several CDER initiatives; notably, he was chair of the group that wrote the risk assessment guidance. He participated in FDA negotiations with the Biotechnology Industry Organization and Pharmaceutical Research and Manufacturers of America regarding the Prescription Drug User Fee Act III and IV. Prior to joining FDA, Meyer was a practicing pulmonologist and critical care specialist on the faculty of the Oregon Health & Science University.

Paul F. Miller

Ph.D., Vice President of AstraZeneca Pharmaceuticals' iScience Group within the Infection iMed Division

Dr. Paul F. Miller received his Ph.D. in microbiology and immunology from the Albany Medical College. Miller joined the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company in Ann Arbor, MI, in 1990 as a senior scientist in the infectious diseases

department, where he developed a number of novel screens and mechanism-of-action tools and used these to discover and advance new antibacterial chemical classes. He moved to Pfizer in 1997 as manager of the Antibacterials Biology Research Group within the Antibacterials, Immunology and Cancer Zone. He eventually became responsible for all antibacterial research activities through early clinical development before joining AstraZeneca in June 2011. His research interests and expertise include mechanisms of intrinsic antibiotic resistance in bacteria as well as the use of novel genetic technologies for the elucidation of antibiotic mechanisms of action. Miller is a member of the American Society for Microbiology, IDSA, and the American Association for the Advancement of Science. He is also a member of the Institute of Medicine's Forum on Microbial Threats, which advises the U.S. government on current and emerging infectious diseases issues.

Chantal Morel

Research Officer, Health Policy and Economics, London School of Economics

Chantal Morel holds a master's degree from the London School of Economics and is completing the final stages of her doctorate, also from the London School of Economics. Her research concerns access to medicines. Part of her work explores upstream determinants, such as research and development, investment drivers, and their relationship to unmet clinical needs. Her research also examines the relationship between pricing and regulation to access. She previously worked in health policy and economics as a research fellow at the London School of Hygiene and Tropical Medicine and as the lead impact assessment advisor for health programs at a large international nongovernmental organization. She co-authored the 2010 report "Policies and Incentives for Promoting Innovation in Antibiotic Research."

David J. Payne

Ph.D., Vice President, Anti-Bacterial Discovery Performance Unit, GlaxoSmithKline

Dr. David J. Payne holds a Ph.D. and D.Sc. from the Medical School, University of Edinburgh. He has 21 years of experience in antibacterial drug discovery and is currently vice president and head of the Antibacterial Discovery Performance Unit within the Infectious Diseases Centre of Excellence in Drug Discovery at GlaxoSmithKline. He is responsible for

GSK's antibacterial research effort, from discovery to clinical proof of concept (up to phase two clinical trials). At GSK, Payne has played a leading role in redesigning the strategy for antibacterial research and has helped create long-term alliances with innovative biotechnology companies, which have expanded the firm's discovery pipeline. He has also created industry-leading partnerships with the Wellcome Trust, Defense Threat Reduction Agency (U.S. Department of Defense), and BARDA to advance GSK's antibacterial programs. He has been involved with the delivery of a broad diversity of novel mechanism antibacterial agents into development and three novel mechanism antibacterials into phase two (GSK322, GSK052, and retapamulin). He has authored more than 190 papers and conference presentations.

John Powers

M.D., FIDSA, FACP, Associate Clinical Professor of Medicine, The George Washington University School of Medicine, University of Maryland School of Medicine

Dr. John Powers received his medical degree and residency training from Temple University School of Medicine and completed his infectious diseases training at the University of Virginia School of Medicine. He is a physician/investigator on faculty as an associate clinical professor of medicine at The George Washington University School of Medicine. Prior to holding his current position, Powers was the lead medical officer for antimicrobial drug development and resistance initiatives at FDA. Powers was co-chair for the U.S. Federal Interagency Task Force on Antimicrobial Resistance. Prior to joining FDA, Powers was assistant professor in the division of infectious diseases at the University of Maryland School of Medicine, where he is still a faculty member. Powers also actively cares for patients weekly in clinic. He has been an investigator on more than 50 clinical trials. Powers has particular expertise in the design, conduct, and analysis of clinical trials and has published on various aspects of clinical trial design. He has won several teaching awards and is a recipient of the 2010 NIH Director's Award.

John H. Rex

M.D., FIDSA, FACP, Vice President Clinical Infection, Infection Therapy Area, AstraZeneca Pharmaceuticals LP

Dr. John H. Rex received his medical degree from Baylor College of Medicine. He trained in internal medicine at Stanford University Hospital and in infectious diseases at the National Institute of Allergy and Infectious Diseases. He served on the faculty of the University of Texas Medical School at Houston from 1992 to 2002, during which time his work focused on laboratory studies of novel antifungal agents, clinical trials of novel antifungal agents, and hospital epidemiology. In 2003, Rex moved to AstraZeneca Pharmaceuticals, where he now serves as vice president Clinical Infection. He is the industry representative on FDA's Anti-Infective Drugs Advisory Committee and is chair of the Area Committee on Microbiology for the Clinical Laboratory Standards Institute. He also is a Highlights advisor for *Nature Reviews Microbiology* and is a member of the Wellcome Trust Seeding Drug Discovery Committee. He serves on several editorial boards; he was also an editor for *Antimicrobial Agents and Chemotherapy* and is currently an emeritus editor for www.doctorfungus.org, a nonprofit website devoted to the dissemination of information about medical mycology.

Steven L. Solomon

M.D., Director, Office of Antimicrobial Resistance, U.S. Centers for Disease Control and Prevention

Dr. Steven L. Solomon received his medical degree from Tufts University. He was previously a staff physician in the Division of Infectious Disease at the Veterans Administration Medical Center in Atlanta, GA. Solomon began his public health service (PHS) career as an epidemic intelligence service officer in the Hospital Infections Program at CDC. Before assuming his current role, he served as acting director of the Epidemiology and Analysis Program Office in CDC's Office of Surveillance, Epidemiology and Laboratory Services. He was also director of the Coordinating Center for Health Information and Service, acting director of CDC's National Center for Health Marketing, CDC's associate director for health systems, and associate director for epidemiological science in CDC's National Center for Infectious Diseases. In 2011, following a 30-year career as a commissioned officer, Solomon

retired from the PHS with the rank of rear admiral. He has authored and co-authored more than 75 publications and serves as an assistant clinical professor of medicine at Emory University School of Medicine.

Brad Spellberg

M.D., FIDSA, Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles Medical Center

Dr. Brad Spellberg is an associate professor of medicine at the David Geffen School of Medicine at UCLA and the Harbor-UCLA Medical Center. He is also associate program director for the Internal Medicine Residency Training Program at Harbor-UCLA Medical Center. He received his medical degree from the Geffen School of Medicine at UCLA. Spellberg works as an academic hospitalist, attending on inpatient medicine wards. His research ranges from basic immunology and vaccinology to pure clinical research and outcomes research. His laboratory research has focused on developing a vaccine that targets the bacterium *Staphylococcus aureus,* which is undergoing clinical development, and the fungus *Candida.* Spellberg is currently working on the immunology and vaccinology of highly resistant *Acinetobacter* infections. He serves as medical director for Clinical Research Solutions, a clinical trials unit that supports conduct of clinical research at Harbor-UCLA Medical Center. Spellberg is a member of IDSA's Antimicrobial Availability Task Force. His research regarding new drug development has been a cornerstone of the IDSA white paper *Bad Bugs, No Drugs.* He is also the author of the book *Rising Plague.*

CONFERENCE AGENDA

APPENDIX B—CONFERENCE AGENDA

8:00–8:30 A.M. Registration and continental breakfast

8:30–8:45 A.M. Welcome and introduction
MODERATOR: **Allan Coukell,** Director, Medical Programs, Pew Health Group

Session #1: The Antibiotics We Need Most: Current and Anticipated Unmet Medical Needs

8:45–9:45 A.M. Expert roundtable discussion *(moderated)*

Paul Ambrose, Pharm.D., FIDSA, Director, Institute for Clinical Pharmacodynamics, Ordway Research Institute

Edward Cox, M.D., M.P.H., Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

David N. Gilbert, M.D., FIDSA, Chief of Infectious Diseases, Providence Portland Medical Center; Professor of Medicine, Oregon Health & Science University; Chair, Infectious Diseases Society of America Antimicrobial Availability Task Force

Duane R. Hospenthal, M.D., Ph.D., FACP, FIDSA, Infectious Diseases Physician, U.S. Army, Brooke Army Medical Center, Fort Sam Houston, Texas

Sheldon L. Kaplan, M.D., FIDSA, Chief, Infectious Disease Service, Texas Children's Hospital; Professor and Vice Chair for Clinical Affairs, Department of Pediatrics, Baylor College of Medicine

Steven L. Solomon, M.D., Director, Office of Antimicrobial Resistance, U.S. Centers for Disease Control and Prevention

DISCUSSION QUESTIONS

- What antibiotics do we need to treat patients today that we don't have?
- What antibiotics are we at the greatest risk of needing tomorrow?
- What are the greatest unmet health needs associated with the dwindling number of antibiotics?

9:45–10:05 A.M. Q & A *(audience)*

10:05–10:20 A.M. Coffee break

Session #2: Overcoming Antibiotics' Unique Scientific and Regulatory Challenges

10:20–11:20 A.M. Presentations

Edward Cox, M.D., M.P.H., Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Helen Boucher, M.D., FIDSA, FACP, Director, Infectious Diseases Fellowship Program, Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center; Associate Professor of Medicine, Tufts University School of Medicine, Member of the Infectious Diseases Society of America's Antimicrobial Availability Task Force

John Powers, M.D., FIDSA, FACP, Associate Clinical Professor of Medicine, The George Washington University School of Medicine, University of Maryland School of Medicine

John H. Rex, M.D., FIDSA, FACP, Vice President Clinical Infection, Infection Therapy Area, AstraZeneca Pharmaceuticals LP

11:20 A.M.–12:20 P.M. Expert roundtable discussion *(moderated)*

Steven L. Barriere, Pharm.D., FIDSA, Vice President, Clinical and Medical Affairs, Theravance

Barry I. Eisenstein, M.D., FIDSA, FACP, Senior Vice President, Scientific Affairs, Cubist Pharmaceuticals

Mark J. Goldberger, M.D., M.P.H., FIDSA, Divisional Vice President, regulatory policy and intelligence, Abbott Pharmaceuticals

Robert Meyer, M.D., Head, Global Regulatory Strategy, Policy, and Safety, Merck Sharp & Dohme Corporation

DISCUSSION QUESTIONS

- What are the scientific and regulatory challenges that antibiotic drug developers face?
- How can researchers, industry, and regulators adapt and collaborate to stimulate more antibiotic innovation? Are there specific steps we can take now to achieve this?
- How do we ensure that the regulatory pathway encourages the development of antibiotics to address the greatest unmet public health needs?

12:20–12:45 P.M. Q & A *(audience)*

12:45–1:45 P.M. Lunch *(provided)*

Session #3: Overcoming Antibiotics' Unique Economic Challenges

1:45–2:30 P.M. Presentations

Chantal Morel, Research Officer, Health Policy and Economics, London School of Economics

Brad Spellberg, M.D., FIDSA, Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles Medical Center

David J. Payne, Ph.D., Vice President, Antibacterial Discovery Performance Unit, GlaxoSmithKline

2:30–3:30 P.M. Expert roundtable discussion *(moderated)*

John Hollway, J.D., Vice President, Business Development, Achaogen

Robert Horne, Senior Health Policy Advisor, Representative Phil Gingrey (R-GA)

Joseph Larsen, Ph.D., Chief, Broad Spectrum Antimicrobials Program, Division of Chemical, Biological, Radiological and Nuclear Countermeasures, Biomedical Advanced Research and Development Authority, U.S. Department of Health and Human Services

Paul F. Miller, Ph.D., Vice President of AstraZeneca Pharmaceuticals' iScience Group within the Infection iMed Division

DISCUSSION QUESTIONS

- Which incentives will have the greatest impact on drug development? Which are the most realistic in the current political and fiscal environment?
- How do we ensure that incentives encourage the development of antibiotics to address the greatest unmet public health needs?
- In what way is the traditional drug development and reimbursement model unsuitable for antibiotics, and how can it be improved?

3:30–4:00 P.M. Q & A *(audience)*

4:00–4:15 P.M. Wrap-up

4:15–6:00 P.M. Reception

HOST ORGANIZATIONS

APPENDIX C—HOST ORGANIZATIONS

About the Infectious Diseases Society of America

The Infectious Diseases Society of America represents nearly 10,000 infectious diseases physicians, scientists, and health care professionals devoted to patient care, prevention, public health, education, and research.

Over the past decade, IDSA has actively engaged policy makers, industry leaders, and health policy experts to raise awareness about the unique role antibiotics play in the practice of medicine and the synergistic crises of rising rates of antibiotic resistance and the rapidly diminishing pipeline of novel antibiotics. IDSA has held multiple congressional briefings and published papers on the growing problem as well as held workshops with FDA and the NIH to explore the regulatory and scientific challenges to antibiotics and related diagnostics development. The society currently is participating in an effort with the foundation for NIH, FDA, NIH, academia, and industry to consider new endpoints for use in antibiotic clinical trials.

IDSA's landmark 2004, report *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, a Public Health Crisis Brews,* sounded the alarm on the market failure that has devastated antibiotic research and development (R&D). IDSA's "10 x '20 initiative," launched in 2010, endorsed by 35 medical societies and other groups, calls for a global commitment to sustain a global antibiotic R&D enterprise. Our short-term goal is 10 new safe and effective, systemic antibiotics by 2020. On World Health Day 2011, IDSA issued *Combating Antimicrobial Resistance: Policy Recommendations to Save Lives,* which recognizes effective antibiotics as an essential shared societal benefit (like energy, forests, etc.)—the availability of which will diminish, harming each of us, unless appropriate policies are in place to protect it.

About the Pharmaceutical Research and Manufacturers of America

The Pharmaceutical Manufacturers Association was founded in 1958. Its name was changed to the Pharmaceutical Research and Manufacturers of America in 1994 to underscore the extraordinary commitment of member companies to research.

Headquartered in Washington, DC, PhRMA represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated $49.4 billion in 2010 in discovering and developing new medicines. Industry-wide research and investment reached a record $67.4 billion in 2010.

America's biopharmaceutical research sector is the global leader in medical innovation, with more than 300 new medicines approved by FDA in the last decade. Roughly 2,900 compounds are currently being studied in the United States—more than all other regions.

Over a quarter century, the biopharmaceutical industry has evolved, with five major trends characterizing the changes: increased complexity of the research and development process; continued investment in R&D; increased use of medicines in health care; increased value for today's patients; and continued importance of patent incentives for innovative medicines.

PhRMA's mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical and biotechnology research companies. To accomplish this mission, PhRMA is dedicated to achieving these goals in Washington, DC, the states, and the world:

- Broad patient access to safe and effective medicines through a free market, without price controls
- Strong intellectual property incentives
- And transparent, efficient regulation and a free flow of information to patients

About Pew's Antibiotics and Innovation Project

The Pew Health Group created the Antibiotics and Innovation Project to address the significant unmet need for new, lifesaving antibiotics. Bacteria can cause serious and sometimes lethal infections, and for the last 70-plus years we have relied on antibiotics to treat them. A growing number of these pathogens, however, are becoming multidrug-resistant, making them more difficult and costly to treat and increasingly deadly. The Antibiotics and Innovation Project develops and supports policies that will spur the innovation of new antibiotics to treat life-threatening, drug-resistant infections.

Based on research and critical analysis, Pew seeks to improve the health and well-being of all Americans. As part of The Pew Charitable Trusts, it advocates for policies that reduce potentially dangerous health risks in consumer, medical, and food products and services.

The Pew Charitable Trusts is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public, and stimulate civic life. We partner with a diverse range of donors, public and private organizations, and concerned citizens who share our commitment to fact-based solutions and goal-driven investments to improve society.

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[8] H.R. 2182. Original co-sponsors: Reps. Gene Green (D-TX), Ed Whitfield (R-KY), Diana DeGette (D-CO), Mike Rogers (R-MI), Anna Eshoo (D-CA), and John Shimkus (R-IL).

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