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EMERGENCE OF THE SUPERBUG: ANTIMICROBIAL RESISTANCE IN THE UNITED STATES

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

ON

EXAMINING THE PUBLIC HEALTH IMPACTS OF ANTIMICROBIAL RESISTANT BACTERIAL INFECTIONS IN THE UNITED STATES, FOCUSING ON CURRENT ANTIMICROBIALS AND CONTINUED DEVELOPMENT OF NEW SOLUTIONS FOR THE FUTURE PROTECTION AGAINST INFECTIOUS DISEASES

JUNE 24, 2008

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STATEMENTS

TUESDAY, JUNE 24, 2008

ADDITIONAL MATERIAL

EMERGENCE OF THE SUPERBUG: ANTIMICROBIAL RESISTANCE IN THE UNITED STATES

TUESDAY, JUNE 24, 2008

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:33 a.m. in Room SD–430, Dirksen Senate Office Building, Hon. Sherrod Brown, presiding.

Present: Senator Brown, Sanders, Burr, and Hatch.

OPENING STATEMENT OF SENATOR BROWN

Senator BROWN. The Senate Health, Education, Labor, and Pensions Committee will come to order. Thank you. Thank the witnesses for joining us. Thanks all of you in the audience for joining us for this important hearing today.

I would notify people that there will be a vote on the Senate floor at 11 o'clock. So we will temporarily recess the committee and come back as soon as I can go vote and return.

I'd like to thank our witnesses on both panels for being here today. Thank you very much. We welcome your insight as the committee examines the phenomenon that clearly has not received the public attention that it deserves.

Over the last year we've seen news reports about outbreaks around the country of dangerous infections for which there are increasingly fewer treatment options. One of the most common is a strain of staph infection that's resistant to penicillin and other related antibiotics commonly referred to by the acronym as you know, MRSA. While MRSA was previously thought to occur only in hospital settings, that's bad enough. Americans have begun to contract it in the community, at schools and through sporting events primarily.

Last year the Journal of the American Medical Association reported that MRSA infections occur in approximately 94,000 people each year and are associated with approximately 19,000 deaths. That supercedes deaths from AIDS, a scourge that has taken hard thinking in legislation to help treat. MRSA is a wake up call. It signals the need, the urgent need to confront antimicrobial resistance.

Antimicrobial resistance can occur whenever antibiotics are not used appropriately, when doctors over prescribe, when patients don't understand the importance of taking their full course of therapy, when animals are fed antibiotics to maintain health rather

than to restore it and when in various ways antimicrobials find their way into the environment. All of this takes its toll. In recent years infections that used to be easily treated with antimicrobials are now drug resistant leading to much more serious, sometimes life threatening infections.

We will hear testimony today from Brandon Noble who will share how his MRSA infection has had such a profound effect on his life. Thank you Brandon, again, for being here.

Unfortunately MRSA is just one of the drug resistant infections setting the clock back on modern medicine. When our soldiers come home from Iraq and Afghanistan they may face yet another deadly threat, drug resistance strains of acinetobacter. There are numerous drug resistant organisms, some of which could be avoided with better infection control practices on the part of medical personnel and hospitals and even simple hand washing as CDC repeatedly suggests us to do.

Our witness, Dr. Brennan, will elaborate on the issue of hospital-based infection control. It's clear we also need new antimicrobial agents which simultaneously move medical science forward. And make up for the ground lost to drug resistance.

But, there are barriers to creating new antibiotics. One of these barriers simply is profitability. Except in a rare case, the antibiotics are short-term treatments which means they don't bring in as much revenue as those for chronic problems. We'll still hear from Dr. Eisenstein and Dr. Tollefson about some of the challenges we face in antibiotic development.

We'll also hear from Dr. Tenover of the CDC, who will describe efforts there to track and combat antimicrobial resistance. Doctors Graham and Vogel will speak about the use of antimicrobials in animal feed, an issue that I worked on in the House almost a decade ago. Chairman Kennedy has been instrumental in raising the profile of this important issue.

In my State of Ohio there were 12 outbreaks of MRSA last year. Ohioans contracted MRSA in health care settings, in the workplace, on sports team, in correctional facilities. I would like to relate the story of Dr. Froncie Gutman of Chagrin Falls, chairman of ophthalmology for 22 years at the Cleveland Clinic.

In April of last year, Dr. Gutman came down with pneumonia. By the time he went to the hospital he was semi-conscious. He was given an antibiotic common in the treatment of bacterial pneumonia.

After a week he wasn't getting better. His blood pressure dropped. He was going into septic shock and his kidneys were shutting down. The doctors were not able to identify the organism that was causing the infection.

He was taken to surgery where a portion of his lung was removed. They were able then to identify the organism which was MRSA. Dr. Gutman was in a coma for more than a week. He fortunately regained consciousness. With the help of a newer antibiotic called Zyvox, Dr. Gutman is recovered.

The message Dr. Gutman asked us to convey about his experience is this, no matter the quality of care he received at the Cleveland Clinic, Dr. Gutman would not be alive today without Zyvox.

Now he's concerned about what will happen when these organisms adapt to Zyvox. The same story.

Antimicrobial resistance is a powerful counter force undermining our Nation's progress against infectious disease. We shouldn't underestimate it. We obviously can't ignore it.

My friend, Senator Hatch, and I introduced the strategies to address Antimicrobial Resistance Act to reinvigorate efforts to combat antimicrobial resistance, efforts that accelerated in the 1990s and then stalled. Our bill would launch a coordinated effort to prevent outbreaks of MRSA and other dangerous drug resistant infections. It would jump start research on superbugs. It would explore strategies to ensure a more robust pipeline, if you will, for new antibiotic drugs.

I thank Senator Hatch for his leadership on this issue and for introducing the bill with me. I look forward to hearing from our witnesses whose testimony will no doubt underscore the importance of moving quickly and decisively against this major public health threat.

The first panel is Dr. Fred Tenover and Linda Tollefson. Dr. Tenover is the Director of the Office of Antimicrobial Resistance at the CDC. He is also Director of the World Health Organization's collaborating Center for Global Monitoring of Antimicrobial Resistance and an adjunct professor of public health at Emory University, my mother's alma mater. He serves on the editorial boards of antimicrobial agents and chemotherapy antimicrobial drug resistance. He has been author or co-author of over 290 journal articles and 31 book chapters. Thank you for joining us, Dr. Tenover.

Linda Tollefson before her appointment as Assistant Commissioner for Science at the FDA, Admiral Tollefson served as Deputy Director of the Center for Veterinary Medicine. She also directs FDA's Offices of Women's Health and Orphan Products Development. She's received many public health service awards and honors including her notorious service, the outstanding service, the commendation medals for his leadership in the Commission Corps.

Thank you both for testifying and especially thank you for your public service to our government and to our country. Dr. Tenover, if you would begin. Thank you.

STATEMENT OF FRED C. TENOVER, PH.D., DIRECTOR OF THE OFFICE OF ANTIMICROBIAL RESISTANCE, CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA, GA

Mr. TENOVER. Thank you and good morning, Chairman Brown. I am Dr. Fred Tenover. It is my pleasure to be here today in my capacity as the Director of the Office of Antimicrobial Resistance at the Centers for Disease Control and Prevention to discuss with you our growing concerns about the problem of antimicrobial resistance.

CDC appreciates this opportunity to share information with you. While antimicrobial resistance is not a new issue for the CDC, the fact that so many different types of microorganisms are becoming resistant to antibiotics is of major importance. Increasing rates of resistance among bacteria, fungi, viruses and even parasites are clearly limiting our options for treating individual patients and are causing the medical community to change many long established

treatment regiments to more complex antimicrobial agents or combinations of agents instead of a single drug.

A small but growing subset of bacterial strains that cause health care associated infections like the acinetobacter and pseudomona species have become resistant to all available antimicrobial agents. Other infections such as those caused by the bacterial species *Clostridium difficile* often cause debilitating diarrhea or even more severe disease in patients that have received antibiotics for other infections. This shows us that taking an antibiotic, even when needed, can be risky. CDC's key responsibilities regarding antimicrobial resistance are to define the scope and magnitude of the problem to try and prevent infections so microorganisms cannot develop resistance, to promote appropriate use of antibiotics and to control the spread of resistant organisms when they do develop.

The public health response to the problem of antimicrobial resistance is best viewed as a continuing series of successes and setbacks. For example in 2000, a new conjugate vaccine became available for children that prevented infections caused by strains of streptococcus pneumoniae, otherwise known as pneumococcus. The vaccine's targets included the most common multi-drug resistant strains of pneumococci.

Since the vaccine was introduced as part of routine childhood immunization, penicillin resistant pneumococcal infections declined by 35 percent. It is estimated that 170,000 severe pneumococcal infections and 10,000 deaths have been prevented by vaccine use. Yet even a CDC surveillance system was recording these record declines in pneumococcal infections, it also noted the rise of infections caused by a new multi-drug resistant strain of pneumococcus called serotype 19A, a strain type that was not covered by the current vaccine. Thus a new vaccine is under development.

In a similar fashion the rates of infections among hospitalized patients in the United States caused by Methicillin Resistant Staphylococcus Aureus or MRSA has been a concern for well over a decade. However, new data from hospitals participating in the National Health Care Safety Network has shown a significant drop over the last 5 years in the incidents of both MRSA and methicillin susceptible staph aureus blood infections in patients within dwelling central lines.

While the incidence of MRSA and MSSA blood stream infections has decreased substantially, MRSA infections are rising dramatically in the community. The number of MRSA-related skin and soft tissue infections resulting in hospitalization doubled between 2000 and 2005. Thus our MRSA successes in hospitals have to be balanced with new challenges of controlling MRSA in the community.

One of the most common communicable infections in the United States is gonorrhea. CDC's efforts to control the spread of gonorrhea suffered a major setback in 2007 when we had to withdraw the recommendation to use fluoroquinolones antibiotics as primary treatment for gonorrhea infections due to a rapid rise in fluoroquinolone resistant strains. This loss of the easy to administer and effective therapy leaves us only with cephalosporin type drugs to treat gonococcal infections. When cephalosporin resistance emerges, the treatment and control of gonorrhea will become much more difficult.

CDC's successful collaborations with several Federal partners on antimicrobial resistance issues have illustrated the benefits of coordinating activities with other Federal agencies. This has led to expanded activities of the Interagency Task Force on Antimicrobial Resistance, specifically to facilitate communication on resistance issues among Federal partners. The Task Force which consists of 10 Federal agencies recently held a consultants meeting to obtain input on revising the Public Health Action Plan to combat antimicrobial resistance. Based on comments from the consultants the Federal agencies are revising the Action Plan and refocusing it.

In summary antimicrobial agents are used in humans, animals, fish, vegetables and fruit, decorative plants and even in marine paint. The pressure for resistant microorganisms to develop and spread is high and continues to grow. Yet our supply of new antimicrobial agents is dwindling.

While we cannot totally stop the development and spread of resistant microorganisms, we can minimize their impact by using antibiotics we have wisely and minimizing the spread of resistant organisms when they develop. In doing so we can preserve our ability to treat life threatening infections while we continue to develop and implement new measures to prevent and control them. Thank you for this opportunity to testify. I will be happy to address your questions.

[The prepared statement of Mr. Tenover follows:]

PREPARED STATEMENT OF FRED C. TENOVER, PH.D.

INTRODUCTION

Good morning Chairman Brown, Ranking Member Enzi, and other distinguished members of the committee. I am Dr. Fred Tenover, and it is my pleasure to be here today in my capacity as Director of the Office of Antimicrobial Resistance at the Centers for Disease Control and Prevention (CDC). While I have certain managerial responsibilities at CDC, I continue to work as an active microbiologist and have authored or co-authored over 290 journal articles and 31 book chapters in the field of clinical medicine and microbiology. I also serve as Director of the World Health Organization's Collaborating Centre for Global Monitoring of Antimicrobial Resistance and am an Adjunct Professor in the Division of Epidemiology at Emory University's Rollins School of Public Health. CDC appreciates the opportunity to address this timely issue and I look forward to discussing with you our growing concerns about the problem of Antimicrobial Resistance

Antimicrobial resistance will always be with us, it is not a new issue; but we need to continue to find manageable solutions. Resistant microorganisms have been reported for over 60 years; however, it is the increasing magnitude of the problem and the fact that so many different types of microorganisms are becoming resistant to antimicrobials, a general term for drugs, chemicals, or other substances that either kill or slow the growth of microbes, that is of major concern to us. Although most bacterial, fungal, viral, and parasitic pathogens remain susceptible to a least some antimicrobial agents, the increasing rates of resistance are requiring more complex options for treating individual patients and are causing the medical community to change long-established treatment regimens for many infectious illnesses to different antibiotics that may be more expensive, or combinations of antibiotics instead of a single drug. When a patient with a resistant organism is treated with an ineffective antibiotic, the organism will continue to infect the patient and could potentially spread to other patients, further extending the resistance problem. However, with surveillance, reduced antibiotic usage, vaccination of persons at high risk, and product development antimicrobial resistance is manageable.

To provide a sense of the problem, unpublished data from CDC's National Nosocomial Infection Surveillance System indicate that >90 percent of strains of *Staphylococcus aureus*, a bacterial species that causes a spectrum of illnesses from minor skin infections to serious life-threatening diseases, are no longer treatable with penicillin, while one third of *Streptococcus pneumoniae* isolates, a common

cause of ear infections, pneumonia, and meningitis, are also no longer treatable with penicillin. Many such penicillin resistant strains are, in fact, multiply resistant to other commonly used drugs like ceftriaxone, erythromycin, and trimethoprim-sulfamethoxazole. In addition, strains of Salmonella Newport, which cause infections in food animals, such as dairy cows, have been shown to be resistant to as many as seven antibiotics. CDC data further show that a small but growing subset of the gram-negative bacterial strains that cause healthcare-associated infections, like *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, have become resistant to all available antimicrobial agents. And worldwide, tuberculosis due to strains resistant to the two most commonly used anti-tuberculosis agents, isoniazid and rifampin, was recently estimated to affect approximately half a million persons annually.

ANTIMICROBIAL USE AND RESISTANCE

Simply put, antibiotics are the most important tool we have to control many life threatening infectious diseases, yet increasing levels of antibiotic resistance are compromising the effectiveness of these drugs. Bacteria, in particular, have developed multiple ways of becoming resistant to antibiotics. The more often bacteria are exposed to antibiotics, the more chances they have to "learn" to survive through one of these mechanisms. Many people may not know the extent to which antimicrobial agents are used. Antimicrobial agents also are widely used in animals (as prevention measures and for growth promotion), fish, vegetables and fruit (to prevent outbreaks of bacterial disease in orchards), decorative plants, and even in marine paint (to inhibit growth of sea life on ships). It is imperative that we assess the use of all antimicrobial agents carefully and use them only when necessary, to avoid promoting the development of resistance among bacteria and other microorganisms. Unnecessary use of antibiotics reduces the effectiveness of the drugs we have at a time when there are relatively few new antimicrobial agents in development.

CDC'S ANTIMICROBIAL RESISTANCE PROGRAM

CDC's key responsibilities regarding antimicrobial resistance are:

- to define the scope and magnitude of the problem,
- to define the risk factors that lead to the development and spread of resistant microorganisms,
- to develop evidence-based guidelines and design and implement programs that minimize the development and spread of resistant infections in humans and animals,
- to respond to outbreaks of resistant microorganisms, and
- to conduct research on the prevention and control of resistant organisms in a variety of settings.

In addition to the responsibilities listed above, CDC laboratories are responsible for:

- tracking the spread of resistant microorganisms both nationally and globally,
- providing national reference laboratory services to confirm unusual antimicrobial resistance patterns, and
- working with professional societies to standardize methods for testing antimicrobial resistance among a variety of microorganisms including fungi, viruses, and parasites.

DEFINING THE SCOPE AND MAGNITUDE OF ANTIMICROBIAL RESISTANCE

CDC uses several types of surveillance systems (including data from laboratories, hospital information systems, and microbiologic examination of retail meats), to monitor the development and spread of resistant microorganisms and the infections that they cause. The organism groups under surveillance include many bacterial species (including *Mycobacterium tuberculosis*), fungi, viruses, and several parasites, such as malaria. Examples of surveillance systems at CDC include the Active Bacterial Core Surveillance (ABCs) system conducted through CDC's Emerging Infections Program (a network of sites that work together to conduct population-based surveillance and research projects), the Gonococcal Isolate Surveillance Program (GISP), and the National Healthcare Safety Network (NHSN). To conduct surveillance for resistant microorganisms and infections, CDC collaborates with many partners, including healthcare facilities; State public health departments; other Federal agencies, including the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA); and international organizations, such as the World Health Organization. Recently CDC also developed a training tool for laboratorians to enhance their understanding and improve their proficiency in performing anti-

microbial susceptibility testing (*M.A.S.T.E.R.*). Accurate antimicrobial susceptibility test results not only help physicians choose the best therapy for their patients, but guide infection control efforts to the most serious infections.

Surveillance data are used not only to monitor resistance rates among microorganisms, but to indicate the effectiveness of prevention programs, to set national benchmarks for infection control efforts, to monitor the effectiveness of treatment guidelines, and to inform timely changes regarding treatment recommendations. In addition, surveillance data collected through the ABCs system provide a source of national, population-based estimates of the antimicrobial resistance disease burden of multiple bacterial species, while NHSN serves both as a system for tracking healthcare-associated infections and as a sentinel warning system for unusual resistant organisms, such as vancomycin-resistant strains of *Staphylococcus aureus*.

Data from CDC's surveillance systems have often identified the emergence of new resistant microorganisms, such as the recent recognition by the ABCs system of the first ciprofloxacin-resistant strains of *Neisseria meningitidis* in the upper Midwestern United States reported this year, or the recognition of first strains of vancomycin-resistant enterococci in U.S. hospitals, reported by the National Nosocomial Infection Surveillance system, the predecessor to NHSN, a decade ago. Such reports have prompted outbreak investigations from which CDC has garnered a wealth of information on the development and spread of resistant organisms.

PROMOTING APPROPRIATE AND OPTIMAL ANTIMICROBIAL USE

Multiple efforts are underway at CDC to promote appropriate antimicrobial use to preserve the effectiveness of the antibiotics we have for the longest period of time. CDC's "Get Smart: Use Antibiotics Wisely" campaign has been very successful in delivering educational messages on appropriate antibiotic use to physicians and the general public. Since its inception in 2003, this program has delivered its message of the importance of prudent antibiotic use through State health department initiatives, physician's offices, on television, over the radio, and in print media. Since the late 1990s, there has been a 25 percent reduction in antibiotic prescriptions generated during outpatient visits for presumed viral infections, for which antibiotics are ineffective, which was a key target of the campaign. Additional educational efforts include developing curricula on prudent antibiotic use for medical schools and primary care residency programs. These programs are designed to raise the awareness of key healthcare providers to the downsides of unnecessary antibiotic use. The "Get Smart" program has expanded to include "Get Smart on the Farm" to focus on use of antimicrobial agents in animals, and has partnered with another CDC program, the "Campaign to Prevent Antimicrobial Resistance," which focuses on educating healthcare-based physicians about antimicrobial resistance issues, in an attempt to further decrease unnecessary antibiotic use.

CDC has long worked to promote the appropriate treatment of tuberculosis, both here and abroad, in order to minimize the development and spread of resistant TB. CDC provides financial and technical assistance to all 50 States and 10 large cities to reduce the spread of TB and ensure curative treatment for those with TB. Important to this effort is ensuring that patients are treated with drugs that will work against the strain that they have contracted. In 2006, over 92 percent of all patients with an initial positive TB culture in the United States were tested for TB drug susceptibility. CDC also supports TB laboratories and funds regional training and medical consultation centers for healthcare workers to ensure appropriate treatment and diagnosis.

In addition to these programmatic educational efforts, CDC sponsors the TB Trials Consortium (TBTC), which conducts clinical trials of TB medications on four different continents to optimize the effectiveness of current tuberculosis treatment regimens and identify new TB drugs that could be used to treat drug-resistant strains. The TBTC includes members from TB control programs, academic medical institutions, and CDC, as well as international partners from the commercial sector, the not-for-profit private sector, and the public sector, all of whom are essential for this work. The Global Alliance for TB Drug Development is a public/private partnership with whom CDC works to stimulate new drug development for treating tuberculosis. Over 30 organizations, including the Bill & Melinda Gates Foundation, National Institute of Allergy and Infectious Diseases at the National Institutes of Health, the Rockefeller Foundation, the U.S. Agency for International Development, the World Bank, and WHO, are stakeholders along with CDC in this innovative partnership. The major goals are to shorten the treatment of TB, minimize the impact of drug-resistant TB, and facilitate TB control in the poorest countries in the world.

SUCCESSES AND SETBACKS IN PREVENTION AND CONTROL ACTIVITIES

Multiply Resistant Pneumococcal Infections

The fight against antimicrobial resistance can best be viewed as a continual series of successes and setbacks. For example, pneumococcal infections resistant to penicillin and multiple other antibiotics became common during the 1990's. But in 2000, a new vaccine called Prevnar® became available for children in the United States and CDC began tracking the vaccine's impact on resistant pneumococcal infections. Since the vaccine was introduced into the routine childhood immunization program in the United States, penicillin-resistant pneumococcal infections declined by 35 percent. Not only has the vaccine been shown to prevent antibiotic-resistant infections, it has been shown to reduce the need for prescribing antibiotics for children with pneumococcal infection in the first place. CDC data also show that adults are getting fewer resistant pneumococcal infections because the vaccine is preventing spread of pneumococci from infected children to adult populations. Since 2001, it is estimated from CDC data that 170,000 severe pneumococcal infections and 10,000 deaths have been prevented by vaccine use. According to data published in the *Archives of Pediatric Adolescent Medicine*, the vaccine is highly cost-effective, saving an estimated $310 million in direct medical costs each year.

Yet, even as infections caused by the most common multi-drug resistant strains of pneumococci were declining in frequency, the CDC began noting, through its Active Bacterial Core Surveillance System, a gradual increase in infections caused by a new multi-drug resistant strain of pneumococcus called serotype 19A. This strain is not covered by the current vaccine. While the amount of serotype 19A invasive pneumococcal disease is small compared with the very large amount of disease averted by introduction of the vaccine, it still emphasizes the continuing struggle public health faces against microorganisms that are uniquely capable of adapting and surviving even our newest prevention measures. Fortunately, CDC's ongoing surveillance through the ABCs system detected this trend and indicated the need to develop a new vaccine that will confer protection against serotype 19A strains. A new vaccine containing 19A strain is already in clinical trials.

MRSA INFECTIONS

In a similar fashion, *Staphylococcus aureus* is a bacterial species that is commonly carried on the skin or in the nasal passages of 25 percent to 30 percent of healthy people in the United States. This organism, however, can and does cause a lot of skin infections, although most of these infections are minor. More importantly, *S. aureus* can cause life-threatening diseases including bloodstream infections, endocarditis (infection of the heart valves), toxic shock syndrome, and pneumonia, particularly among hospitalized patients. Methicillin-resistant strains of *S. aureus* (also called MRSA) first emerged in Europe in 1961 but by the 1980s were causing infections in patients in many U.S. hospitals. The continued increase in the rates of MRSA infections in U.S. hospitals has been a topic of considerable concern for over a decade and has resulted in a series of local, regional, and national interventions to halt its spread. For example, CDC in collaboration with the Veterans Affairs Pittsburgh Healthcare System achieved a 50 percent reduction in the rate of MRSA infections after it implemented a series of infection control procedures based on CDC guidelines designed to decrease the transmission of MRSA in hospitals. The measures included strict attention to hand hygiene, enhanced surveillance for infections, effective use of isolation rooms, and behavior modification techniques to emphasize the importance of the new procedures. These interventions are being implemented in VA medical centers nationwide and in multiple other healthcare systems. In addition, CDC is working with the Agency for Healthcare Research and Quality (AHRQ) to improve MRSA prevention in the healthcare facilities.

New national data from CDC's National Healthcare Safety Network (NHSN), a surveillance tool for hospitals and State health departments that measures healthcare associated infections (HAIs), show that there has been a significant drop in the incidence of both MRSA and methicillin-susceptible *S. aureus* (MSSA) central line-associated bloodstream infections among intensive care unit patients in U.S. hospitals over the last 5 years. The incidence of MRSA bloodstream infections per 1,000 central line days (i.e., a measurement of infection burden derived from the number of patients who have a central line, or catheter, whether infected or not) decreased by 49.6 percent, while the incidence of central line-associated MSSA infections decreased even more substantially, by 70.1 percent. Data on invasive MRSA infections from the Active Bacterial Core Surveillance system for 2005–2006 also show a decrease in hospital-onset and healthcare-associated MRSA infections, confirming this downward trend. Thus, it appears that these practical efforts to reduce

the transmission of MRSA in hospitals are working thereby, further reducing the need for antibiotic usage.

Yet, even as we document success in controlling MRSA in hospitals, CDC, through the ABCs system and other public health agencies around the world, have noted an increase in MRSA infections in community settings. While most of these are skin infections, severe and often fatal cases of necrotizing pneumonia continue to be reported among otherwise healthy people in the community with no links to the healthcare system. Based on national hospital discharge data analyzed by CDC, the number of *S. aureus*-related skin and soft tissue infections resulting in hospitalization doubled from 2000 through 2005; most, if not all, of this increase is likely due to community strains of MRSA. Thus, our MRSA successes in hospitals have to be balanced with the new challenges of controlling MRSA in community settings and CDC will continue to look for practical efforts to reduce these infections in community settings as have been done in hospitals.

Fluoroquinolone-resistant Neisseria gonorrhoeae

While CDC's efforts to control the spread of pneumococci in the community and MRSA in hospitals show success, CDC's efforts to maintain cost-effective strategies for preventing the spread of gonorrhea in the United States had a setback in 2007. In 2007, the level of fluoroquinolone (a family of drugs that includes the well-known Ciprofloxacin) resistance among surveillance isolates submitted to CDC's Gonococcal Isolate Surveillance Program (GISP) exceeded the 5 percent level, which has been used as the threshold for changing nationally recommended treatment. In response, CDC was compelled to announce the withdrawal of fluoroquinolone antibiotics as a primary treatment of gonorrhea infections, due to the rapid rise of fluoroquinolone resistance among strains of *Neisseria gonorrhoeae*. The loss of fluoroquinolones will likely have a significant impact on the treatment of gonorrhea in the United States as we are now left with only one class of recommended antibiotics, the cephalosporins, to treat gonococcal infections. When cephalosporin resistance emerges, the treatment and control of gonorrhea will become extremely difficult. Currently, there is no recommended treatment available for infected patients who have severe allergies to cephalosporins, and treatment in these patients requires the use of therapies that have greater side effects and for which resistance has already begun to develop.

Although the detection of the increase in gonococcal resistance to fluoroquinolones was timely, it highlights another challenge in CDC's effort to prevent and control this infectious disease, which is the critical need to identify the emergence of cephalosporin resistance in a timely fashion both nationally and locally. When cephalosporin resistant gonococci emerge, preventing their spread will be challenging—but even more so without expansion of existing capacity, since emergence may occur in populations not covered by the current surveillance system, allowing the gonococci to spread before effective control measures can be put in place.

Clostridium Difficile Infections

Another example of the fact that taking antibiotics is not without risk is the rapid increase in the United States since 2000 of the number of *Clostridium difficile* infections primarily in hospitalized patients. *C. difficile* disease can range from mild to debilitating diarrhea, to more severe life-threatening infections. The development of *C. difficile* infections among patients treated with antibiotics has long been considered an unintended consequence of antibiotic use. Recognized in the 1970s as a cause of "antibiotic associated diarrhea," in the 1980s and 1990s this anaerobic bacterial species caused increasing numbers of outbreaks of diarrheal disease in hospitals and long-term care facilities.

Recently, however, CDC and others have recognized the emergence of *C. difficile* disease, including more life-threatening forms of disease, among otherwise healthy patients in the community. A number of the community patients had not taken antibiotics prior to their illness. Based on data from Ohio, estimates suggest that currently there may be as many as 500,000 cases of *C. difficile* infection occurring annually in the United States, contributing to between 15,000 and 30,000 deaths. Some antibiotic-resistant strains of *C. difficile*, including those resistant to macrolides and fluoroquinolones, are emerging. These strains appear to be more virulent due to increased toxin production and the presence of a novel virulence factor called the binary toxin. Surveillance data from other public health agencies around the world show such strains are spreading globally. While this antimicrobial resistance doesn't directly affect therapy for the *C. difficile* infection, since such infections are treated with other drugs, the resistance may allow *C. difficile* to spread more readily among patients who have received either a macrolide or fluoroquinolone antibiotic. This broadens even further the number of people at risk for acquiring dis-

ease. CDC will begin to collect data from healthcare institutions using NHSN to track *C. difficile* infections.

Some challenges to future surveillance activities include limited public health infrastructure for detecting resistance and the heavy reliance on hospital microbiology laboratories around the United States to provide the antibiotic resistance data. While hospital microbiology laboratories recognize the importance of tracking antimicrobial resistance patterns nationwide, many of these laboratories cite increasing pressures from their institutions to discontinue these services due to limited resources and competing priorities.

WORKING WITH FEDERAL PARTNERS

CDC's successful collaborations with several Federal partners on antimicrobial resistance issues have illustrated the benefits of coordinating activities with other Federal agencies. For example, CDC worked closely with the Food and Drug Administration, which works with manufacturers to implement recalls of contaminated products, such as in the recent outbreak of contaminated mouthwashes containing resistant *Burkholderia* species in multiple States. In addition, monitoring the development and spread of antimicrobial resistance among foodborne bacterial pathogens like Salmonella, Shigella, and Campylobacter, such as is done through the National Antimicrobial Resistance Monitoring System, requires the cooperation of three Federal agencies (CDC, FDA, and USDA) to screen isolates from humans, animals, and the food supply. Another example is the current AHRQ–CDC partnership to fund a community-wide MRSA initiative to assess the role of and strategies to reduce inter-facility MRSA transmission. The necessity of Federal agencies working together highlights the need for the Interagency Task Force on Antimicrobial Resistance, specifically to facilitate communication among Federal partners on the issue of antimicrobial resistance.

THE INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE

The Interagency Task Force on Antimicrobial Resistance consists of 10 Federal agencies (Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, Department of Agriculture, Department of Defense, Department of Veterans Affairs, Environmental Protection Agency, Food and Drug Administration, Health Resources and Services Administration, and the National Institutes of Health) and is co-chaired by CDC, FDA, and NIH. Recently, the Task Force held a consultants meeting to obtain input and recommendations for revising and updating "A Public Health Action Plan to Combat Antimicrobial Resistance, which was first released in 2001." In addition to over 50 consultants from the United States, 9 international consultants from Canada, Denmark, France, Germany, The Netherlands, and the United Kingdom participated in the meeting. The consultants included experts from human and veterinary medicine, the pharmaceutical and diagnostics industries, animal husbandry industry, clinical microbiology, epidemiology, infectious disease and infection control specialists, and State and local public health departments. Representatives of most of the Federal agencies also participated. The open meeting also was attended by members of the public, including representatives of a variety of professional societies, advocacy groups, and concerned citizens. The discussions centered on four topic areas: surveillance; prevention and control; research; and product development. The consultants focused on issues that they felt were critical to address over the next 3–5 years.

Based on comments from the consultants and the Federal agencies, the revised draft Action Plan has been reformatted around five focus areas:

- reducing inappropriate antimicrobial use,
- reducing the spread of antimicrobial resistant microorganisms in institutions, communities, and agriculture,
- enhancing laboratory capacity to detect resistant microorganisms,
- encouraging the development of new anti-infective products, vaccines, and adjunct therapies, and
- supporting basic research on antimicrobial resistance.

The Task Force plans on submitting the revised Action Plan for public comment this fall.

SUMMARY

In summary, given the growing worldwide usage of antimicrobial agents (including antibacterials, antifungals, antivirals, and antiparasitic agents), the pressure for resistant microorganisms to develop and spread remains high. CDC's strengths in

surveillance, research, prevention and control, and education have proven to be critical assets in fighting resistance and have been rewarded with some remarkable successes in controlling the spread of resistant infections. Yet, CDC has also seen its share of setbacks, due to the ability of microorganisms to adapt to our prevention measures. We are hopeful that we can retain the vital core needed to continue to monitor the most important resistant organisms, while we develop and implement new measures to prevent and control resistant infections.

Thank you again for the opportunity to testify today. I am happy to answer any questions you may have.

Senator BROWN. Thank you, Dr. Tenover. Before Admiral Tollefson speaks, Senator Hatch would like to make some comments. The co-sponsor of our legislation too.

STATEMENT OF SENATOR HATCH

Senator HATCH. Well thank you. Thank you, Mr. Chairman. We welcome all of the witnesses here today.

For more than 60 years since their discovery, antibiotics have saved millions of lives and helped patients cope with suffering related to infection. But as we've seen, our country continues to face a growing number of troubling questions about whether we are prepared to address the increasing problem of drug-resistant bacterial infections. Data from the Centers for Disease Control and Prevention (CDC), indicate resistant strains of infections have spread rapidly.

These infections can strike anyone, and antibiotic resistance is an elevated problem for those with comprised immune systems; for example, individuals with HIV and patients in intensive or critical care units. Treatment options are few while this alarming trend continues to worsen.

Antibiotic resistant organisms have been in existence for about 60 years, too. This is not a new issue. The issue is that national surveillance data and studies show antibiotic resistant bacteria have multiplied and spread at disquieting rates in recent years.

Infections that were once easily cured with antibiotics are now becoming difficult and in some cases impossible to treat. This is happening not just in hospitals, but also community settings and homes. We have heard the news reports of MRSA, outbreaks within schools in New York, Kentucky and Virginia.

Resistant infections also strain public health systems by leading to higher health care costs because they require more expensive treatment and care. According to estimates from the Institutes of Medicine and the former Congressional Office of Technology Assessment, the economic burden placed on our national health care system as a result of resistant bacteria totals billions of dollars annually.

These are reasons why Senator Brown and I introduced S. 2313, the STAAR Act. We recognize that antibiotic resistance is a complex problem and our bill is not the sole answer to that problem.

Our bill focuses on providing adequate infrastructure within the government to collect the data, coordinate the research and conduct the surveillance necessary to stop drug resistant infections in their tracks.

The STAAR Act lays out the framework by which we can begin to take action against this serious public health threat. At a minimum, we need better testing, hospital controls, medications and

funding to support these efforts, particularly the works of the Centers for Disease Control and Prevention.

I am interested to hear the Agency's testimony and thank its representatives for being here.

I would like to conclude with three thoughts on incentives to encourage the development of new classes of antibiotics.

First, this committee worked hard last year to include provisions in the Food and Drug Administration Amendments Act of 2007 to encourage the development of new antibiotics. This law included language to strengthen the Office of Orphan Drugs and its FDA grant program and our hope was to have this language apply to antibiotics as well. Unfortunately that does not appear to be the case, so any assistance the FDA can give Congress in this area would be greatly appreciated by the committee.

Second, I believe it's important for the FDA to issue guidance regarding the development of antibiotics. It is my hope that the guidance will lower the costs of development and speed up the approval process so patients will have access to new antibiotics to treat drug resistant infections.

Finally, I believe that Congress should consider adding additional incentives for new antibiotics that treat life threatening conditions. Currently, these types of drugs are held in reserve and not used until there is a drug-resistant outbreak. I believe that if these drugs are held in reserve and not used, at minimum, their developers should be rewarded and the exclusivity should be extended to them for the period in which the use is significantly limited.

I am pleased to have all of our witnesses here today who took time out of their busy schedules to be with us today. Thank you and I look forward to hearing from you all.

Senator BROWN. Thank you. Thank you, Senator Hatch. Thank you also for being here, Senator Burr. Thank you for your leadership, Senator Hatch.

Senator HATCH. I want to thank you for your leadership. I think without it we wouldn't be here.

Senator BROWN. Thanks. Admiral Tollefson, I need to let people know the vote has been moved to 11:15. We will probably get through this first panel. We'll do our best. Admiral Tollefson, thank you for being here.

STATEMENT OF RADM LINDA R. TOLLEFSON, D.V.M., M.P.H., ASSISTANT COMMISSIONER FOR SCIENCE, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MD

Admiral TOLLEFSON. Thank you. Good morning, Senators. I am Rear Admiral Linda Tollefson, Assistant Commissioner for Science at the Food and Drug Administration and the FDA Co-chair of the Federal Agency Task Force on Antimicrobial Resistance. Thank you for the opportunity to discuss FDA's role with regard to antimicrobial resistance.

Successful management of current antimicrobials and the continued development of new ones is absolutely vital to protecting human and animal health against infectious microbial pathogens. Approximately 2 million people acquire bacterial infections in U.S. hospitals every year. Ninety thousand die as a result. About 70 percent of those infections are resistant to at least one antibiotic.

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Resistant pathogens lead to higher health care costs as Senator Hatch mentioned, because they often require more expensive drugs and extended hospital stays. The problem is not limited to hospitals. As we've heard community acquired infections are also frequently resistant to multiple antibiotics, such as community acquired Methicillin-resistant *Staphylococcus aureus*, common respiratory pathogens including *streptococcus pneumoniae* and gram negative *bacilli* which can infect humans through food.

Antimicrobial agents have been used in human and veterinary medicine for more than 50 years with tremendous benefits to both human and animal health. However, after several decades of successful antibacterial use we have seen and continue to see the emergence of multi-resistant bacterial pathogens which are less responsive to therapy. Antimicrobial resistant bacterial populations emerge because of the combined impact of the various uses of antimicrobial drugs including their use in humans and animals.

As I mentioned, FDA co-chairs, along with CDC and NIH, the U.S. Interagency Task Force on Antimicrobial Resistance and in 2001 we published the Public Health Action Plan to combat antimicrobial resistance. This provides a blueprint for specific, coordinated Federal actions to address the emerging threat of resistance. It reflects a broad-based consensus of Federal agencies which was reached with input from consultants from State and local health agencies, universities, professional medical societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups and other members of the public.

The Action Plan has four major components: surveillance, prevention and control, research, and product development. FDA has the lead on the product development focus area. As antimicrobial drugs lose their effectiveness, new products must be developed to prevent, rapidly diagnose and treat infections.

Our Center for Drug Evaluation and Research has launched several initiatives to address resistance including drug labeling regulations, emphasizing the prudent use of antimicrobials and has been revising its guidances to industry on the development of drugs for the treatment of bacterial infections.

For example, in January of this year, FDA co-sponsored a workshop at the Infectious Diseases Society of America on the topic of clinical trial designs for community-acquired pneumonia. The workshop provided the platform for the discussion of issues in trial designs. The Agency followed that with the meeting of the Advisory Committee, April 2008, to get additional advice. We are now actively engaged in writing a draft guidance document that will provide the Agency's thinking on informative trial designs for this disease.

Our Center for Biologics Evaluation and Research has a robust research program to investigate vaccine development because measures, any measures which reduce the need for antibiotic use also serve to reduce the emergence of antibiotic resistant microorganisms. Prevention of infections through the use of vaccines has effectively eliminated or markedly decreased the problem of resistance in organisms such as *haemophilus influenzae*, type B and as Dr. Tenover mentioned, the *streptococcus pneumoniae*. Vaccines

also contribute to the control of resistance by decreasing the use of the antibiotics.

In addition, development of increasingly sensitive diagnostic assays for the detection of resistance allows for more rational and more targeted antibiotic use. Our Center for Devices and Radiological Health has led several efforts to clarify the regulatory requirements to clear such devices. For example, they recently assisted device manufacturers by quickly clearing an alternative method for detecting vancomycin resistance in *Staphylococcus aureus* through use of our expedited review process.

Finally our Center for Veterinary Medicine is addressing potential human health risks associated with the use of antimicrobial drugs in food producing animals.

In summary FDA in alignment with the Federal Interagency Task Force on the Antimicrobial Resistance has been working for several years to develop and implement programs to combat or mitigate antimicrobial resistance in all relevant sectors, humans, animals and the environment. Antimicrobial resistance is a very important public health issue that can only be addressed by collaborative efforts of the relevant Federal agencies, State health departments and the private sector.

Thank you for the opportunity to discuss FDA's role. I would be happy to answer any questions.

[The prepared statement of Rear Admiral Tollefson follows:]

PREPARED STATEMENT OF RADM LINDA TOLLEFSON, D.V.M., M.P.H.

INTRODUCTION

Mr. Chairman and members of the committee, I am Rear Admiral Linda Tollefson, Assistant Commissioner for Science at the Food and Drug Administration (FDA or the Agency), which is a part of the Department of Health and Human Services (HHS), and the FDA co-chair of the Interagency Task Force on Antimicrobial Resistance. Thank you for the opportunity to discuss FDA's role with regard to antimicrobial resistance.

Successful management of current antimicrobials, and the continued development of new ones, is vital to protecting human and animal health against infectious microbial pathogens. Approximately 2 million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug. The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating. Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays. Resistant infections impact clinicians practicing in every field of medicine. The problem is not limited to hospitals. Community-acquired infections are also frequently resistant to multiple antibiotics, such as community-acquired methicillin-resistant *Staphylococcus aureus* (CA–MRSA), common respiratory pathogens including *Streptococcus pneumoniae*, and gram-negative bacilli, which can infect humans through food.

In my testimony, I will provide background information on antimicrobial resistance, discuss FDA's involvement with the Interagency Task Force on Antimicrobial Resistance, and describe FDA's actions to combat resistance and promote product development.

BACKGROUND

Antimicrobial drugs are used to treat infections caused by microorganisms. This statement focuses mainly on the development of resistance in bacterial organisms to antibacterial drugs; however, it should be noted that resistance is also a problem in other microorganisms, including viruses, tuberculosis, parasites (such as malaria), and fungi.

Another term commonly used to describe an antibacterial drug is "antibiotic." The term refers to a natural compound produced by a fungus or another microorganism that kills bacteria that cause disease in humans or animals. Some antibacterial

drugs may be synthetic compounds (not produced by microorganisms), and thus do not meet the technical definition of antibiotic but are referred to as antibiotics in common usage.

Many factors contribute to the spread of antimicrobial resistance. In some cases, doctors prescribe antibiotics too frequently or inappropriately. Sometimes patients do not complete the prescribed course of an antibiotic, making it more likely that surviving microbes will develop resistance. In addition, antibiotics used to prevent infections in livestock may contribute to the emergence of resistant germs that can infect people. Through international trade and travel, resistant microbes can spread quickly worldwide.

Antibiotics have had an enormous beneficial effect. Many infections that were fatal, or left individuals with severe disabilities, are now treatable or preventable. Antibiotic resistance is the ability of bacteria or other microbes to resist the effects of an antibacterial drug. Antibiotic resistance occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to cure or prevent infections. The bacteria survive and continue to multiply causing more harm. Antibiotic resistance is expected. Bacteria, also referred to as microbes, are adept at surviving and adapting to their environments. Therefore, regulation of antibacterial drugs is essential to delay the development of resistance. Misuse and overuse of these drugs contribute to an even more rapid development of resistance.

Antimicrobial agents have been used in human and veterinary medicine for more than 50 years, with tremendous benefits to both human and animal health. However, after several decades of successful antibacterial use, we have seen and continue to see the emergence of multi-resistant bacterial pathogens, which are less responsive to therapy. Antimicrobial resistant bacterial populations emerge because of the combined impact of the various uses of antimicrobial drugs, including their use in humans and animals. However, all of these pathways are not clearly defined or understood.

New classes or modifications of older classes of antimicrobials over the past six decades have been matched slowly but surely by the systematic development of new bacterial resistance mechanisms. As of today, antimicrobial resistance mechanisms have been reported for all known antibacterial drugs that are currently available for clinical use in human and veterinary medicine. In some cases, strains have been isolated that are resistant to multiple antibacterial agents.

U.S. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE

FDA co-chairs, along with the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), the U.S. Interagency Task Force on Antimicrobial Resistance (Task Force), which was created in 1999.

The Task Force also includes the Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), the Department of Agriculture (USDA), the Department of Defense, the Department of Veterans Affairs, and the Environmental Protection Agency. In 2001, the U.S. Agency for International Development joined the Task Force to help address global antimicrobial resistance issues.

Public Health Action Plan to Combat Antimicrobial Resistance

In 2001, the Task Force published the "Public Health Action Plan to Combat Antimicrobial Resistance" (Public Health Action Plan or the Action Plan). The Action Plan provides a blueprint for specific, coordinated Federal actions to address the emerging threat of antimicrobial resistance. It reflects a broad-based consensus of Federal agencies, which was reached with input from consultants from State and local health agencies, universities, professional societies, pharmaceutical companies, healthcare delivery organizations, agricultural producers, consumer groups, and other members of the public.

The Action Plan has four major components: surveillance, prevention and control, research, and product development. Highlights of the Action Plan include:

Surveillance. Information and statistics about the emergence and spread of resistant microbes and the use of antimicrobial drugs can help experts interpret trends and identify strategies to prevent or control antimicrobial resistance. CDC is working with State health departments and other Task Force members to design and implement a strategy to coordinate national, regional, State, and local surveillance efforts. In addition, FDA, CDC, and USDA developed and expanded systems to monitor patterns of antimicrobial resistance among foodborne bacteria in human medicine, in agriculture, and in retail meat.

Prevention and Control. Research shows that controlling the use of antibiotics can help reduce the incidence of antimicrobial resistance. In 2003, FDA partnered with CDC's launch of its *Get Smart: Know When Antibiotics Work* campaign. The goal of the campaign is, and has been, to educate consumers and healthcare professionals on the appropriate use of antibiotics. In partnership with doctors and other medical professionals, CDC has developed clinical guidelines for health professionals on how best to use antimicrobials, and supports pilot projects to identify effective strategies to promote appropriate antimicrobial drug use. FDA has promulgated regulations for labeling antibiotics regarding their appropriate use for infections caused by bacteria. FDA's Center for Veterinary Medicine (CVM) has developed, in conjunction with stakeholders in-depth antimicrobial prudent use principles for beef, dairy, swine, poultry, and more recently, aquatic veterinarians. In 2003, FDA published Guidance for Industry #152 ("Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern"). Guidance #152 outlines a recommended approach for conducting a qualitative risk assessment to evaluate the likelihood that an antimicrobial drug used to treat a food-producing animal may cause an antimicrobial resistance problem in humans. The risk assessment approach recommended in the guidance considers a broad set of information, including the importance of the drug in question to human medicine. This information is collectively considered in determining whether the proposed antimicrobial product will pose a risk to public health.

Measures that reduce the need for antibiotic use also serve to reduce the emergence of antibiotic-resistant microorganisms. Prevention of infections through the use of vaccines has effectively eliminated or markedly decreased the problem of resistance in organisms such as *Haemophilus influenzae* type b (virtually eliminated in the United States while still a problem in other parts of the world) and *Streptococcus pneumoniae*, also known as pneumococcus. Published research has confirmed that the latter pneumococcal vaccine has lowered common infections that are often treated with antibiotics. Vaccines also contribute to the control of resistance by preventing or decreasing the use of antibiotics. For example, vaccines against respiratory viruses, such as influenza, by preventing respiratory illnesses, decrease infections which often lead to unnecessary antibiotic use and also prevent complicating, sometimes serious secondary infections caused by bacteria such as staphylococcus or pneumococcus. In addition, development of increasingly sensitive diagnostic assays for detection of resistance allows for rational targeted antibiotic use.

Research. The Action Plan promotes expanding existing research in antimicrobial resistance and related fields in an effort to improve treatments and outcomes. NIH is leading a team of agencies to provide the research community with new information and technologies, including genetic blueprints for various microbes, to identify targets for desperately needed new diagnostics, treatments, and vaccines to combat the emergence and spread of resistant microbes. NIH supports clinical studies to test new antimicrobials and novel approaches to treating and preventing infections caused by resistant pathogens. NIH also continues to support and evaluate the development of new rapid diagnostic methods related to antimicrobial resistance, in conjunction with FDA's Center for Devices and Radiological Health (CDRH). In addition, AHRQ funds various studies on the use of antimicrobial drugs and antimicrobial resistance, including ongoing research on reducing unnecessary prescribing of antibiotics to children. FDA's Center for Biologics Evaluation and Research (CBER) conducts research that facilitates vaccine development for diseases in which resistance is an issue, such as malaria, staphylococcus (MRSA), and enteric diseases.

Product development. As antimicrobial drugs lose their effectiveness, new products must be developed to prevent, rapidly diagnose, and treat infections. The priority goals and action items in the product development focus area address ways to:

- Ensure researchers and drug developers are informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics, and of potential markets for these products;
- Stimulate development of priority antimicrobial products for which market incentives are inadequate, while fostering their appropriate use;
- Optimize the development and use of veterinary drugs and related agricultural products that reduce the transfer of resistance to pathogens that can infect humans; and
- Facilitate development of effective prophylactic vaccines: in particular, focusing on vaccines against microbes that are known to develop antibiotic resistance (e.g., MRSA), thereby reducing the need for antibiotics and the occurrence of antibiotic resistant strains.

On December 12 and 13, 2007, the Task Force held a meeting in Atlanta, GA, to obtain input from outside consultants for revising and updating the Action Plan. The consultants, including a diverse group of experts from the United States and six other countries, reviewed the 2001 Action Plan in detail and participated in discussions on updating the Action Plan for the next 5 years.

FDA ACCOMPLISHMENTS ON ANTIMICROBIAL RESISTANCE

Since 1996, FDA has actively addressed the issue of antimicrobial resistance. As an Agency composed of several product centers, FDA has addressed antimicrobial resistance through a variety of initiatives, primarily through four key areas:

- **Surveillance:** Monitoring and surveillance of antimicrobial resistance and then promptly and effectively responding to current threats from drug resistance.
- **Product Development:** Facilitating and encouraging development and appropriate use of products to help address the issue including new drugs, vaccines, and improved, more timely tests for infectious diseases.
- **Education:** Facilitating the safe and effective use of antibiotics and thus prolonging the life of products by helping improve the quantity and quality of information available to consumers and health professionals regarding antibiotic resistance and principles of appropriate usage. In addition, FDA has an important role in informing the public and healthcare professionals both through educational outreach and by assuring useful and accurate product labeling and appropriate marketing.
- **Research:** Maximizing and coordinating FDA's scientific research to address needs in antimicrobial resistance.

Specific activities by the various Centers within FDA include the following:

Center for Drug Evaluation and Research (CDER)

CDER has launched several initiatives to address antimicrobial resistance. Through CDER's initiatives, FDA has issued drug labeling regulations, emphasizing the prudent use of antibiotics. The regulations encourage healthcare professionals to prescribe antibiotics only when clinically necessary, and to counsel patients about the proper use of such drugs and the importance of taking them as directed.

We are living in challenging times for antibacterial drug development. Over the last several years, CDER has been evaluating the design of clinical trials that are used to study the safety and efficacy of drugs for the treatment of a variety of infections. CDER recognizes the importance of ensuring that antibacterial drugs are approved based on sound, informative clinical trials, because the clinical use of marginally effective antibiotics can contribute to the development of antibiotic resistance. For milder infections that are often self-resolving over time, we are recommending different types of studies than what were used in the past. The Agency is doing this in order to have studies that have the capacity to provide informative data to assess an antibacterial drug's effects in these milder conditions. It is essential that clinical trials evaluating a new drug be performed in a manner that allows for assessment of the benefits and the risks of the drug in the condition under study. A better assessment of the benefits that a drug may provide and balancing these benefits with risks should provide better quality information on antibacterial drugs to foster appropriate use and ideally reduce inappropriate use that is also contributing to the development of resistance.

To that end, CDER has been revising its guidance to industry on the development of drugs for the treatment of bacterial infections. Revision of these guidances is an important first step. In October 2007, CDER published a draft guidance document on appropriate use of non-inferiority trials for antimicrobial drugs. CDER has also recently published draft guidance documents on developing drugs for acute bacterial sinusitis (October 2007) and acute bacterial otitis media (January 2008). These two draft guidance documents were two of the three listed in section 911 of the Food and Drug Administration Amendments Act (FDAAA) of 2007. The Agency is working on the third of the three listed documents; a draft guidance document for acute bacterial exacerbation of chronic bronchitis.

In January of this year, FDA co-sponsored a workshop with the Infectious Diseases Society of America on the topic of clinical trial designs for community acquired pneumonia (CAP). The workshop provided a platform for the discussion of issues in trial designs for CAP. The Agency also convened an advisory committee meeting in April 2008 to get additional advice and the Agency is now actively engaged in writing a draft guidance document that will provide the Agency's thinking on informative trial designs in CAP.

By providing these draft guidance documents on developing drugs for these conditions we have provided some clarity on the types of study designs that will be informative in these conditions. It is also important to keep in mind that these more

sophisticated types of trial designs are different than the types of studies that have been used previously in these conditions. Hence, a company conducting a clinical trial that is different than what has been used in the past is faced with the uncertainty as to whether their drugs will work, as well as the uncertainties that are inherent in utilizing a trial design with which there is less experience. Therefore, FDA is working as expeditiously as possible to clarify what is needed in a clinical trial design as we make it through this necessary transition period.

Most of the discussion of drug development has focused on resistance in common bacterial infections, but resistance is also a problem in conditions such as tuberculosis (TB), fungal infections, and malaria. CDER has participated in a working group with representatives from FDA and the European Medicines Agency to discuss strategies for developing drugs for TB. CDER also published a draft guidance document describing approaches to the development of drugs for malaria in June 2007.

Appropriate use of antibacterial drugs is guided not only by understanding the safety and effectiveness of risks and benefits of these drugs, but also by having information on whether a particular drug is active against a patient's infection when culture results are available. Laboratory testing to assess whether a bacterial isolate is "susceptible" to a particular antibacterial drug can provide such information. There are a number of antibacterial drug labels that are in need of updating of the information on susceptibility testing. FDA just recently published a draft guidance document on "Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices" (published June 2008). This draft guidance, in compliance with Section 1111 of FDAAA, describes options for updating the antibacterial susceptibility testing information in antibacterial drug product labeling and we believe could facilitate the timely updating of this information.

Section 1112 of FDAAA requires FDA to convene a public meeting "regarding which serious and life threatening infectious diseases, such as diseases due to gram-negative bacteria and other diseases due to antibiotic resistant bacteria, potentially qualify for available grants and contracts under section 5(a) of the Orphan Drug Act . . . or other incentives for development." In compliance with section 1112 of FDAAA, FDA held a public hearing on April 28, 2008, to discuss, in part, potential incentives to encourage pharmaceutical companies to develop new antimicrobial drugs.

Center for Biologics Evaluation and Research (CBER)

Research and regulatory efforts have contributed to the development and continued availability of effective vaccines which have eliminated or markedly decreased antibiotic resistance by reducing or even nearly eliminating some types of infections. Other vaccines contribute by reducing the need for use of antibiotics. CBER has initiated a new research program to facilitate vaccine development of MRSA and has ongoing research programs to foster the development of vaccines to prevent other frequent infectious diseases problems such as *Salmonella* or *E. coli* gastroenteritis, and TB, as multidrug-resistance has emerged as a national and international threat to health. In addition, CBER works with sponsors to develop safe and effective vaccines against emerging infectious diseases problems. Additional efforts at CBER address new diagnostic tests and evaluation of emerging technologies and test kits for detecting bacteria as it relates to transfusion medicine, mechanisms of resistance, alternative therapies for highly resistant organisms, and regulatory pathways to assess the potential value of probiotics to help reduce the development and spread of antibiotic-resistant bacteria.

Center for Devices and Radiological Health (CDRH)

CDRH leads several efforts to clarify regulatory requirements to both industry and the scientific community on clearance of diagnostic tests for use in antimicrobial resistance initiatives. For example, CDRH assisted device manufacturers in the most efficient way to get an alternative method for detecting vancomycin resistant *Staphylococcus aureus* to market and assured timely introduction of this critically important new product through use of its expedited review process. CDRH has published guidance documents to ensure the safe and effective use of in vitro diagnostics for detecting novel influenza A or A/B viruses from human specimens. CDRH recently cleared a new assay developed by CDC for the detection of human infection with H5 Avian Influenza virus. Other recent approvals include a rapid test for confirming methicillin resistant *Staphylococcus aureus*, a rapid DNA test for detecting Group B Streptococcus in pregnant women and a rapid test for detecting Shiga toxins 1 and 2 produced by *E. coli* in stools specimens to aid in the diagnosis of diseases caused by enterohemorrhagic *E. coli* infections.

Center for Veterinary Medicine (CVM)

CVM is addressing potential human health risks associated with the use of antimicrobial drugs in food-producing animals. This approach uses risk assessment methodologies to quantify the human health impact from antimicrobial use in animals, in conjunction with robust monitoring, research, and risk management. In addition, the Agency participates in public meetings with various stakeholders to strengthen and promote science-based approaches for managing the potential human health risks associated with the use of antimicrobial drugs in food-producing animals.

One of the key components of FDA's CVM strategy to assess relationships between antimicrobial use in agriculture and subsequent human health consequences is the National Antimicrobial Resistance Monitoring System (NARMS). NARMS is a multi-faceted monitoring system that takes advantage of the expertise and resources of a number of Federal agencies and State public health laboratories. NARMS data provides regulatory officials and the veterinary medical community with critical data to help assess the risk associated with antimicrobial use in food animal production, and to devise policy guidelines for their safe use.

CONCLUSION

In summary, the Federal Interagency Task Force on Antimicrobial Resistance has been working for several years to develop and implement programs to combat or mitigate antimicrobial resistance in all relevant sectors—humans, animals and the environment. Progress has been steady with notable achievements. The Task Force holds a public meeting annually to discuss progress through the previous calendar year, receive comments, and redirect efforts for the following year. The current Action Plan is 70-plus pages long. The Task Force is now revising the plan focusing on those activities that are critical to address over the next 3–5 years. The revised plan is expected to be ready for public comment in the fall of 2008.

Antimicrobial resistance is an important public health issue that can only be addressed by collaborative efforts of the relevant Federal agencies, State health departments, and the private sector. The international health community is facing the same issues so it is imperative that we work as much as possible with our international public health colleagues.

Thank you for the opportunity to discuss FDA's role with regard to antimicrobial resistance. I would be happy to answer any questions.

Senator BROWN. Thank you, Admiral Tollefson. Dr. Tenover, you mentioned vaccines in your testimony. With the decreasing effectiveness of some antimicrobials, should research be focusing on more vaccines? Is that a practical response?

Mr. TENOVER. I think it is because preventing the infections in the first place is one of our major strategies.

Senator BROWN. Tell me about the process of how far you think we've come on dealing with a lot of these antimicrobials in preventing them with vaccines. How far along are we?

Mr. TENOVER. Well the pneumococcus is a really good success story in the number of infections we have been able to prevent with that. We have been working on staphylococcal vaccines. Those are coming along, but they still have a ways to go.

Again, our strategy is wherever we can prevent the infection, that's what we're going to try and do.

Senator BROWN. Are drug companies doing that kind of research for vaccines too or is that all public dollars?

Mr. TENOVER. No. Pharmaceutical companies are actively involved in vaccines.

Senator BROWN. Do they see potential bottom line success, potential profit on vaccines more or less than they do in finding some kind of antimicrobials?

Mr. TENOVER. I can't answer that question. I don't have an answer on that.

Senator BROWN. Can you look at their behavior and make some kind of educated assertion one way or the other about it?

Mr. TENOVER. Dr. Tollefson, can you address that?

Admiral TOLLEFSON. I think in partnership with the National Institutes of Health they've been able to take some basic research, the pharmaceutical companies, and then so that their expense in the beginning is less. The pneumococcal vaccine is a very interesting example because that was approved for infants and young children. What we found was that the rate of infections in elderly, for example, decreased because the carrier population, if you will, was vaccinated.

Yes, I think in answer to your question, vaccines definitely hold promise and even in a marketable sense.

Senator BROWN. Ok. One other question for Dr. Tenover, you mentioned anything we can do to prevent the need for antimicrobials. The CDC has made simple recommendations, hand washing, making sure towels are washed in locker rooms, especially if they have Astroturf surfaces on football fields, that kind of thing.

Talk to me about the issue of the widespread use of antibacterial hand soaps or hand gels. I've heard that the Director of the CDC recommended that they be used. Is there an antimicrobial resistance issue there with those?

Mr. TENOVER. There may be. Let me explain. I mean anything we can do to get people to wash their hands more is a good thing. The question is if your soap contains an antibacterial agent, is it more effective than plain soap? The data right now say the answer to that is no. It isn't.

However, what we have seen is some of the antibacterial agents that are put into those hand soaps like triclosan, may select for resistant organisms in the laboratory. The reason is that a bacteria can deal with that disinfectant by pumping it out of the cell just like it does an antibiotic. In the laboratory there are concerns that if you use those types of antibacterials you will select for resistant organisms.

However, in community studies that have been done where they have compared resistance rates with those people using plain soap and antibacterial soaps, we haven't seen that materialize as a definitive problem.

Senator BROWN. Is there a third soap? There were in the antibacterial, the regular soap and the alcohol substance soap, if you will, that's not antibacterial, right?

Mr. TENOVER. That's right. Alcohol-based hand gels are being recommended by CDC. They are very effective in health care settings.

They reduce transmission of organisms. They also don't dry the skin out as much as regular hand soap does. I think we've seen widespread acceptance of those in the hospital setting.

Senator BROWN. They have no antimicrobial resistance issues because they aren't antimicrobials, right?

Mr. TENOVER. That's correct, not directly. The alcohol is bactericidal so it does do that. We've never seen anything that amounts to alcohol resistance in an organism and that would be very unlikely. That's why they're effective.

Senator BROWN. Admiral Tollefson, my time's running out. I wanted to, few people understand the sort of intersection here I think of antimicrobial resistance and in the animal population. I understand you're an M.P.H. and a doctor and a veterinarian, correct?

The Center for Veterinary Medicine has a $3-million-line item in its budget to re-examine the resistance implications have already improved antibiotics. What specific activities at CVM have been supported by that budget line item and has the CVM initiated action to take any drugs off the market as a result of those reviews?

Admiral TOLLEFSON. Thank you, Senator. The $3 million was very well received. We appreciate that. It allowed us to do quite a few things in the area of antimicrobial resistance that we couldn't previously.

Microbiologist within our Microbiology Safety branch in the Office of Food Safety has been looking at the currently approved antimicrobials, specifically the penicillin and tetracycline products in great detail. They are going through the files of the new animal drug applications for each of those products. As you're probably aware, there are pioneer products, but also many generic versions of the penicillins and tetracyclines.

Looking for information both on efficacy and on safety as it regards antimicrobial resistance. They have finished that process. They have also undertaken an extensive literature search to look to see if there's any new information on either the penicillins or the tetracyclines.

My understanding is that they are close to reaching summary evaluation. As far as I know there has been no move to take those products off the market.

Senator BROWN. Ok, thank you. Senator Burr. Oh, in that case, Senator Hatch is next.

Alright, one of you two has got to go next.

[Laughter.]

You're way more polite—Senator Hatch.

Senator HATCH. To both of you we appreciate what your agencies are doing to try and help with these problems and especially domestically on antimicrobial resistance, but would each of you please tell the committee what global efforts are being done in this case and also what Pan American efforts are being done as well? Because we have people crossing the borders at all times and I just would like to kind of get caught up to speed on that.

Mr. TENOVER. Well I think one of the things to acknowledge is that a lot of our antibiotic resistance issues here are home grown. One of the things that we've done at CDC is to try and develop relationships with other CDC-like organizations around the world. We work with the World Health Organization on projects to define antimicrobial resistance and to monitor the spread of resistant organisms in a variety of the regional offices of WHO.

One of those, of course, is the Pan American Health Organization. We have very strong ties with them. We've worked with them in terms of developing our surveillance systems, both in Central and South America and coordinated those. We've also worked on a number of training programs with them to increase their labora-

tory capacity so that they can detect resistant organisms as they develop and spread.

Admiral TOLLEFSON. I'd like to reiterate that the antimicrobial resistance is definitely a global problem. We can't work alone. When we work very closely with the World Health Organization and the Pan American Health Organization—you may be interested, Senator Hatch in knowing that our Center for Veterinary Medicine had an extensive program with Mexico to develop an antimicrobial resistant surveillance system in carried pathogens from animals and from retail food in Mexico.

We supported that in 5 States and Mexico for 3 years. It was so successful that the Mexican government then picked it up. And it's continuing to grow.

Senator HATCH. That's great.

Admiral TOLLEFSON. That's a very practical application of a global. We did it primarily because of the flow of the food across the borders.

Senator HATCH. Admiral, the FDA has an office for some drugs that has a grant program that would help with antibiotics particularly for narrowing indications or infrequent infections. In Section 1112 of the Drug Administration Amendments Act, we discuss ways in which that office's activities could be expanded and even publicized. Would you discuss what the FDA is doing to encourage or speed the development and approval of new antibiotics?

Admiral TOLLEFSON. Sure. Thank you. We recently held a public meeting on that specific provision of the FDA Amendments Act on whether the Orphan Drug Act could be used to provide incentives for treatment for resistant organisms or new antimicrobials for them. We also broadened it to sort of widen the questions we ask about antimicrobial resistance.

The input we got from that meeting was very valuable. They talked about various incentives. At this point we don't believe that the Orphan Drug Act is a particularly good model for a number of legal and practical reasons.

That isn't to say that those same incentives couldn't be used. The Orphan Drug Act——

Senator HATCH. You're criticizing my bill you know.

Admiral TOLLEFSON. Yes. I know.

[Laughter.]

The Orphan Drug Act has very specific provisions about how many people have to be affected with the disease. What we've seen with resistant infections, unfortunately, is that that number is broadening. It was a valuable meeting and we continue to look at incentives. We think that it's key to the overall approach to controlling resistance.

Senator HATCH. Well, I agree with you on that observation. Dr. Tenover, in the strategies to address antimicrobial resistance in the STAAR Act, Senator Brown and I have suggested a holistic approach to the problem of antibiotic resistance and establish a network of experts across the country to conduct regional monitoring of resistant organisms as they occur and get kind of a snap shot, to pick up the problems earlier. Can you discuss the importance of augmenting the CDC's current surveillance system with some sort of an expert system?

Mr. TENOVER. Our National Health Care Safety Network now is growing and our focus is specifically on identifying health care associated infections and the resistant microorganisms that are causing those infections. Right now we have over 1,500 hospitals that are participating in a National Health Care Safety Network. We plan to expand that to around 2,000 by the end of the year. This will help in that sort of surveillance.

Also we have several surveillance programs in place through our emerging infections program at CDC. These are State-based, population-based programs designed to do exactly what you're talking about which is to try and detect emerging resistance problems as quickly as possible.

Senator BROWN. Thank you, Senator Hatch.

Senator Burr.

Senator BURR. Thank you, Mr. Chairman. Dr. Tenover, welcome. Admiral Tollefson, welcome.

Doctor, last October a high school student at Virginia died after being hospitalized for more than a week with an antibiotic resistant staphylococcus infection. This was publicized around the country. In North Carolina, the press highlighted cases in hospitals and locker rooms and referred to it as a superbug.

Now maybe it was coincidence but on the same day an article was published in JAMA estimating the incidence of MRSA infections in the United States. In that article the authors described differences in MRSA infections by race, socio-economic status, geographical differences. To what extent do we understand those differences today?

Mr. TENOVER. That's a very important question. Thank you for asking that. That's a major part of our investigations now into our MRSA infections in the community. We found in a pilot study that we did several years ago that there were suggestions of these. They're very important for us to try and discern. Those studies are ongoing at this point.

Senator BURR. Clearly the results of what we find out will be important.

Mr. TENOVER. Yes, very much so.

Senator BURR. Admiral Tollefson, there's an Interagency Task Force on Antimicrobial Resistance that currently exists. How often does that group meet and what takes place at those meetings?

Admiral TOLLEFSON. We try to meet about four times a year. The entire group, which is composed of many Federal agencies, all those that have something in their mission having to do with health. We also have smaller group meetings among agencies when a particular issue needs to be addressed or discussed, like NIH and CDC, FDA and CMS or something like that.

Also once a year we have a public meeting where we talk about the progress that has taken place over the previous calendar year. That actually is going to take place tomorrow at the National Foundation for Infectious Diseases Conference in Bethesda. I would say that we meet fairly frequently.

We're in the process of extensively revising the action plan to bring it more up-to-date and probably most importantly to focus on what we can accomplish over the next 3 to 5 years, rather than make it this massive blueprint of all types of effort.

Senator BURR. What's the goal of the task force?

Admiral TOLLEFSON. Well, the goal is to mitigate or combat or mitigate antimicrobial resistance. We do that in various areas. It's research. It's surveillance. It's prevention and control. It's new products being developed.

Senator BURR. Do you think the FDA has harmed human health by approving antibiotics for use in food animals?

Admiral TOLLEFSON. Well I'll answer that question in one way. We recently removed fluoroquinolone for poultry from the market because it definitely harmed human health. That action took place in 2005, successful action.

Senator BURR. The legislation that Senator Brown and Senator Hatch have proposed calls for the FDA to consult with other Federal agencies before acting upon an antibiotic submission. Does the FDA currently consult with other Federal agencies or outside bodies when reviewing antibiotic drug applications?

Admiral TOLLEFSON. We may, yes. We have a number of advisory committees that will advise us on approval of antimicrobials. Those advisory committees could contain, you know, employees of other agencies or if we have a particular question we won't hesitate to ask them.

Senator BURR. Well that latitude exists.

Admiral TOLLEFSON. That latitude definitely exists.

Senator BURR. It's something that is currently utilized.

Admiral TOLLEFSON. Yes.

Senator BURR. For example under the FDA process?

Admiral TOLLEFSON. Exactly, as needed.

Senator BURR. Let me move just very briefly to vaccines where Senator Brown was. Clearly we went through several decades of vaccine decline in this country. Not because the threats were any less, but because the return on investment didn't exist for the manufacturers that were in it.

When we looked at it almost a decade ago, the primary reason for that was the liability exposure.

Admiral TOLLEFSON. Right.

Senator BURR. Because the human body processes vaccines differently for each person, some percentages were going to have an adverse reaction. Do either one of you honestly believe that we will return to robust vaccine production and innovation in this country without addressing liability for the larger population like we have for the children's vaccines?

Admiral TOLLEFSON. I think the area of vaccines is right to address the issue of antimicrobial resistance. I think we could have some real success there. Whether we need an indemnity type program, I think that's for others to decide, others that have more experience in that area.

I understand your thoughts that you won't get development.

Senator BURR. Would you disagree that when we've looked in the rear view mirror to understand the decline of vaccine innovation and production in the United States we found the liability exposure to be a major factor in their decision? If one used that historical reference to try to design a pathway in the future one would conclude that that would have a great effect——

Admiral TOLLEFSON. Yes, I agree.

Senator BURR [continuing]. Of willingness of manufacturers to commit innovation dollars and two, to actually manufacture and distribute domestically.

Admiral TOLLEFSON. Yes, I agree. Fred, do you want to——

Senator BURR. Thank you. I thank the Chair.

Senator BROWN. Thank you very much, Senator Burr for your interest in this. I want to follow up on your comments in response to a very good question from Senator Burr about baytril in the fluoroquinolone class. I remember I had been working in 1999–2000 on the issue of antibiotic resistance in prophylactic use of antibiotics in cattle, but mostly if I recall from back then, mostly poultry.

In my understanding was this just removed from the market, baytril was removed because there was already evidence of antibiotic resistance in humans when in fact, baytril, this class of fluoroquinolone had only been used in poultry. It had never been used in humans. Is that correct?

Admiral TOLLEFSON. Not in the United States. We had information from other countries that it had never been used in humans, had been used in animals. We found fluoroquinolone resistant campylobacter in those humans. Our basis for removal of that drug from poultry was based on quite a bit of evidence of human health harm.

Senator BROWN. No, that's sort of my point. I remember that some fast food restaurants——

Admiral TOLLEFSON. Yes.

Senator BROWN. Farms, large purchasers of poultry, chicken especially were already at that point saying that they were no longer going to buy poultry——

Admiral TOLLEFSON. Poultry.

Senator BROWN [continuing]. From farms that used baytril. My point is that that is so very clear cut that there is human resistance build up and it hadn't been used in humans. It had been used in poultry. No agency could come up with any other explanation for it.

Does that suggest, and that's the only time I understand that the FDA through CVM has or through—help me with this. The CVM, I'm sorry.

Admiral TOLLEFSON. The Center for Veterinary Medicine.

Senator BROWN. That they've acted to take a drug off the market that way. Does that suggest that you're not aggressive enough that it only took one that was so, so clear, it took 5 years to remove it from the market? Are you being aggressive enough to—been moving forward as you should be perhaps, on those antimicrobials that may in fact cause some problems in humans?

Admiral TOLLEFSON. I think we're being aggressive to the point that we can base on other priorities. It's very complicated, scientifically.

Senator BROWN. Sure.

Admiral TOLLEFSON. It's not always as clear cut as it was in the case of the fluoroquinolones. So we need to look at each approved antimicrobial, look at the risk and then moved either to take it off the market or we could do something much less than that. You know, we can work with the sponsor to change the labeling of the

product. We can work with the sponsor to limit its use to certain species or certain disease indications or even how it's being used.

We have quite a few options short of withdrawing an antimicrobial from the market.

Senator BROWN. Seven or so years ago I had an amendment in fiscal year 2001 Appropriations requesting that FDA review the safety of non-therapeutic use of antibiotics in farms. In 2004, letters were sent from the FDA to the manufacturers of penicillin and other drugs requesting more information because the FDA reassessed their safety and found that the use of those drugs for growth promotion and feed efficiency and weight gain proposed a high risk of producing resistant organisms and potential harm to human health. To my knowledge these requests were never answered? What gives?

Admiral TOLLEFSON. Some of the companies did actually answer with data, submitted data to us. Some of it was redundant to what we had in the original new animal drug applications. That is the same issue that they, the Center for Veterinary Medicine decided to do an extensive literature search on. That's the same issue that's ongoing.

Senator BROWN. Ok. Any other questions from Senator Hatch? Senator Burr?

Ok, thank you very much. I very much appreciate Admiral Tollefson, your testimony and public service. Dr. Tenover, you too. Thank you.

The Chair calls up the next panel. If they would come forward.

We have a vote at 11:15. Yes. But they called it.

Thank you. We'll begin the next panel. The vote will be any minute and we might have to interrupt at some point. Thank you all for joining us.

Brandon Noble is a 5-year veteran of the National Football League. Mr. Noble has seen both sides of one of sports greatest rivalries having played on the Washington Redskins and on the Dallas Cowboys. He started every game in 2004 and received the Redskins Ed Block Courage Award for perseverance through injury. He and his wife, Mary Kate, live in Virginia with their three children.

Dr. Patrick Brennan currently serves as the President of The Society for Healthcare Epidemiology of America. He is the Chief of Healthcare Quality and Patient Safety at the University of Pennsylvania Health System and Professor of Medicine at the School of Medicine. At the Hospital of the University of Pennsylvania he served as Chair of the Healthcare Infection Control Practices Advisory Committee for the Department of Health and Human Services. Dr. Brennan, welcome to you.

Dr. Jay Graham served as Consultant to the Pew Commission on Industrial Farm Animal Production. He is currently a research fellow at Johns Hopkins School of Public Health where his research focuses on epidemiological and environmental health studies of animal production in the United States and abroad. In addition he's worked with the United Nations to understand risks of avian influenza in farm animal populations and might have some comments on Senator Hatch's question a few minutes ago. Dr. Graham, thank you for joining us.

Dr. Lyle Vogel is Assistant Executive Vice President of the American Veterinary Medical Association. Dr. Vogel served in the U.S. Army Veterinary Corps for 26 years as a food safety and public health specialist. He is a diplomat at the American College of Veterinary Preventative Medicine, has won many awards including the AVMA's President's award and a special citation from the FDA's Commissioner in the area of combating antimicrobial resistance. Dr. Vogel, thank you for joining us.

Dr. Barry Eisenstein has served as the Senior Vice President of Scientific Affairs for Cubist Pharmaceuticals since July 2004. He has previously held management positions at ActivBiotics, Inc. and Eli Lily and was Vice President of Science and Technology at the Beth Israel Deaconess Medical Center in Boston. Dr. Eisenstein currently serves as Clinical Professor of Medicine at Harvard Medical School, is editor of the Journal of Antimicrobial Agents and Chemotherapy. Dr. Eisenstein, welcome.

Mr. Noble, would you begin?

STATEMENT OF BRANDON NOBLE, FORMER NFL PLAYER AND MRSA SURVIVOR, CHESTER SPRINGS, PA

Mr. NOBLE. Thank you, Mr. Chairman, Senators. I'm pleased and very thankful to be here today—fortunate to be here today after what I've gone through.

Thank you for letting me share my story, the story of my family as we have dealt with MRSA for the past few years. Four or five years ago I couldn't have told you what MRSA was. Then playing for the Washington Redskins I blew my knee out, which started a chain of events that ended in the end of my football career of which MRSA had a huge part.

In my first year in Washington, I tore my ACL, my MCL, my PCL and dislocated my knee cap all in one fell swoop. I thought at that point that was probably the most painful thing I would ever experience in 20 years of football and I was wrong. As I came back from that injury, overcompensating one leg for the other, I injured my right knee which required a quick scope, a week off of training and I'd be back getting ready for the next season.

Eight days afterwards they took the stitches out I developed a "hot spot," started feeling very sick. Felt like somebody was lighting me on fire in bed at night. All of these symptoms were going on in Washington with the Redskins, some of the best medical people around, didn't know what was happening to me.

They put me on keflex which is just your basic antibiotic that they give everybody for infections. It had no effect. Two days later after the "hot spot" developed, it was now covering most of my leg.

My mother in law is a nurse. She came down. It happened to be my daughter's second birthday party. She came down and I was laying on the couch, in and out of, not necessarily consciousness, but waking up, sleeping, moaning, sweating, feeling pretty bad. She told my wife, you need to get him to the hospital right now.

I was rushed to the hospital. The doctors that admitted me to the emergency room came, talked to me, talked to my parents, while my daughter's second birthday party is going on and basically informed my parents that another 24 hours and this could have potentially been much worse, including loss of life or loss of a leg.

From there I recovered, 7 days in the hospital, only one surgery, thankfully.

Then I got to take home my first PICC line which is an IV that you use at home. It's attached to the inside of your arm. It limits you immensely. I had two children at the time and none of them are under 5 pounds, nor were they ever.

[Laughter.]

You're not allowed to lift anything over 5 pounds or do anything strenuous. This is during my off season conditioning program which to be a professional athlete, it's a 12-month-a-year job. I missed a lot of it.

I suffered through about 3 weeks of vancomycin. Then I developed a reaction to that. The dose of vancomycin is administered three times a day for an hour and a half.

You have to go sit down and hook yourself up to an IV. One of them went through me too fast. I developed Red Man Syndrome, which is where you get a rash that covers your whole body and is very uncomfortable, very itchy. From there I recovered. I came back. I was ready to play football again.

I crammed 6 months worth of work into about 3 weeks. I wasn't in great shape but, I got back on the field.

Within 2 weeks I injured my other knee, my reconstructed knee. I had a bone bruise because I was overcompensating for a weak right knee. And the process started over again. Had another surgery, put on injured reserve, went home.

I found out my wife was pregnant with our third child so took the opportunity away from the NFL to take care of my kids while she was pregnant. Chasing two little children around, it re-injured the knee. Over the course of about a month, draining it, draining it, draining it, somehow or another I picked up another infection.

Had emergency surgery on a Thursday night, my wife came in on Friday morning to deliver our third child. The doctors, thankfully, allowed me to go into the delivery room. Obviously, with what I had, that was a risk, but it was one where I needed to be there. I was there for the other two and I wanted to be there for the third.

It has affected us in that way and now having three children and watching them grow up, two boys and a girl. The boys are all boys. They're cut. They're scraped. They're always getting dinged. Every little bump, everything we see, because of my experience, now affects us because we're keeping an eye on it.

They're in school. They're around other people. I've become a complete germaphobe. I'm scared to death to touch anything in public places. I'm all over my children about that also.

It has been something that we're going to live with for the rest of our lives. As a father, you know, to watch one of my children go through what I went through, scares me to death. Working with the IBSA, I've met parents who have lost children to MRSA. I couldn't imagine going through that personally. I couldn't imagine having my children in the kind of pain that I was in physically.

I'm a tough person. I've broken bones, blown knees out, had teeth knocked out. You name it, I've done it. To watch my children suffer like I did would be very difficult.

I thank you for what you're doing here today, for bringing light to this issue. I think it's an issue that the American public doesn't pay attention to enough. Mostly because it affects all of us as opposed to one single group.

It's very important because it will kill you. It hurts and it's painful. It doesn't care if you're old or young or white or black. When you get it, it's serious. The medical profession needs help taking care of it. Thank you very much.

[The prepared statement of Mr. Noble follows:]

PREPARED STATEMENT OF BRANDON NOBLE

Mr. Chairman and Senators, I'm pleased to be with you today to tell my story, and that of my family, of living with an infection resistant to most antibiotics. Not that long ago, most of us hadn't heard of "MRSA." However, today, many of us know someone affected by it or at least have heard of it. Thank you for giving attention to this important issue. I urge you to take action to protect others and prevent them from going through what I've been through.

Being a football player, there are certain things you can expect—including injuries. But MRSA is the worst and most unexpected thing that I have come up against in my 20-year football career. A tiny little thing that I cannot see which has hurt me more than any of the other injuries combined. MRSA had a hand in ending my career.

In 2005, while playing for the Washington Redskins, I had routine knee surgery and expected to fully recover and to be ready for the upcoming season. The surgery was performed and I was fine for about 8 days, then the stitches were taken out. That night, a hot spot developed over the porthole used for the surgery. I began feeling sick—flu-like symptoms and my knee hurt like someone was lighting me on fire. By the time I was put in the hospital 2 days later, the infection had spread from a quarter-sized red spot to cover a good portion of my leg. One of the first doctors that I saw told my parents that if I had waited another 24 hours we could be talking about the loss of my leg or worse. Surgery was performed and the infection was washed out.

But now I had to deal with the rest of the treatment, including home IV for 6 weeks on the drug vancomycin—which wears you out. It took my energy and appetite. I was told not to lift anything over 5 pounds with my arm that had the IV port in it. With kids and normal activity, that was pretty limiting. Three times a day, for 1½ hours, I had to sit down and get my treatment. Then due to a reaction to the vanco, I was taken off that antibiotic and placed on Zyvox, an oral med that is very strong and has very uncomfortable side effects. I completed my treatment and was given a clean bill of health.

By this time, I had missed the entire off-season workout program. This is my career and livelihood. Now I was playing catch up and tried to cram an off-season into 3 weeks. I was able to come back and play during pre-season camp, but in compensating for the knee that had been infected, I hurt my other leg and required surgery again. I was placed on injured reserve and forced to sit out for the season.

While all this was going on we found out that my wife was pregnant with our third child. So, since I was on injured reserve I was able to stay home and help my wife out. Chasing two little kids around all day, I re-injured my knee and after having the knee drained several times over a couple weeks, I started to get sick again. Same symptoms as before—burning in the knee and the worst flu symptoms you can imagine.

I was admitted to the hospital for surgery. The next day, my wife was admitted to the hospital and our third child was born. Because of my MRSA they were hesitant to let me in the delivery room. But, with necessary precautions, my wife's doctor said I could be there. Missing the birth of a child is not acceptable and would have been devastating. I was scared to hold my son for fear of getting him sick. Again, I was sent home with IV antibiotics.

I continue to live with MRSA. The thing that scares me the most is that I could be a carrier of this bug and have to worry about my wife and kids getting it. Knowing how painful and serious it is, that is the last thing I want to happen. I have three young children who will have a lifetime of cuts and scrapes. I will keep a close eye on each child because I am incredibly paranoid about them getting MRSA. Any small red bump on any of my kids and I am pestering my wife to keep an eye on it, ready to go to the doctors at the drop of a hat.

My wife has been incredible through this experience. In fact, because of it, she's gone back to school to become a nurse and to help others.

An unwelcome complication from my last surgery was developing two blood clots, one in each lung. Because of the clots and the MRSA, I lost my career as a professional football player. This infection has had a huge impact on my life and continues to impact me and my family. Hopefully, I am not a carrier and will not have to worry about this forever.

Please remember, my story is only one of many, and I'm lucky to be here to share it with you. As lawmakers, I urge you to look at the growing problem of resistant infections that have few, if any, antibiotics to treat them. MRSA outbreaks have impacted sports teams, school children, our military, and others. But, there are many other infections which antibiotics are failing to treat.

Mr. Chairman and Senator Hatch, I greatly appreciate your dedication to this issue and your recognition that much more needs to be done to protect public health. Your legislation, the STAAR Act, would better focus the Federal Government on this issue. I understand the government has an Action Plan that is nearly 8 years old and much of it has yet to be implemented—even those items identified as priorities. Your bill makes sure there's a point person, a coach more or less to lead the team and hold all the players accountable.

Also, your bill improves what is known about antibiotic use and assist research in this area. We need to learn more about these infections and the ability to treat them. Finally, your bill will make a difference in prevention. It would monitor new or problematic infections and hopefully prevent their spread. It would collect and study samples of these emerging infections so that physicians will know more about them and help to identify them. For patients like me, it makes all the difference if your physician is on the look out for these infections and can properly treat them as soon as possible.

And, of course, we need to make sure new antibiotics are developed to keep ahead of these bad bugs. These infections take down the strongest and healthiest of us. I hope my experience points out that this truly can happen to anyone.

Thank you.

Senator BROWN. Thank you, Mr. Noble. Dr. Brennan, I wouldn't normally go in that order, but since you're going to talk about the health acquired infections and health care-related infections, I'd like you to go next. Thanks.

STATEMENT OF PATRICK J. BRENNAN, M.D., PRESIDENT, THE SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA, PHILADELPHIA, PA

Dr. BRENNAN. Thank you, Senator Brown for inviting the Society for Healthcare Epidemiology of America to present our views on the challenges of hospital acquired infections in light of the emergence of antibiotic resistant infections. I'm Patrick J. Brennan, President of the Society for Healthcare Epidemiology of America and Chief Medical Officer of the University of Pennsylvania Health System. I'm also a fellow of the Infectious Diseases Society of America.

SHEA, as my society is known and IDSA are sister organizations, many of whose members overlap and a mutual interest in the prevention and elimination of healthcare associated infections and the development of better tools including antimicrobial agents to combat these infections. These infections are diseases caused by microbes primarily bacteria, viruses and fungi and their toxins that occur during the delivery of healthcare and were not present or incubating at the time of entry into the healthcare system. They're often related to the delivery of healthcare itself.

Four diseases are most common: infections of the urinary tract, pneumonies, infections that reach recent sites of surgical procedures and infections involving the bloodstream. Often times these infections are related to the use of a medical device such as a uri-

nary/bladder catheter or a ventilator to support respiration. Such devices when used appropriately are necessary to support patients through their recovery from illnesses. However, devices represent double edged swords whose beneficial effects must be weighed against the risk of infection they pose through proper or improper placement, maintenance and unnecessary use.

As healthcare is delivered more frequently outside the hospital, in clinics, surgical oncology centers, extended care facilities and even private homes, the line between community and healthcare associated infection has become blurred and prevention of HAIs has become more challenging. Reducing preventable HAIs is a complex challenge that requires multiple interventions. No single intervention is a sufficient solution.

Combinations of strategies or bundles of activities such as appropriate hand hygiene during patient care, careful placement and maintenance and removal of supported medical devices is essential. Isolation practices are often necessary to prevent transmission of germs and must be rigorously followed. Antibiotic resistance complicates the management of HAIs.

Since the discovery of antibiotics it has been recognized that microbes possess the ability to resist the killing and inhibitory affects of these drugs. While most germs possess their own native resistance to one or more antibiotics. Germs causing infection in healthcare settings have become more resistant to our commonly available antibiotics, for example, Methicillin-resistant Staph aureus or MRSA infections, thereby limiting our therapeutic options.

Compounding the problem of resistance is the limited availability of our antibiotic choices when resistance arises. In some situations we have moved beyond second and third line choices to the need to re-introduce into common practice agents that have been relegated to the pharmacy shelf decades ago because of their toxic side effects or limited efficacy. Now as our options have been limited by resistance, it has been necessary to re-introduce into practice such drugs.

I've had the experience in my career of seeing a patient die of a drug resistant infection when he developed a rare, but serious allergic reaction to the only available effective drug to treat his infection. We were without therapeutic alternatives.

Hospitals must have flexibility in their choice of prevention strategies because they develop their own microbial ecology and patterns of infection. As a result must tailor their prevention strategies. MRSA is a good example of this. This is an extremely important pathogen. And as Mr. Noble has described, can have a profound impact on the life and career of patients.

While this is a very virulent and important germ, many mistakenly believe it is the only significant cause of HAIs. In fact MRSA constitutes approximately 8 percent of healthcare associated infections. While we have begun to make progress against MRSA, the incidence of which has fallen by more than 50 percent in the past 10 years in some hospital units, much more work remains to be done.

There are promising options to treat MRSA. However for many other types of infections such as gram negatives or armamentarium

is more limited. Increasing levels of resistance are being identified against some classes of antibiotics through an analysis by the ID society is apparent that the pipeline is in decline. This is an important resource that must be restored.

The drugs in development will not be able to address the growing number of antimicrobial resistant infections in the various settings. In particular, there are no drugs in the pipeline to address many gram negative bacteria. It seems likely that it will be necessary for Congress to establish measures to ensure the development of new antimicrobials and a commission to study to understand the measures should be convened by Congress.

What Federal action is most needed with regard to HAIs? Our society supports the conclusions of the recent GAO report in coordination among health and human services agencies related to HAI prevention. We believe that coordinated action is necessary among CDC, CMS and ARC.

CDC in its division of healthcare quality promotion should function as the lead agency, we believe, in surveillance and prevention activities related to HAIs at the Federal level because of its historic and successful role in this area. It has had an enviable record of prevention. Its development and management of the foremost surveillance system of its kind, the National Healthcare Safety Network has created a national resource that many States have now mandated as their public reporting tool. Its guidelines developed by the Federal Healthcare Infection Control Practices Advisory Committee are widely regarded as standards for the field.

We believe that Federal action would have the greatest impact on HAI prevention and antimicrobial resistance by supporting and strengthening the infrastructure currently in place and by taking the following actions.

First, to protect and improve resources for implementation of programs of standardized measurement and appropriate HAI outcomes and performance measures.

Second, to enact the STAAR Act, to reauthorize the Interagency Antimicrobial Resistance Task Force, improve coordination and accountability of HHS and its agencies to combat resistance, to improve upon and further strengthen existing surveillance efforts and create a joint blueprint for antimicrobial research.

Third, Congress should support the development of the next generation of experts in this field. Many of the experts in this field are now mid-career and beyond and the pipeline there is limited as well; create demonstration projects to test real world effectiveness of various implementation strategies and address the prevention of HAI broadly, rather than focusing on specific pathogens.

Thank you. I'll be happy to answer your questions.

[The prepared statement of Dr. Brennan follows:]

PREPARED STATEMENT OF PATRICK J. BRENNAN, M.D.

Chairman Kennedy, Ranking Member Enzi and Members of the Senate Health, Education, Labor, and Pensions Committee, thank you for inviting the Society for Healthcare Epidemiology of America (SHEA) to present our views on the challenges of healthcare-associated infections in light of the emergence of antibiotic-resistant infections. I am Patrick J. Brennan, President of SHEA and Chief Medical Officer of the University of Pennsylvania Health System. I am also a Fellow of the Infectious Diseases Society of America (IDSA). SHEA and IDSA are sister organizations, many of whose members overlap. Our societies have mutual interests in the preven-

tion and elimination of healthcare-associated infections and in the development of better tools, including antimicrobial agents to combat these infections.

SHEA was organized to foster the development and application of the science of infection prevention and control and healthcare epidemiology through research and education in such areas as surveillance, risk reduction, device and procedure management, and epidemiologic investigation. I would like to be clear from the outset that our testimony is provided strictly for the good of the public's health and the patients we treat. We are not here on behalf of any other interest or industry and our advocacy is not financed in any way by industry.

SHEA and its members are committed to implementing evidence-based strategies to prevent healthcare-associated infections. SHEA members have scientific expertise in evaluating potential strategies for eliminating preventable HAIs. We collaborate with a wide range of infection prevention and infectious disease societies, specialty medical societies in other fields, quality improvement organizations, and patient safety organizations in order to identify and disseminate best practice evidence. Our principal partners in the private sector have been sister societies such as IDSA and the Association of Professionals in Infection Control and Epidemiology (APIC). The Centers for Disease Control and Prevention (CDC), its Division of Healthcare Quality Promotion (DHQP) and the Federal Healthcare Infection Practices Advisory Committee (HICPAC), and the Council of State and Territorial Epidemiologists (CSTE) have been invaluable Federal partners in the development of guidelines for the prevention and control of HAIs and in their support of translational research designed to bring evidence-based practices to patient care.

HEALTHCARE-ASSOCIATED INFECTIONS

Healthcare-associated infections (HAIs) are diseases caused by microbes, primarily bacteria, viruses, and fungi and their toxins that occur during the delivery of healthcare and were not present or incubating in the patient at the time of entry into the healthcare system. They are often related to the delivery of healthcare itself. Four diseases represent the most common HAIs. They are: (1) infections of the urinary tract; (2) pneumonia resulting from the aspiration of the contents of the mouth, throat, or stomach; (3) infections at the site of a recent surgical procedure; (4) infections involving the bloodstream that are usually related to the use of an intravenous catheter. Oftentimes these infections are related to the use of a medical device, such as a urinary bladder catheter or a ventilator to support respiration. Such devices when used appropriately are necessary to support patients through their recovery from illness. However, devices represent double edge swords whose beneficial effects must be weighed against the risks of infection they pose through proper or improper placement and maintenance and unnecessary use.

As healthcare is delivered more frequently outside the hospital, in clinics, outpatient surgical and oncology centers, extended care facilities, and in private homes, the line between community-acquired and healthcare-associated infection has become blurred, and prevention of HAIs becomes even more challenging. Reducing preventable HAIs is a complex challenge that requires multiple interventions. No single intervention is a sufficient solution. Combinations of strategies, or bundles of activity, such as appropriate hand hygiene during patient care and careful placement maintenance and removal of supportive medical devices, is essential. Isolation practices are often necessary once infection occurs and must be carefully followed.

Accurate measurement of the occurrence of HAIs and the impact of preventive strategies is important. Measurement of infection rates and the public disclosure of rates can be useful in part because it allows hospitals to have a frame of reference for their performance. It enables patients, purchasers and payors to hold hospitals accountable, and creates the opportunity for dialogue between patients and providers on these issues. Transparency enables providers to better understand the successes and failures that others have had in process improvement related to HAIs and to adopt strategies that have been found to be effective in other facilities treating similar patient populations. The process of collecting and disclosing HAI rates must be balanced with the likelihood that the data collected can lead to actionable information and performance improvement. If data are collected that are not actionable, scarce hospital resources will be diverted to meaningless activities from more valuable interventions.

Antibiotic resistance complicates the management of HAIs. Since the discovery of antibiotics, it has been recognized that microbes possess the ability to resist the killing and inhibitory effects of these drugs. While most germs possess their own native resistance to one or more antibiotics, germs causing infection in healthcare settings have become more resistant to our commonly available antibiotics (e.g. methicillin-resistant *Staphylococcus aureus* or "MRSA" infections) thereby limiting our thera-

peutic options. Compounding the problem of antibiotic resistance is the overuse of antibiotics in humans and animals and the limited availability of alternate antibiotic choices when resistance arises. In some situations we have we moved beyond second and third line drug choices to the need to re-introduce into common practice antimicrobial agents that had been relegated to the pharmacy shelf decades ago because of their toxic side effects. Now, as our therapeutic options have been limited by resistance it has been necessary to re-introduce such drugs into practice. I have had the experience in my career of seeing a patient die of a drug-resistant infection when he developed a rare but serious allergic reaction to the only available, effective drug to treat his infection. We were left without therapeutic alternatives.

Hospitals must have flexibility in their choice of prevention strategies. There has been a growing interest in legislative mandates for action against specific germs. We believe such mandates are unfounded and potentially hazardous. Hospitals develop their own microbial ecology and patterns of infection and as a result must tailor their prevention strategies to their experience. MRSA is a good example of this. This is an extremely important pathogen and one that has had a serious impact on the life and career of one our panelists, former-Washington Redskin Brandon Noble, as well as many patients. While this is a virulent and important germ, many mistakenly believe is the only significant cause of HAIs in the United States. In fact, MRSA constitutes approximately 8 percent of HAIs in the United States. While we have begun to make progress against MRSA, the incidence of which has fallen by more than 50 percent in the past 10 years in hospital medical/surgical intensive care units, much more work remains to be done. Although there are promising options to treat MRSA, the antibiotic pipeline for other types of infections is more limited. Mandates for all hospitals to specifically address MRSA may divert activity away from the increasing resistance in gram-negative infections. Decisions as to appropriate resource allocation can only be made by local risk assessment processes. Appropriate institutional oversight ("stewardship") of antibiotic use is an important aspect of the prevention of some HAIs and may impact the subsequent development of drug resistant pathogens in healthcare settings.

Increasing levels of bacterial resistance are being identified against some classes of antibiotics. Through an analysis done by the Infectious Diseases Society of America, it is apparent that the antibiotic pipeline is in decline and is not strong enough to meet the challenges that we face. Antibiotic research development is an important resource that must be restored. The drugs in development will not be able to address the growing number of antimicrobial resistant infections in the various healthcare settings. In particular, there are no drugs in the pipeline to address many gram-negative bacteria. It will first be necessary to understand what measures are needed to ensure the development of new antibiotics. Congress should commission such a study.

The extent to which HAIs are preventable and the number of lives that can be saved remains a matter of debate. What is not debatable is that we should attempt to prevent every infection and save every life possible through the application of the best evidence to practice. SHEA recently provided Congress with a white paper (See Appendix) with a range of estimates for the number of infections that can be prevented and the potential number of lives saved. Those estimates did not conclude that all infections are preventable at this time. There are significant limitations to the available information from which the estimates are derived but the elimination of HAIs remains an aspirational goal.

Protecting the health of our patients and preventing HAIs in the settings where healthcare is delivered in the United States will require a multi-faceted approach that includes identification and widespread adoption of evidence-based best practices. Where evidence does not exist, uniformity in practice should be adopted and studied to determine effectiveness. Failed practices should be discarded and successes widely disseminated. Prevention and control of HAIs also will require better tools in the form of new and novel antimicrobial agents, better knowledge of strategies to effect implementation and adherence to proven prevention methods, and accountability for performance.

WHAT FEDERAL ACTION IS MOST NEEDED WITH REGARD TO HAIS?

SHEA supports the conclusions of the recent GAO report on coordination among Health and Human Services Agencies related to HAI prevention. We believe that coordinated action among CDC, CMS and AHRQ is critical. CDC and its Division of Healthcare Quality Promotion should function as the lead agency in surveillance and prevention activities related to HAIs at the Federal level because of its historic and successful role in this area. CDC has had an enviable track record of prevention and its development and management of the foremost surveillance system of its

kind, the National Healthcare Safety Network (NHSN) has created a national resource that many States have now mandated as their public reporting tool. Furthermore, guidelines developed by the Federal Healthcare Infection Control Practices Advisory Committee are widely regarded as the standards for the field. Coordinated activity among the agencies can lead to better informed public policy and payment reform.

SHEA urges enhanced support for CDC and its sister agencies including the Agency for Health Care Research and Quality (AHRQ), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) to further the goals of prevention and control of HAIs, and the establishment of a robust pipeline of effective, new antimicrobial agents for treatment and the coordination of efforts to improve the health of our citizens.

SHEA believes that Federal action would have the greatest impact on HAI infection prevention and anti-microbial resistance by supporting and strengthening the infrastructure currently in place to implement evidence-based interventions. Important actions include:

• Protect and improve resources for implementation of programs that standardize measurement of appropriate HAI outcomes and performance measures. Our most valuable resource in this regard is the CDC National Healthcare Safety Network (NHSN). The current administration budget proposes to reduce the source of most NHSN resources at a time when many States consider NHSN the best option for implementing standardized reporting of HAI data. NHSN has now been adopted by 17 States and more than 25 percent of all U.S. hospitals for the surveillance and reporting of HAIs. It is an enormously important national resource and effective funding and support is essential.

• Enactment of the Strategies to Address Antimicrobial Resistance (STAAR) Act to reauthorize the Interagency Antimicrobial Resistance Task Force, improve coordination and accountability of HHS and HHS agencies to combat antimicrobial resistance; improve upon and further strengthen existing surveillance efforts; create a joint blueprint for antimicrobial research; collect comparable and reliable data to allow government to better assess the antimicrobial resistance problem including how antibiotic use in humans and animals triggers the development of resistance; and establish demonstration projects to encourage more appropriate use of existing antibiotics.

• Congress should support the development of the next generation of experts in this field. Designate grants to State and local health departments, and private organizations to support specialized education and training is essential to ensure that adequately trained personnel are available to meet the growing needs throughout the United States.

• Support standards and HAI preventive measures that assure availability of local expertise in infection prevention in every State and locality and in every healthcare facility. Such standards might set a minimum number of infection control professionals and healthcare epidemiologists based on size and acuity level of a facility and/or population of a State.

• Create demonstration projects to test the real world effectiveness of various implementation strategies for evidence-based interventions to prevent infections.

• Support States' efforts to create appropriate statutes to ensure optimal HAI prevention activities and, in some cases, public reporting standards that fit their own HAI challenges.

• Ensure that unintended consequences of well-intended mandates such as public reporting of HAIs (for example, avoidance of surgery on patients thought to be at higher risk of infection, or inappropriate antimicrobial treatment of asymptomatic patients where such treatment is not indicated) are considered prior to adoption of surveillance or reporting requirements.

• Address the prevention of HAIs broadly (rather than focusing on specific organisms) to ensure that healthcare institutions can adequately allocate resources to HAIs of highest priority to local needs. As an example, SHEA endorses the emphasis the Joint Commission places on conducting a risk assessment in order to target preventive efforts effectively. We believe that this strategy allows healthcare facilities to use local information to develop and implement optimal and individualized prevention plans designed to reduce healthcare-associated infections that are identified as local problems. Goals should be written in such a way to allow hospitals the flexibility to identify and target their own safety threats within the domains that are considered critical, and healthcare facilities should be expected to be able to justify their infection prevention program based on local risk assessments.

• Allow flexibility for healthcare facilities to select locally appropriate interventions from among "evidence-based practices" in creating a prevention program that is effective. This flexibility recognizes the influence of local conditions on the control

of healthcare-associated infections, and allows rapid modification of strategies as new knowledge is gained.

Thank you. I will be happy to answer any questions.

Senator BROWN. Thank you, Dr. Brennan. Now I think we will recess for 20 to 25 minutes and I will obviously return as quickly as I can. Thank you.

[Recess]

Senator BROWN [resuming the Chair]. Thank you. I again, Senator Hatch and I apologize for the interruption. Now Dr. Graham, thank you—you're next.

STATEMENT OF JAY P. GRAHAM, PH.D., MBA, CONSULTANT, THE PEW COMMISSION ON INDUSTRIAL FARM ANIMAL PRODUCTION, BALTIMORE, MD

Mr. GRAHAM. Thanks a lot. Good morning or good afternoon, maybe? My name is Jay Graham.

I'm a public health researcher at Johns Hopkins Bloomberg School of Public Health. In addition I was the co-author of a report for the Pew Commission on industrial farm animal production titled, Antibiotic Resistance in Human Health. I appreciate the chance to speak to you today.

Antimicrobials play an essential role in the fight against infectious bacteria that can cause disease in humans, disease and death in humans. Their role however, is being jeopardized by the current practice of feeding low doses of antimicrobials to billions of animals. This practice facilitates the spread of resistant disease causing bacteria and compromises the ability of medicine to treat disease.

Under conditions of constant antimicrobial use, resistant bacterial strains have an advantage in terms of reproduction and spread. Because of the speed with which bacteria replicate these changes can come about quickly. While much of the discussion of antimicrobial use centers on the importance of human medicine, it is estimated that most antimicrobials used in the United States are used as growth promoters in food animal production, not in human medicine. A wide range of antimicrobial drugs are permitted for use in food animal production in the United States. These drugs represent most of the major classes of clinically important antimicrobials including drugs like penicillin, tetracycline and many others.

This practice of feeding antimicrobials to animals began before we really understood how resistance can spread. We now understand that bacteria can share genetic material, DNA, that encodes the resistance to antimicrobials. It is estimated that this transferable resistance, these resistance genes, account for more than 95 percent of antibiotic resistance.

In our research at the School of Public Health we've isolated multi-drug resistant bacteria and resistance genes in animal waste stored over long periods of time, in food products, in streams downstream from swine confinement operations, in people who work with live poultry and in the air at swine operations. The food routes are the most well-studied exposure route. In the United States, drug resistant bacteria are highly prevalent in meat and poultry products including disease causing organisms, in meats

that are resistant to the broad spectrum of antimicrobials, penicillin, tetracycline, erythromycin.

Humans are also exposed through environmental routes. Waste disposal is the major source of antimicrobial resistant bacteria entering the environment from animal feeding operations. Each year confined animals produce more than 40 times the amount of waste that is produced from publicly owned treatment works.

The difference is that this waste isn't treated. It goes on to the land right after production. Antimicrobial resistant E. coli and resistance genes have been detected in ground water sources for drinking water sampled near hog farms in North Carolina, Maryland, and Iowa. As you're likely aware, ground water provides drinking water for nearly all U.S. rural populations.

What is most surprising is that the economics don't justify the routine use of antimicrobials. There have been two recent large scale studies, one with poultry and one with swine, that found the actual economic benefits were miniscule to nonexistent. These studies just looked at the economic benefits at the production level.

They didn't include the shortened useful life of existing antimicrobials. They didn't include the loss of disease treatment options in humans and animals nor the increased health care costs, nor the more severe and enduring infections. Those weren't included in those economic analysis.

In closing I would like to reiterate that antimicrobials are a precious resource that should be safeguarded. Routine use of antimicrobials in food animal production should be ended. Economic analyses demonstrate that there's little to no economic benefit from using antimicrobials as feed additives. And that equivalent improvements in growth and feed consumption or feed conversion efficiency can be achieved by improved management. Thank you.

[The prepared statement of Mr. Graham follows:]

PREPARED STATEMENT OF JAY P. GRAHAM, PH.D., MBA

Good morning Mr. Chairman and members of the Senate Health, Education, Labor, and Pensions Committee. My name is Jay Graham and I am a public health researcher at the Johns Hopkins Bloomberg School of Public Health. In addition, I was the co-author of a report for the Pew Commission on Industrial Farm Animal Production titled *Antibiotic Resistance and Human Health*. I appreciate the opportunity to speak to you today.

Antimicrobials are a critical defense in the fight against infectious bacteria that can cause disease and death in humans. Their value as a resource in human medicine is being squandered through inappropriate use in animals raised for food. The method that now predominates in food animal agriculture—applying constant low doses of antimicrobials to billions of animals—facilitates the rapid emergence of resistant disease-causing bacteria and compromises the ability of medicine to treat disease, making it clear that such inappropriate and indiscriminate use must end.

A wide range of antimicrobial drugs are permitted for use in food animal production in the United States. (Sarmah, et al. 2006). These drugs represent most of the major classes of clinically important antimicrobials, from penicillin to third-generation cephalosporin compounds. In some cases, new drugs were licensed for agricultural use in advance of approvals for clinical use. In the case of quinupristin-dalfopristin—an analog of virginiamycin, which is used in food animal production—this decision by the FDA resulted in the emergence of resistance in human isolates prior to eventual clinical registration (Kieke, et al. 2006), thus demonstrating how feed additive use can compromise the potential utility of a new tool in fighting infectious disease in humans. Agricultural use can also significantly shorten the "useful life" of existing antimicrobials for combating human or animal disease (Smith, et al., 2002).

While discussion of the issue of declining effectiveness of antimicrobials often centers on the importance of ensuring the proper use of antimicrobials in human medicine, the fact is that most antimicrobials used in the United States are used as "growth promoters" in food animal production, not human medicine (Mellon, et al. 2001). In North Carolina alone, the use of antimicrobials as a feed supplement has been estimated to exceed all U.S. antimicrobial use in human medicine. A relatively small percentage of antimicrobial use in food animal production is to treat sick animals, and much of what is needed for therapeutic purposes is the direct result of the animal husbandry practices of crowding large numbers of food animals in small confined spaces, thereby increasing the chance that diseases will spread through food animal populations.

Exposure of bacteria to sub-lethal concentrations of antimicrobial agents is particularly effective in driving the selection of resistant strains, and under conditions of constant antimicrobial use, resistant strains are advantaged in terms of reproduction and spread. Because of the rapidity of bacterial reproduction, these changes can be expressed with great efficiency.

Exacerbating the problem of using antimicrobials for growth promotion of food animals is the fact that bacteria can share genetic material that encodes resistance to antimicrobials. It is estimated that transferable resistance genes account for more than 95 percent of antibiotic resistance (Nwosu, 2001). These events have been frequently detected in resistant *E. coli* isolated from consumer meat products (Sunde and Norstrom 2006). At this point, most research has focused on specific patterns of resistance in selected disease-causing organisms—a "one bug, one drug" definition of the problem (Laxminarayan, et al. 2007). But this discounts the fact that it is the community of genetic resources that determines the rate and propagation of resistance (Salyers and Shoemaker 2006).

From a public health perspective, it clearly makes good sense to remove antimicrobials for growth promotion in food animal production. When this is done, resistance in disease-causing organisms tends to decrease significantly. Studies carried out in Europe have demonstrated a rapid decrease in the prevalence of antimicrobial resistant *Enterococcus faecium* recovered from pigs and broilers after antimicrobials were removed (from Aarestrup, et al. 2001). The prevalence of resistant enterococci isolates from human subjects also declined in the European Union (EU) over the same period (Klare, et al. 1999).

Addressing other animal agriculture practices, such as more thorough and frequent cleaning of animal feeding operation facilities, may also be needed in conjunction with cessation of using antimicrobials to eliminate reservoirs of antibiotic resistance bacteria from farms.

Recent studies call into question the assumed economic benefits of using antimicrobials in animal feeds. Historically, economic gains from using antimicrobials to promote growth have been thought to justify the expense of the drugs. Two recent large-scale studies—one with poultry and one with swine—found that the actual economic benefits were miniscule to nonexistent, and that the same financial benefits could instead be achieved by improving the management of the animals (e.g., cleaning out poultry houses) (Graham 2007; Miller 2003). Even when improvements from growth promoting antimicrobials have been observed, their benefits are completely offset if costs from increased resistance are considered: loss of disease treatment options in humans and animals, increased health care costs, and more severe and enduring infections. These costs are usually "externalized" to the larger society and not captured in the price of the meat and poultry sold to consumers.

There are industry trade groups that argue that using antimicrobials in the food animal production process does not pose a threat to public health. But, numerous studies support a strong link between the introduction of an antimicrobial into animal feeds and increased resistance in disease-causing organisms isolated from humans (Silbergeld, et al. 2008). Resistant disease-causing organisms can affect the public through food routes and environmental routes.

Food routes: In the United States, antimicrobial resistant disease-causing organisms are highly prevalent in meat and poultry products, including disease-causing organisms in meats that are resistant to the broad-spectrum antimicrobials penicillin, tetracycline and erythromycin (Johnson, et al. 2005; Simjee, et al. 2002). Animals given antimicrobials in their feed contain a higher prevalence of multidrug-resistant *E. coli* than animals produced on farms where they are not exposed to antibiotics (Sato, et al. 2005), and the same disparity shows up when one compares the meat and poultry products consumers purchase from these two styles of production (Price, et al. 2005; Luantongkum, et al. 2006).

Environmental routes: Waste disposal is the major source of antimicrobial resistant disease causing organisms entering the environment from animal feeding operations. Each year, confined food animals produce an estimated 335 million tons

of waste (dry weight) (USDA), which is deposited on land and enters water sources. This amount is more than 40 times the mass of human biosolids generated by publicly owned treatment works (7.6 million dry tons in 2005). No treatment requirements exist in the United States for animal waste before it is disposed of, usually on croplands—even though levels of antimicrobial resistant bacteria are present at high levels.

Antimicrobial resistant *E. coli* and resistance genes have been detected in groundwater sources for drinking water sampled near hog farms in North Carolina (Anderson and Sobsey 2006), Maryland (Stine, et al. 2007), and Iowa (Mackie, et al. 2006). Groundwater provides drinking water for more than 97 percent of rural U.S. populations. In addition, antibiotics used in food animal production are regularly found in surface waters at low levels (Sarmah, et al. 2006).

Resistant disease-causing organisms can also travel through the air from animal feeding operation facilities. At swine facilities using ventilation systems, resistant disease-causing organisms in the air have been detected as far away as 30 meters upwind and 150 meters downwind (Gibbs, et al. 2006).

Farm workers and people living near animal feeding operations are at greatest risk for suffering the adverse effects of antimicrobial use in agriculture. Studies have documented their elevated risk of carrying antibiotic-resistant disease-causing organisms (Van den Bogaard and Stobberingh 1999; Price, et al. 2007; Ojeniyi 1998; Saenz 2006; Smith, et al. 2005; and KE Smith, et al. 1999).

The rise of antimicrobial resistance in bacteria, in response to exposure to antimicrobial agents, is inevitable as all uses of antimicrobial agents drives the selection of resistant strains. Thus, there is the potential to lose this valuable resource in human medicine, which might well be finite and nonrenewable—once a disease-causing organism develops resistance to an antimicrobial, it may not be possible to restore its effectiveness. Declining antimicrobial effectiveness can be equated with resource extraction. The very notion of antimicrobial effectiveness as a natural resource is a new concept, so it is not surprising that there has been very little public discussion about the ethical implications of depleting this resource for non-essential purposes, such as for growth promotion in food animal production.

In 2003, the American Public Health Association (APHA), in its policy statement, said:

> "the emerging scientific consensus is that antibiotics given to food animals contribute to antibiotic resistance transmitted to humans." APHA, the world's largest public health organization, also remarked that "an estimated 25–75 percent of feed antibiotics pass unchanged into manure waste."

For its part, the World Health Organization (WHO) has recommended that "in the absence of a public health safety evaluation, [governments should] terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans."

For an industry that has become accustomed to using antimicrobials as growth promoters, the idea of stopping this practice might seem daunting. But, consider the case of Denmark, which in 1999 banned the use of antimicrobials as growth promoters. In 2002, the World Health Organization reported that:

> ". . . the termination of antimicrobial growth promoters in Denmark has dramatically reduced the food animal reservoir of enterococci resistant to these growth promoters, and therefore reduced a reservoir of genetic determinants (resistance genes) that encode antimicrobial resistance to several clinically important antimicrobial agents in humans."

The World Health Organization also reported there were no significant differences in the health of the animals or the bottom line of the producers. The European Union has followed suit with a ban on growth promoters that took effect in 2006.

Finally, prudent public health policy thus indicates that nontherapeutic uses of antimicrobials in food animal production should be ended. Economic analyses demonstrate that there is little economic benefit from using antimicrobials as feed additives, and that equivalent improvements in growth and feed consumption can be achieved by improved hygiene.

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Senator BROWN. Thank you, Dr. Graham.

Dr. Vogel, welcome.

STATEMENT OF LYLE P. VOGEL, D.V.M., M.P.H., DACVPM, ASSISTANT EXECUTIVE VICE PRESIDENT, AMERICAN VETERINARY MEDICAL ASSOCIATION, SCHAUMBURG, IL

Mr. VOGEL. Thank you, Mr. Chairman and Senator Hatch for giving the American Veterinary Medical Association the opportunity to speak to you today. I am Dr. Lyle Vogel, Assistant Executive Vice President of the AVMA. Because veterinarians are ethically charged with promoting public health in addition to protecting animal health and welfare, we participate in the prevention and control of both human and animal disease.

Antimicrobial resistance is a complex issue that is not going to be solved by seemingly simple solutions such as bans on certain label uses on antimicrobials without performance of a risk assessment on those individual drugs or drug classes. Let me first say that not all antimicrobials are equal in their probability of it creating a risk to human health. As a result non-risked-based bans of approved uses of antimicrobials will negatively have an impact on animal health and welfare without predictably improving public health and may even harm public health.

The AVMA believes that the current science-based FDA approval process for new antibiotics and review of previously approved antibiotics under Guidance for Industry provides sufficient safeguards for public health. The AVMA advocates for improved monitoring systems for foodborne disease and antimicrobial resistance such as the Food Net and the National Antimicrobial Resistance Monitoring System, sometimes called NARMS. Since 1996 NARMS has provided a great deal of useful information. For example, NARMS data, when combined with Food Net data demonstrates that the case rate of human illness with multi-drug resistance salmonella species has decreased by 49 percent since 1996.

NARMS data also show that salmonella from humans are one half as likely to be resistant in 2004 as they were in 1996. Also resistance of enterococci to synercid in the United States is 10 times less than that in Denmark where the drug equivalent has been banned for almost a decade from use in animals. This information indicates that there is not a public health crisis related to human pathogens that are thought to originate in animals.

In the late 1990s Denmark began to ban antimicrobials used for growth promotion. The use of antimicrobials in feed and water for prevention, control and treatment of disease was not banned. The results in humans and animals have been very mixed.

For example, resistance to vancomycin in enterococcus from humans stayed at 0 percent from 1997 to 2006. There have been dra-

matic increases in resistance to tetracyclines since salmonella from humans. As I mentioned resistance to synercid is 10 times greater in Denmark than it is in the United States.

While the total quality of antimicrobials used in food animals in Denmark has decreased by 27 percent, the increase in disease has resulted in 143 percent increase in the quantity of antimicrobials used for therapeutic purposes. The antimicrobials now used more frequently are in classes which are also used in humans, such as tetracyclines.

Even though the results of the Danish ban are very mixed, proposals within the United States go beyond the Danish example by proposing to ban uses for the prevention and control of disease in addition to uses to promote growth. Several risk assessments have been performed that demonstrate a very low risk to human health from the use of antimicrobials in food animals. Some of the models predict an increased human health burden if the use is withdrawn. Inappropriate reactions to the potential problem could have unintended consequences that negatively affect animal health and welfare and ultimately could create public health risks.

The AVMA does not believe that the Food and Drug Administration needs new authority to regulate the human safety of animal drugs. Instead the FDA needs additional resources to fulfill its existing missions. Improved surveillance and timelier reporting of resistance, research to better understand the causality of resistance, decisions based on risk and continued compliance with judicious use guidelines by veterinarians and producers are sufficient to protect human health against the current small risk associated with veterinary medicine and animal agriculture without compromising the health of food animals or public health.

Thank you for the opportunity to appear before you today and speak about this important issue. Additional information is provided in the written testimony that has been submitted.

[The prepared statement of Mr. Vogel follows:]

PREPARED STATEMENT OF LYLE P. VOGEL, D.V.M., M.P.H., DACVPM

Thank you, Mister Chairman and members of the subcommittee, for giving the American Veterinary Medical Association the opportunity to speak about antimicrobial resistance.

I am Dr. Lyle Vogel, Assistant Executive Vice President of the American Veterinary Medical Association. The vast majority of my 41-year veterinary career has been engaged in the practice of protecting and advancing public health.

The AVMA represents more than 76,000 U.S. veterinarians engaged in every aspect of veterinary medicine and public health. Among other things, our members protect the health and welfare of our Nation's animals, help ensure food safety, and protect animal and human health through prevention and control of zoonotic diseases.

As veterinarians, charged ethically with promoting public health in addition to protecting animal health and welfare, we have great interest in the prevention, control, and treatment of disease. Prevention and control of disease are key elements in the practice of veterinary medicine, particularly in animal agriculture, where the focus is on population medicine. This concept of disease prevention and control through herd health is analogous to public health efforts. The AVMA supports the use of multidisciplinary approaches to address issues affecting public health and food safety. In addition to our support of improved animal husbandry practices and the use of biologics, we also support the continued availability and use of antimicrobials to ensure that we are doing our best to safeguard the Nation's food supply.

Antimicrobial resistance is a complex problem that is not going to be solved by simple solutions. The AVMA opposes seemingly simple bans on certain labeled uses

of antimicrobials, such as growth promotion, feed efficiency, and disease prevention that are not science-based or risk-based. Not all antimicrobials nor all their uses are equal in their probability of developing resistance or creating a risk to human health. The European Union's Scientific Committee on Animal Nutrition has agreed that there is insufficient data to support such bans, yet *possible* theoretical human health concerns continue to be the focus while *probable* and scientifically based benefits to human and animal health are largely ignored (1).

Banning approved uses of antimicrobials will negatively impact animal health and welfare without significantly or predictably improving public health. Based on the results of a limited ban enacted in Denmark (i.e., the banning of growth promotants, not uses to prevent and control disease), we do not believe the public would benefit from such a ban. Non-science based, broad bans of preventive uses of antimicrobials have the potential to harm public health, such as through increased foodborne disease.

These significant decisions need to be science- and risk-based decisions. Decisions made without the benefit of a thorough evaluation of risks and benefits have the potential to further divert resources away from more appropriate disease control measures. Additionally, the AVMA believes that the judicious and regulated use of antimicrobials—through scientifically based FDA approvals and post approval review under Guidance for Industry #152 of previously approved antimicrobials—provides a sufficient safeguard for public health.

ACTIONS ADDRESSING ANTIMICROBIAL RESISTANCE

AVMA'S EFFORTS

The AVMA has acted with three objectives in mind:

1. Safeguarding public health,
2. Safeguarding animal health, and the
3. Continued availability of effective therapeutic antimicrobials for veterinary medicine, including the retention of currently approved, safe drugs and, hopefully, future approvals of new drugs.

Since 1998, the AVMA has actively worked to mitigate the development of antimicrobial resistance related to the use of antimicrobials in food animals. The AVMA Guidelines for the Judicious Therapeutic Use of Antimicrobials were developed to safeguard public health by emphasizing prudent and judicious therapeutic use of antimicrobials. With support and input from the Centers for Disease Control and Prevention, Infectious Disease Society of America, Food and Drug Administration, and the U.S. Department of Agriculture, the guidelines were developed in collaboration with our species specific allied veterinary organizations. These guidelines were based upon carefully reviewed, scientifically sound research, and we believe that our members conscientiously adhere to the principles of judicious therapeutic use of antimicrobials to ensure the protection of human health, as well as animal health and welfare.

We actively encouraged and assisted our allied veterinary organizations to use the AVMA general principles as a template to develop more detailed guidelines appropriate to each species, disease and type of client. The AVMA also worked with these groups to develop and deliver a continuing education program to raise awareness within the profession and to encourage utilization of the principles. Fundamentally, the guidelines encourage scientifically based therapeutic practices, the use of antimicrobials only when needed, and compliance with all existing regulatory requirements when antimicrobials are used.

The AVMA has also continually advocated for improved, more robust monitoring and feedback systems for foodborne disease and antimicrobial resistance such as FoodNet and the National Antimicrobial Resistance Monitoring System (NARMS). We have also advocated for more research to support scientifically based therapeutic practices, such as epidemiological studies that assess the effects of antimicrobial use. In addition, we advocate for increased resources for the FDA's Center for Veterinary Medicine so the agency can adequately implement its regulatory authority.

The AVMA provided start-up funding for projects to create a nationally coordinated laboratory system to test for and report on resistance in animal pathogens and to create a decision support system to assist veterinarians when making antimicrobial use decisions. Unfortunately, while the latter project received follow-on funding by the FDA, neither project has been sustained or finished.

THE FDA ROLE AND ACTIONS

The FDA approves antimicrobials for four purposes:

1. Treatment of disease,

2. Prevention of disease,
3. Control of disease, and
4. Growth promotion or feed efficiency.

The first three uses are classified as therapeutic uses by the FDA, AVMA, and Codex Alimentarius Commission (an organization of the World Health Organization and the Food and Agricultural Organization of the United Nations), and the fourth has also been shown to have health-promoting effects.

The FDA process for the evaluation of food animal antimicrobials is at least as stringent as, and often more stringent than, the approval process for human antimicrobials. In addition to the testing for efficacy and safety to the individual (human or animal) receiving the drug that is common to the human and animal drug approval process, each food animal antimicrobial undergoes an assessment for human and environmental safety as part of the review by the FDA. The FDA's Center for Veterinary Medicine (CVM) uses a very strict safety assessment approval process that requires sponsors to submit data proving the antibiotic is safe for both humans and animals. This is a zero-risk procedure for human safety—benefits to animals are not weighed to offset risks to humans, but rather, drugs that possess risks beyond "a reasonable certainty of no harm" to human health are rejected.

Another safety measure was instituted in 2003 (Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern,") that outlines a comprehensive, evidence-based approach to preventing the emergence and selection of antimicrobial resistant bacteria that may adversely affect human health. The Guidance requires antimicrobial manufacturers to provide information to the FDA showing that a proposed animal drug will not harm public health. The current FDA risk assessment on a drug-by-drug basis provides a scientifically sound process to protect human health. In the event that a determination is made that human health is jeopardized, FDA will not approve the antimicrobial or may limit the use of the antimicrobial in order to mitigate the adverse effect.

Since the mid-1990s, the FDA has coordinated the National Antimicrobial Resistance Monitoring System (NARMS) in cooperation with the Centers for Disease Control and Prevention and the U.S. Department of Agriculture. NARMS is a multi-agency program that includes monitoring for resistant bacteria in retail meats by the FDA, monitoring for resistant foodborne pathogens in humans by the CDC, and monitoring for resistant bacteria in animals on farms and animal products in slaughter and processing facilities by the USDA. NARMS has provided a great deal of useful information since 1996.

Therefore, the AVMA does not believe that The Food and Drug Administration needs new authority to regulate the human safety of animal drugs. Instead, the FDA needs additional resources to fulfill its existing mission. Some of those resources can be furnished through passage of the Animal Drug User Fee Act Amendments of 2008.

RESULTS

United States Monitoring/Surveillance Data

NARMS data, when combined with FoodNet data, demonstrates that the case rate of human infections with multi-drug resistant *Salmonella* spp. has decreased 49 percent between the NARMS baseline years of 1996–1998 and 2004 (the most current, publicly available human data from NARMS). In addition, there has been a 65 percent reduction in the case rate of penta-resistant *Salmonella* Typhimurium infections. The case rate for *Campylobacter* infections in humans that are resistant to ciprofloxacin have remained constant over that period (2).

Additional important resistance trends[1] reported by NARMS (3) (Isolates from humans with clinical disease):

- *Salmonella* spp. (non-Typhi)—½ as likely to be resistant in 2004 than in 1996.
  - a highly significant[2] improvement in susceptibility[3] (20 percent relative increase in susceptibility, from 66.2 percent in 1996 to 79.6 percent in 2004).
- *Salmonella* Typhimurium—less than ½ as likely to be resistant in 2004 than in 1996.

[1] Odds ratios were calculated based upon available data from NARMS assuming the reported isolates were representative of the bacterial population.

[2] "Marginally significant" indicates a p-value between 0.05 and 0.10; "significant" indicates a p-value between 0.01 and 0.05; "highly significant" indicates a p-value of less than 0.01.

[3] No resistance detected to any of 5 subclasses of antibiotics.

- a highly significant[2] improvement in susceptibility[3] (60 percent relative increase in susceptibility from 37.9 percent in 1996 to 60.7 percent in 2004).

• *Campylobacter*—only 0.03 times more likely to be resistant in 2004 compared to 1997.

- a marginally significant[2] decrease in susceptibility[3] (2 percent relative decrease in susceptibility from 47 percent in 1997 to 46.1 percent in 2004).
- However, *Campylobacter* was significantly less likely to be resistant in 2003 when compared to 1997; there was a significant[2] improvement in relative susceptibility[3] (8.2 percent increase from 47 percent in 1997 to 50.9 percent in 2003).

• *Enterococcus faecium*—Decreased resistance to quinupristin/dalfopristin (Synercid) from 20.9 percent in 2001 to 3.7 percent in 2004.

• *E. coli O157*—⅓ as likely to be resistant in 2004 compared to 1996.

- a highly significant[2] improvement in susceptibility[3] (10 percent relative increase in susceptibility).

In addition to trends of improved susceptibility, trends regarding multi-drug resistance[4] also showed improvement:

• *Salmonella* spp. (non-Typhi)—nearly ½ as likely to be multi-drug resistant[4] in 2004 when compared to 1996.

- a highly significant[5] improvement (44 percent relative decrease) in multi-drug resistance[4] (decreased from 27.0 percent in 1996 to 15.0 percent in 2004).

• *Salmonella* Typhimurium—nearly ½ as likely to be multi-drug resistant[4] in 2004 when compared to 1996.

- a highly significant[5] improvement (34 percent relative decrease) in multi-drug resistance[4] (decreased from 56.2 percent in 1996 to 37.2 percent in 2004).

• *Campylobacter*—slightly less likely to be multi-drug resistant[4] in 2004 when compared to 1997.

- a marginally significant[5] improvement (10 percent relative decrease) in multi-drug resistance[4] (decreased from 15.7 percent in 1997 to 14.1 percent in 2004).
- However, when comparing 1997 to 2003, isolates were half as likely to be multi-drug resistant[4] and there was a highly significant[5] improvement (46 percent relative decrease) in multi-drug resistance[4] (decreased from 15.7 percent in 1997 to 8.5 percent in 2003).

Most foodborne infections do not require treatment with antimicrobials. Information shows that there is a decreasing trend of foodborne diseases, thereby decreasing the potential numbers of treatments (4). The trends of increasing susceptibility/decreasing resistance mean more successful treatments when needed. This information indicates that there is not a public health crisis related to human pathogens that are thought to originate in animals.

Danish Experience

In the late 1990s, Denmark instituted a voluntary ban on the use of antimicrobials for growth promotion (AGPs). (A complete ban of AGPs was initiated in 2000.) The use of antimicrobials in feed and water for controlling and treating disease was not banned. The following has been observed as a result of the ban on the use of antibiotics for growth promotion in Denmark:

• There is little evidence to demonstrate a general decline in antimicrobial resistance in humans and there is no evidence of an improvement in clinical outcomes of antimicrobial treatment of humans, the desired consequence of the antibiotic ban in livestock. The results have been mixed. In fact, resistance in humans to some of the banned drugs has increased dramatically.

• There has been increased death and disease in the swine herds, especially at the weaning stage (info inferred from DANMAP 2005 and other reports on pigs). According to published news reports, there was a relative increase of 25 percent in the number of pigs that died from illnesses from 1995 to 2005.

• While the total quantity of antimicrobials used in food animals has decreased by 27 percent, the increase in disease has resulted in a 143 percent increase in the

[4] Resistant to 2 or more antibiotic subclasses.

[5] "Marginally significant" indicates a p-value between 0.05 and 0.10; "significant" indicates a p-value between 0.01 and 0.05; "highly significant" indicates a p-value of less than 0.01.

quantity of antimicrobials used for therapeutic purposes. And the antimicrobials now used are classes such as tetracyclines that are also used in humans (5).

• Resistance to some antibiotics has decreased in some animals while resistance to other antibiotics has increased.

The ban on antibiotic growth promoters in Denmark has not resulted in a significant reduction of antibiotic resistance patterns in humans. It has, however, resulted in an increase in disease and death in the swine herds and an increase in the use of antimicrobials for therapeutic uses in swine herds that discontinued the use of antibiotic growth promoters.

Some important resistance trends reported by DANMAP:

• *Salmonella* Typhimurium from human isolates[6] has shown 34–49 percent *increase* in resistance to tetracycline, sulfonamides, and ampicillin from 1997–2006; increases in resistance to nalidixic acid and ciprofloxacin were 3.8 percent from 1997–2006.

- In contrast, during the same period of time, poultry isolates have shown only minimal increases (2–6 percent) in resistance to the same antimicrobials.
- Isolates from pigs have also shown a lesser increase (25–27 percent) in resistance to tetracycline and ampicillin than human isolates during that time.

• *Campylobacter jejuni* from human isolates[6] has shown 5–11 percent *increase* in resistance to tetracycline, nalidixic acid, and ciprofloxacin from 1997–2006.

- In contrast, during the same period of time, poultry isolates have shown lesser increases (4–6 percent) in resistance to the same antimicrobials.

• *Enterococcus faecium* isolates from healthy human volunteers has shown no increase in resistance to vancomycin (the equivalent of avoparcin) from 1997–2006, and remains at 0 percent.

- However, resistance to virginiamycin (quinupristin/dalfopristin, e.g., Synercid) had been steadily increasing (up to 25 percent) from 1997 to 2005 until the definition of resistance was changed in 2006, bringing the level of resistance down to 0 percent.[7]
- During the same period of time, *Enterococcus faecium* isolates from pigs and poultry has shown 8–20 percent *decrease* in resistance to avoparcin,[8] virginiamycin, erythromycin and tetracycline from 1997–2006 (using the same definition of resistance as the human isolates from 1997–2005).

Even though the results of the Danish experiment with antimicrobial growth promotant drug bans is very mixed, proposals within the United States go far beyond the Danish example by proposing to ban uses for the prevention and control of disease in addition to uses to promote growth and feed efficiency. Evidence shows that the Danish ban (and a ban in the United States, if instituted) will cause animal health and welfare problems.

RISK ASSESSMENTS/ HUMAN HEALTH IMPACT

Antibiotics as a Tool to Prevent and Control Disease in Animals and Humans

The use of drugs in animals is fundamental to animal health and well-being. Antibiotics are needed for the relief of pain and suffering in animals. For food animals, drugs additionally contribute to the public health by helping keep animals healthy and thereby keeping bacteria from entering the food supply. The hypothesis, supported by scientific information, is that a reduction in the incidence of food animal illness will reduce bacterial contamination on meat, thereby reducing the risk of human illness (6), (7), (8), (9), (10) (11), (12), (13).

Several risk assessments have been performed that demonstrate a very low risk to human health from the use of antimicrobials in food animals, and some of the models predict an increased human health burden if the use is withdrawn. The unique farm-to-patient risk assessment performed by Hurd demonstrates that the use of tylosin and tilmicosin in food animals presents a very low risk of human treatment failure because of macrolide resistance, with an approximate annual probability of less than 1 in 10 million with *Campylobacter* infections and approximately 1 in 3 billion *E. faecium* infections (14). Cox performed a quantitative human health risks and benefits assessment for virginiamycin and concluded that there would be a significant human health risk if virginiamycin use is withdrawn. There

[6] Domestically acquired clinical cases.

[7] The rationale for this change is unknown, but appears to introduce bias in reporting. DANMAP decided to use a preliminary European Committee on Antimicrobial Susceptibility Testing breakpoint instead of the previously used breakpoint established by the Clinical and Laboratory Standards Institute.

[8] Avoparcin has never been approved for use in the United States.

would be 6,660 excess cases per year of Campylobacteriosis, which far outweighs the 0.27 per year reduction of cases of streptogramin-resistant and vancomycin-resistant *E. faecium* (VREF) resulting from the withdrawal (15). Cox also performed a risk assessment regarding macrolide and fluoroquinolone use and concluded that withdrawal is estimated to cause significantly more illness days than it would prevent (11). Cox also examined the impact of the use of penicillin-based drugs in food animals on penicillin/aminopenicillin resistant enterococcal infections and concluded that not more than 0.04 excess mortalities per year (under conservative assumptions) to 0.18 excess mortalities per year (under very conservative assumptions) might be prevented in the whole U.S. population by discontinuing current use of penicillin-based drugs in food animals. The true risk could be as low as zero (16). This equates to one potentially preventable mortality in the U.S. population roughly every 7–25 years. Alban's risk assessment concluded that the risk associated with veterinary use of macrolides in Danish pigs resulted in a low risk to human health (17). Others have estimated that risk management strategies that focus on eliminating resistance are expected to create <1 percent of the public health benefit of strategies that focus on reducing microbial loads in animals or on foods (1). In another paper, the authors concluded,

> "We came to some surprising conclusions that were robust to many uncertainties. Among these were that antimicrobials that benefit animal health may benefit human health, while regulatory interventions that seek to reduce antimicrobial resistance in animals may unintentionally increase illness rates (and hence antimicrobial use and resistance rates) in humans. . . . In conclusion, our analysis suggests that the precautionary-principle approach to regulatory risk management may itself be too risky (18)."

Information derived from studies of organic or antibiotic-free production practices compared to traditional production practices is inconclusive, but there are indications that organically grown meat may have less-resistant organisms but greater prevalence and quantities of pathogens on the meat. So the greater risk of foodborne illness is somewhat offset by an increased likelihood of treatment success if treatment is necessary (2), (19), (20), (21).

The question of what the nature and magnitude of the risk to humans is can only be answered by performing systematic risk assessments. Such risk assessments must include identification of the endpoints of concern (e.g., increased illness or mortality caused by bacteria resistant to antibiotics used to treat the disease in humans), the nature of the treatment protocols in food animals, the potential routes of exposure, characterization of the population at risk, and the probability of occurrence.

Just because resistant bacteria may develop in animals that then are transferred to the environment or humans does not necessarily equate to a human health risk. First, the pathogen may not colonize in humans to create a foodborne disease. Second, if disease does occur, antimicrobial therapy may not be needed. In the majority of cases, treatment is not needed. Supportive therapy, such as fluids, is all that's needed for most *Salmonella*, *Campylobacter* and *E. coli infections*. In fact, antimicrobial therapy of E. coli O157 infections is contra-indicated because such treatment makes the effects of the disease worse. Third, if antimicrobial therapy is needed, the pathogen may be susceptible to the drug of first choice. The Therapy Guidelines for Enteric Infections for non-typhi *Salmonella* are:

> "In uncomplicated infections antimicrobial therapy is not indicated because it has no effect on clinical illness and prolongs carriage and excretion of the organism. . . . Treatment recommended only for young infants (< or = 6 m) and immunocompromised individuals. Resistance is common. Agents that can be used include a fluoroquinolone or a third-generation cephalosporin such as ceftriaxone for 5–7 days. Ampicillin and co-trimoxazole can be used if the infecting organism remains susceptible (22)." NARMS (3) reports the following resistance percentages of non-typhi *Salmonella* to fluoroquinolone (ciprofloxacin)—0.2 percent; third-generation cephalosporin (ceftriaxone)—0.6 percent; ampicillin—12.0 percent; and co-trimoxazole (trimethoprim-sulfamethoxazole)—1.8 percent. These resistance levels do not indicate a public health crisis associated with foodborne *Salmonella*.

CONCLUSION

The American Veterinary Medical Association is committed to ensuring judicious veterinary use of antimicrobials. To further safeguard public health and to maintain the long-term effectiveness of antibiotics, the AVMA established a profession-wide initiative to create and implement judicious use guidelines for the therapeutic use

of antimicrobials by veterinarians, and we launched an educational campaign to raise the awareness of the profession to the issue.

The spread of antibiotic resistance is a public and animal health concern. There is no question that the human medical profession is facing extreme challenges because of hospital- and community-acquired resistant human pathogens. The human medical problem with resistant nosocomial and community-acquired infections has increased the concern of possible development of resistant pathogens in animals that could be transferred to humans through the food supply or environment.

The AVMA shares the concerns of the human medical community, the public health community, governmental agencies and the public regarding the potential problem of resistant zoonotic pathogens developing in animals and then being transferred to humans. However, we emphasize the importance and primacy of using these medicines to prevent and treat diseases before they enter our food supply. Passing legislation that would ban the use of these antibiotics before science-based studies and risk-based evaluations are done would be detrimental to animal and human health. Inappropriate reactions to the potential problem could have unknown and unintended consequences that negatively affect animal health and welfare, and ultimately, could create other public health risks, such as increased foodborne disease.

The AVMA is committed to working in concert with CDC, FDA, and USDA to provide consumers—not only in the United States, but all over the world—with the safest food possible. The judicious use of antimicrobials is but one of the essential components of the process that enables animal agriculture to meet that demand. Other components include veterinary care, good management practices, biosecurity, proper nutrition and good husbandry.

The AVMA supports the ongoing scientific efforts of monitoring and surveillance of foodborne disease and resistant foodborne pathogens, education, development of new antimicrobials, and other research to better define the challenges presented by antimicrobial resistance. We also support adequate funding for such efforts to combat antimicrobial resistance. These efforts were high-priority tasks in the 2001 version of the Public Health Action Plan to Combat Antimicrobial Resistance that was created by a Federal Interagency Task Force on Antimicrobial Resistance. The Action Plan reflected a broad-based consensus of Federal agencies and stakeholders on actions needed to address antimicrobial resistance and provided a blueprint for specific, coordinated Federal actions that included the full spectrum of antimicrobial use: human medicine, veterinary medicine and animal agriculture. We are disappointed that the Action Plan was not adequately funded and prioritized by Congress. We are also concerned that the new Action Plan under development appears to not be as collaborative, broad-based and acceptable to the diverse community of stakeholders.

The AVMA does not believe that additional legislation is needed to regulate the uses of antimicrobials in veterinary medicine and animal agriculture. Additional legislation can put animal health and welfare and public health at risk. FDA has adequate authority for oversight but lacks the resources to accomplish its many priorities.

An analysis that compared the regulatory strategy of the European Union to ban or restrict animal antibiotic uses with the United States' approach of continued prudent use to prevent and control animal infections, together with measures to improve food safety, has some pertinent conclusions. Among these, prudent use of animal antibiotics may actually improve human health, while bans on animal antibiotics, intended to be precautionary, inadvertently may harm human health (10).

Increased surveillance of resistance, as well as continued compliance with judicious use guidelines for veterinarians and producers, may be sufficient to protect human health against the current small risks without compromising the health of food animals.

Thank you for the opportunity to appear before you today and speak about this important issue.

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Senator BROWN. Dr. Vogel, thank you for being here.
Dr. Eisenstein.

STATEMENT OF BARRY I. EISENSTEIN, M.D., SENIOR VICE PRESIDENT OF SCIENTIFIC AFFAIRS, CUBIST PHARMACEUTICALS, INC., LEXINGTON, MA

Dr. EISENSTEIN. Good afternoon. Mr. Chairman, Senator Hatch, thank you for the opportunity to testify before you today about the serious consequences of antimicrobial resistance. My name is Barry Eisenstein. I am an infectious diseases physician as well as Senior Vice President of Scientific Affairs at Cubist Pharmaceuticals, a Lexington, MA-based company focused on research, development

and commercialization of pharmaceutical products that address unmet medical needs in the acute care environment.

Cubist manufactures CUBICIN for the treatment of skin and bloodstream infections caused by certain bacteria including MRSA. During the last several decades the prevalence of antimicrobial resistant organisms in the U.S. hospitals and medical centers has increased to the point where it is a serious and frightening threat to public health which must be immediately addressed. We have concurrently reached a crisis in the lack of available therapies that are still effective against many bacterial pathogens as you have already heard.

As a class of drugs, antibiotics face a perfect storm of unique challenges not relevant to other drugs. Which create economic disincentives for industry to invest the substantial time and resources necessary to develop an antibiotic.

First, given the rapid evolution of bacteria development of resistance is a foregone conclusion. Therefore antibiotics by their very nature have a limited clinically effective lifespan.

Second, when faced with the reality that antibiotics have finite lifespan, healthcare providers, not inappropriately, engage in the practice of optimizing antibiotic utilization, known as antibiotics stewardship, which can result in physicians reserving the newest antibiotics for use only as a last resort and the most difficult to treat cases.

Finally, antibiotics are used in acute care setting for short duration. To make matters worse, the government's largest health care program, Medicare has limited coverage of home infusion administration of IV antibiotics which detrimentally impacts patient care as well as limits market penetration of the antibiotics that are used this way. Taken together these realities limit the return on investment for the pharmaceutical company, discouraging industry from investing and developing new antimicrobial products.

As we approach the crisis in the lack of available, effective drugs, patient care is seriously compromised. One way to mitigate the effects of antimicrobial resistance and improve patient outcomes is to utilize currently marketed therapies rationally. Moreover one of the most significant economic disincentives and impediments to state-of-the-art patient care is the reluctance by the FDA to apply current standards of measuring resistance to older FDA approved antimicrobial compounds.

Congress recognized removal of this impediment as one method to combat antibiotic resistance when it required the FDA to periodically update and review the "break points" of all antibiotic drugs. We commend the agency for release of draft guidance, which outlines the process for reviewing antimicrobial break points and look forward to the public comments on the draft guidance.

Cubist also appreciates the FDA lowering the break point of vancomycin, an older commonly used antibiotic. Many experts however agree that this is only the first step. An additional review and further lowering of vancomycin break points is warranted.

In addition to measures that reduce demand for antibiotics it is critically important to establish incentives. As also supported by the Infectious Diseases Society of America and SHEA to encourage industry to develop a steady supply of new, effective antibiotics to

ensure therapy is available for patients who do develop resistant infections. Such incentives could include:

No. 1, stockpiling in the strategic national stockpile and by individual hospitals with antimicrobials to treat resistant infections.

No. 2, R and D tax credits for antimicrobial products to offset the enormous, sometimes prohibitive costs of investing in antimicrobial R and D.

No. 3, extension of Orphan Drug Grants and associated Orphan Drug exclusivity or some such to antimicrobials or development of a parallel grant program specific to antimicrobial products.

No. 4, greater utilization of rapid approval programs at the FDA such as fast track and priority review for antimicrobials.

And No. 5, federally guaranteed loans and/or market pull mechanisms for advanced purchase of antimicrobials to stimulate investment in antibiotic R and D.

To effectively combat the growing prevalence of antibiotic resistance, it will be important to implement practices to reduce demand for antibiotics and transmission of infections to provide better guidance on older antibiotics, e.g. review breakpoints as well as establish incentives to guarantee an adequate supply of new products. Risk to investment would also be lowered with decreased regulatory uncertainty especially clearer FDA guidance.

I encourage you to refer to my written testimony for additional details on all of these proposals. Thank you for listening. I look forward to your questions.

[The prepared statement of Dr. Eisenstein follows:]

PREPARED STATEMENT OF BARRY I. EISENSTEIN, M.D.

Mr. Chairman, Ranking Member, and members of the committee, thank you for the opportunity to testify before you today about the need to develop and implement comprehensive policy initiatives to address the public health impacts of antimicrobial resistant bacterial infections.

I am Dr. Barry Eisenstein, Senior Vice President of Scientific Affairs at Cubist Pharmaceuticals. Cubist is a biopharmaceutical company focused on the research, development and commercialization of pharmaceutical products that address unmet medical needs in the acute care environment. Headquartered in Lexington, MA, we currently market CUBICIN® (daptomycin for injection), the first intravenous (IV) antibiotic from a class of anti-infectives called lipopeptides. CUBICIN received FDA approval for the treatment of complicated skin and skin structure infections caused by certain susceptible strains of Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). CUBICIN is also approved in the United States for the treatment of *S. aureus* bloodstream infections (bacteremia), and is the only IV antibiotic approved for this indication based on the results of a prospective, randomized, controlled registration trial. In the wake of a highly successful launch of CUBICIN, the company has a growing early stage pipeline of programs which can leverage Cubist's scientific, clinical and regulatory expertise as well as its proven infectious disease and acute care commercial organization.

As Senior Vice President of Scientific Affairs, I am responsible for leading the efforts at Cubist to understand the medical needs best answered by Cubicin, to interact with leading scientists and health care providers in the United States and elsewhere, and to advise our scientific staff regarding ongoing needs related to infectious diseases, particularly those due to resistant bacteria. I am trained in internal medicine, infectious diseases, and microbiology. I have been a hospital epidemiologist, chief of an Infectious Diseases division, chair of an academic department of microbiology and immunology, the leader of infectious diseases discovery and clinical development at a major pharmaceutical company, and am presently, in addition to my job at Cubist, Clinical Professor of Medicine at Harvard Medical School, where I teach. I hold leadership positions with the Infectious Diseases Society of America, the National Foundation for Infectious Diseases, and the American Society for Microbiology, and am currently an editor of the journal, Antimicrobial Agents

and Chemotherapy. I have been studying antibiotic resistance and treating patients with infectious diseases for over three decades, have edited major textbooks, and published over 100 scholarly articles in the field.

ANTIMICROBIAL RESISTANCE: A PUBLIC HEALTH THREAT

During the last several decades, the prevalence of antimicrobial resistant organisms in U.S. hospitals and medical centers has increased. According to 2002 data from the Centers for Disease Control and Prevention (CDC), more than 1.7 million people acquire bacterial infections in U.S. hospitals each year, and 99,000 die as a result. CDC estimates that up to 70 percent of those bacterial infections are resistant to at least one drug, at a cost of approximately $5 billion annually.[1] A recent study published in the Journal of the American Medical Association (JAMA), extrapolated data from nine U.S. communities to estimate that there were 94,360 invasive MRSA infections alone in the United States in 2005 which resulted in 18,650 deaths[2]—to say nothing of the prevalence of other drug resistant infections. Antimicrobial resistance is increasingly a public health threat: patients who contract a resistant infection require more days of antimicrobial therapy than patients who do not; require more days in the hospital than those who do not; and generally face worse outcomes than those who do not.[3] We *must* implement effective measures to combat antimicrobial resistance.

Unfortunately, given the rapid evolution of bacteria, development of antibiotic resistance is almost inevitable, thus policy efforts to address antimicrobial resistance must focus on: (1) adoption and maintenance of practices that reduce the rates of transmission of resistant infections; (2) appropriate use of existing antimicrobials to delay development of resistance; and (3) implementation of incentives to encourage the continued research and development of new antimicrobials to ensure, to the extent possible, a steady supply of effective drugs.

LACK OF EFFECTIVE ANTIMICROBIALS IS REACHING A CRISIS POINT

My testimony today will focus on suggestions for incentives to encourage innovative antimicrobial research and development (R&D). We are approaching a "crisis point" with antimicrobial resistance and lack of new therapies, particularly against gram negative bacteria, (e.g., *Acinetobacter*, which is infecting both intensive care patients in American hospitals and our troops in the Middle East conflicts at alarming rates and which is often untreatable).[4] Among the gram positive bacteria, the disturbing rates of MRSA and the emergence of vancomycin-resistant enterococci (VRE) increasingly leave infectious disease doctors with few, if any, effective therapies for certain strains of bacterial infection.

Overuse and misuse of antibiotics has contributed to the development of resistance and has left hospital shelves increasingly barren of effective antimicrobial therapies. In addition, as a class of drugs, antibiotics face unique therapeutic challenges, which other treatments do not encounter. As I mentioned above, bacteria evolve so quickly that development of resistance is inevitable and thus each new antibiotic is a "wasting asset." In other words, each therapy has a finite period of time during which it will be effective. For example, the discovery of penicillin in 1928 was nothing short of a medical miracle. Yet only 4 years after the drug became widely commercially available during World War II, reports of resistant microbes began emerging. This has far reaching consequences for patients and physicians who may be left without therapeutic options, but it also impacts the willingness of industry to invest in antimicrobial R&D as newer agents effective against the most important antibiotic-resistant pathogens, like MRSA, are often viewed as niche products to be used highly selectively by practicing physicians.

Industry's hesitancy to invest in antimicrobial development is compounded by the consequences of the depreciating nature of antimicrobials—when faced with the reality that antibiotics have a finite lifespan, health care providers engage in the practice of optimizing antibiotic utilization ("antibiotic stewardship"). While this can result in more appropriate use of antimicrobials through measures that limit exposure to antibiotics (e.g., prescribing antibiotics only when necessary, effectively using di-

[1] Centers for Disease Control and Prevention *at http://www.cdc.gov/ncidod/dhqp/ar.html*.

[2] R.M. Klevens, et al., *Invasive Methicillin-Resistant Staphylococcus Aureus Infections in the United States*, JAMA, 2007;298:1763–1771.

[3] A. Shorr et al., *Bacteremia Due to Staphylococcus aureus: Acquisition, Methicillin Resistance, and Treatment Issues,* Medscape Clinical Review, October 2004; M.A. Abramson, D.J. Sexton, *Nosocomial Methicillin-Resistant and Methicillin Susceptible Staphylococcus aureus Primary Bacteremia: At What Costs?* Infection Control and Hospital Epidemiology, 1999;20:408–411.

[4] L.L. Maragakis and T.M. Perl, Acinetobacter baumannii: *Epidemiology, Antimicrobial Resistance, and Treatment Options*, Clinical Infectious Diseases, 2008;46:1254–1263.

agnostic techniques to select the most appropriate antibiotic, and acquiring appropriate culture and sensitivity data to ensure suitable dosing), it can also result in physicians simply reserving the newest antibiotics for use only as a last resort in the most difficult-to-treat cases.[5] This apparent virtue of preserving antibiotics (i.e., helping the "demand side") paradoxically hurts the "supply side" by making commercial return on these antibiotics more difficult to realize, thereby causing economic *disincentives* for industry to engage in cutting edge antimicrobial R&D. The consequence is loss rather than gain in the antibiotics armamentarium, a fact not well appreciated by practicing physicians or by some proponents of antibiotic stewardship.[6]

Finally, antimicrobials are used in acute settings, for limited timeframes (7–10 days), rather than daily for the life-time of the patient, as with treatments for chronic diseases, making it difficult to rely on commercialization of an antimicrobial as a steady source of financial returns.

In addition to challenges inherent to antibiotics as a class of drugs (emergence of resistance, prescribing habits, and resulting antimicrobial stewardship), over the last decade, regulatory uncertainty, including impractical and changing FDA guidelines has had a significant negative impact on approval of antibiotics. According to Extending the Cure, 14 classes of antibiotics were introduced for human use between 1935 and 1968; since then only five have been introduced.[7] While many factors, as discussed above, have contributed to this decline, unpredictable approval requirements and timelines only add to already existing economic disincentives for industry to invest in antimicrobial R&D.[8]

Taken together and without further incentives to encourage investment in antimicrobial development, both big and small pharmaceuticals and biotechnology companies have already begun limiting their R&D investment in anti-infectives, preferring instead to focus on other, more financially certain therapeutic areas. The consequences of this lack of antimicrobial R&D has become devastating for patients, leaving us with increasing rates of antimicrobial resistance and fewer and fewer available therapies.[9]

SUPPORT FOR ONGOING INITIATIVES TO COMBAT ANTIMICROBIAL RESISTANCE

Cubist supports several ongoing initiatives at the Department of Health and Human Services (HHS) to effectively address antimicrobial resistance, and encourages HHS to continue to work toward completion of these programs, including:

(1) Activities of the Food and Drug Administration (FDA) to implement sections of the Food and Drug Administration Amendments Act (FDAAA) (Pub. L. No. 110–85).

Specifically, Cubist is pleased that the FDA issued a draft guidance outlining the agency's proposed procedures for complying with section 1111 of FDAAA, which requires the FDA to periodically review and update antibiotic "breakpoints." An antibiotic breakpoint is the dosing concentration (mcg/mL) after which the drug is no longer considered clinically effective. Breakpoints are critical because they determine bacterial resistance. During antibacterial susceptibility testing to identify which antibiotics will kill or inhibit the growth of the isolated bacterial culture, if the bacteria are not inhibited at the "breakpoint" concentration, it is considered resistant.

Cubist, as well as the Infectious Diseases Society of America and the Clinical Laboratory Standards Institute believe that the breakpoints included in the labels of

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[5] K. Kaye et al., *The Deadly Toll of Invasive Methicillin-Resistant Staphylococcus Aureus Infection in Community Hospitals*, Clinical Infectious Diseases, 2008;46:1568–1577.

[6] R. Laxminarayan and A. Malani, *Extending the Cure: Policy Responses to the Growing Threat of Antimicrobial Resistance* (2007), *available at http://www.extendingthecure.org/research_and_downloads.html*.

[7] See, Extending the Cure, *Policy Responses to the Growing Threat of Antibiotic Resistance, Policy Brief 6: The Antibiotic Pipeline, May 2008, available at http://www.extendingthecure.org/downloads/policy_briefs/Policy_Brief6_May08_newdrugs.pdf.*

[8] *See*, Docket No. FDA–2008–N–0225–008.1 and -008.2, Comments of the Infectious Diseases Society of America, *available at http://www.regulations.gov/fdmspublic/component/main?main=*
DocketDetail&d=FDA-2008-N-0225.

[9] *See, Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates . . . A Public Health Crisis Brews*, Infectious Diseases Society of America, July 2004, *available at http://www.idsociety.org/WorkArea/showcontent.aspx?id=5554*; G.H. Talbot et al., *Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America*, Clinical Infectious Diseases, 2006;42:657–668; B. Spellberg et al., *The Epidemic of Antibiotic Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America*, Clinical Infectious Diseases 2006;42:155–164.

many older antibiotics do not reflect emerging resistance. Thus these labels are outdated, compromising physicians' ability to appropriately and effectively treat patients, often giving them a false sense of confidence about an older antibiotic, like vancomycin.[10] We are pleased that the FDA has already revised the label for vancomycin injection to reflect a breakpoint of 2 mcg/ML against *Staphylococcus aureus*.

However, while we appreciate this first step by the FDA, many in the infectious disease community, including academic and clinical experts, feel that even this lower breakpoint for vancomycin does not reflect true clinical resistance to the drug, putting patients at serious risk of receiving ineffective treatment. To quote from a recent paper on the topic:

> "It is becoming clear that vancomycin is losing potency against *S. aureus*, including MRSA. Serious infections due to MRSA defined as susceptible in the laboratory are not responding well to vancomycin. This is demonstrated by increased mortality seen in patients with MRSA infection and markedly attenuated vancomycin efficacy caused by vancomycin hetero-resistance in *S. aureus*. Therefore, it appears that our definition of vancomycin susceptibility requires further scrutiny as applied to serious MRSA infections, such as bacteremia and pneumonia." [11]

This apparent reluctance by the FDA to apply current standards of measuring resistance to older antibiotic compounds is one of the most significant economic disincentives to industry investment in R&D, as well as a significant barrier to state-of-the-art patient care. We encourage FDA to lower the vancomycin breakpoint and to continue to be vigilant in monitoring the efficacy of it and other antibiotics, as required under FDA Section 1111.

Cubist also appreciates that the agency convened a public meeting on April 28, 2008 as required by section 1112 of FDAAA, to discuss and debate measures to combat antimicrobial resistance. We hope the FDA will strongly consider some of the suggestions offered at this meeting.[12]

(2) Implementation of the Hospital Acquired Condition (HAC) rule, by the Centers for Medicare and Medicaid Services (CMS) as a measure to encourage hospitals to engage in proven, evidence-based behavior to prevent the transmission of hospital-acquired infections, including resistant bacterial infections.

In the development of these policies, it is critical for CMS to be mindful of the challenges that hospitals face in detecting and preventing conditions that are often considered hospital-acquired. Due to factors outside the control of hospitals, certain conditions are not reasonably preventable. In those circumstances, payment policies based on the presumption that hospitals can prevent these conditions from occurring will not produce the desired results and could impact quality of care. CMS must take these factors into account as it implements the HAC provisions. For example, while many infections are preventable through proper hospital protocols and safety measures, data has shown that hospitals lack the ability to reasonably prevent infections caused by MRSA. Individuals can become colonized with MRSA in the community as well as in health care settings, and while hospitals can take steps to prevent MRSA from spreading between patients in the hospital setting, they cannot reasonably prevent a patient who is colonized with MRSA from developing an active infection in the hospital setting.

(3) Efforts by Congress to extend Medicare coverage for home infusion to include ancillary services associated with home administration of IV drugs, including antibiotics.

Home infusion would allow patients in need of antibiotic treatment, including those with MRSA or other resistant bacterial infections, to administer the drug themselves, in a non-hospital setting. However, in contrast to many private insurance plans, Medicare does not cover necessary services related to home administration of injectable drugs, such as the supplies, nursing services or equipment. This lack of coverage prevents many Medicare beneficiaries from taking advantage of these services and forces these patients to remain in the hospital longer than nec-

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[10] G. Sakoulas and R.C. Moellering, Jr., *Increasing Antibiotic Resistance Among Methicillin-Resistant Staphylococcus Aureus Strains*, Clinical Infectious Diseases, 2008;46:S360–S367.

[11] G. Sakoulas and R.C. Moellering, Jr., *Increasing Antibiotic Resistance Among Methicillin-Resistant Staphylococcus Aureus Strains*, Clinical Infectious Diseases, 2008;46:S360–S367. *See also*, I.M. Gould, Editorial, *The Problem With Glycopeptides*, International Journal of Antimicrobial Agents 30 (2007):1–3.

[12] *See e.g.*, Docket No. FDA–2008–N–0225–0011, Comments of the Clinical Laboratory Standards Institute, *available at http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-N-0225*.

essary simply to receive their antibiotics. Extended hospital stays are costly, inconvenient, and most importantly, compromise the health of other patients who are at risk of contracting the resistant bacterial infection from their neighbors. We encourage Congress to extend Medicare coverage to include home infusion services as one measure to improve patient care and reduce unnecessary transmission of MRSA and other bacterial infections. Extension of Medicare coverage would also open additional markets for IV antibiotics, providing an incentive to industry to engage in antibiotic R&D.

ADDITIONAL SUGGESTED POLICY PROPOSALS

In addition to working toward the achievement of the ongoing initiatives described above, Cubist also believes that to directly address the unique barriers to industry investment in innovative antimicrobial research and development, Congress should enact additional incentives which will encourage such research. Specifically, Cubist proposes the following options:

(1) Establish research and development tax credits for antimicrobials, modeled after bills introduced by Senator Schumer and Representative Towns.

By allowing innovative companies a tax credit equal to a percentage of their expenses devoted to research and development of "qualified" products (e.g., antimicrobials and antivirals), such expenses, which can run as high as $1 billion to bring a drug to market, are mitigated, thus incentivizing industry to devote more time and resource toward the research and development of these critical new products. To ensure that the tax credit encourages research and development of innovative new products, rather than reformulations or variations on already existing drugs or diagnostics, the credit could be limited to research on new molecular entities or new diagnostics. The Federal Government, as well as several States (including Massachusetts) have in place broader R&D tax credits to encourage job creation and cutting edge pharmaceutical research. However, a Federal R&D tax credit specific to antimicrobials and similar qualified products would focus pharmaceutical and biotech R&D on meeting unmet antibiotic medical needs for patients.

(2) Encourage the CDC and the Department of Homeland Security to stockpile antibiotics in the Strategic National Stockpile; similarly encourage hospitals to "stockpile" antimicrobials.

The Federal Strategic National Stockpile (SNS) is managed jointly through the Department of Homeland Security and the Department of Health and Human Services. The SNS is housed at CDC and has large quantities of medicine and medical supplies to protect the public if there is a public health emergency and local supplies run out. Certain antimicrobials are already stockpiled by the SNS, as well as other medical countermeasures, but this list could be expanded to include additional categories of antimicrobial products effective against resistant pathogens. While the SNS is primarily designed to ensure sufficient public access to life-saving medicines in the event of an emergency, by advance purchasing in large quantities certain drugs and biologics, the SNS also incentivizes the research and development of such products. Similarly, if hospitals were encouraged to stockpile or enter into advanced purchase contracts for antimicrobials for use against resistant infections, this would encourage much needed antimicrobial R&D.

(3) Create infectious disease product development grants modeled on FDA's successful orphan product development (OPD) grants and provide additional 7 years of exclusivity for certain antimicrobial products.

Orphan development grants are intended to encourage clinical development of products for use in rare diseases or conditions. They are authorized under current law, and could include antimicrobials, if certain infectious diseases meet the statutory criteria for a "rare disease." In fact, under Section 1112 of FDAAA, FDA was directed to (and did) hold a public meeting to consider which infectious diseases would be considered "rare diseases," and thus which products would be eligible for OPD grants. In addition to the OPD grants, these antibiotics should be eligible for orphan drug status and the associated 7-year period of exclusivity to stimulate innovation and provide an adequate return on investment. The lengthened exclusivity would also take into account the unique, slow uptake of new antibiotics into the marketplace based on the usual practices of antibiotic stewardship. (By contrast there is no such delay in the use of the newest life-saving cancer drugs, which, like antibiotics, work by ridding the patient of noxious, life-threatening cells.)

In the alternative to including antimicrobials/infectious diseases under the umbrella of orphan drug grants, similar to the OPD grants, Congress could authorize grants specifically directed at antimicrobials and other infectious disease products. Like the orphan product grants, grants for infectious disease product development

would focus on targeted Federal dollars in an area of critical public health need but limited commercial potential. Additional exclusivity could also be granted for these products upon approval if certain criteria were met.

(4) Continue utilizing rapid approval mechanisms at FDA, such as Fast Track and Priority Review; expand the FDAAA Tropical Disease Priority Review voucher system to additional categories of antimicrobials.

FDA "Fast Track" designation (requested by the sponsor) is a process designed to facilitate the development, and expedite the review of new drugs or biologics indicated to treat serious or life-threatening diseases and which fill an unmet medical need. "Priority Review" is one of two review designations for a product. To hasten approval of drugs or biologics that offer major advances in treatment, FDA designates such drugs, at the request of the sponsor, as Priority Review drugs. The goal for FDA pre-market review of a Priority Review drug is 6 months, compared to 10 months for standard review drugs. Antibiotics which are indicated to treat serious or life-threatening diseases, or which provide major advances in treatment are eligible for Fast Track or Priority Review. Cubist encourages product sponsors and the FDA to effectively utilize these approval options.

In addition, to encourage sponsors to engage in innovative antimicrobial R&D, Congress could expand the tropical disease priority review voucher system enacted under FDAAA to include additional categories of antimicrobials (e.g., those that are indicated for serious or life threatening diseases). The FDAAA provision establishes a system of rewarding priority review vouchers to sponsors who file an NDA for a drug indicated for the treatment or prevention of a tropical disease. The priority review voucher entitles the holder of the voucher to priority review of a single new human drug or biologic application (separate from the NDA for the tropical disease product) and is transferable. Extension of the provision to include other categories of antimicrobials would provide additional incentives for industry to engage in cutting edge R&D.

(5) Provide additional regulatory guidance at FDA for approval of antimicrobials.

In addition to expediting approval times through Fast Track and Priority Review, to address the increasing regulatory uncertainty antimicrobial sponsors face when submitting a new antibiotic for approval, the agency should clarify approval requirements and re-establish consistency, predictability and timeliness in pre-market review of antimicrobials. This should include release and periodic review of the guidance on conduct of antimicrobial clinical trials, as required by Section 9111 of FDAAA, as well as careful review and consideration of the GAO report required by Section 1114 of FDAAA examining how certain FDAAA provisions related to antibiotics have encouraged development of new antibiotics.

(6) Authorize study and establishment of guaranteed market contracts and other "pull" mechanisms.

Apart from the SNS discussed above, HHS could create advance purchase commitments or other "promised market" mechanisms (e.g., an antimicrobial purchase fund) to encourage the development of future antimicrobials. Guaranteed contracts in small amounts (less than $50-$100 million) could provide an important market foundation to focus hospital, private payor and physician attention to novel therapies.

(7) Establish a Commission on Infectious Diseases Product Development, modeled after legislation introduced by Representatives Baird and Cubin, to increase public-private development collaboration.

The Beating Infections through Research and Development Act (H.R. 1496) requires establishment of a Commission on Infectious Disease Product Development to identify the most dangerous infectious disease pathogens that are or are likely to become a danger to public health. Establishment of such a commission would be beneficial in directing limited R&D resources to the most critical areas of need. The Commission should include members of relevant government agencies, including the Department of Health and Human Services, the Food and Drug Administration, CDC, the Department of Homeland Security, and the Department of Defense, as well as pharmaceutical and biotechnology companies, venture capital firms, financiers, and other experts in the economics of drug development. Public sessions and hearings of the Commission should be mandated to explore the issues of unmet need as well as different mechanisms to better encourage the development of innovative antimicrobials.

(8) Authorize federally-guaranteed loans for product development and infrastructure.

Congress could authorize small business or targeted Business and Industry (B&I) Guaranteed Loans similar to those administered by the USDA Rural Business-Cooperative Service (RBS) and the Small Business Administration (SBA) Certified

Development Company (504) Loan Program. These programs offer such maximum loan sizes of $25 million with 30-year terms at market advantageous rates. Loans would serve to reduce small, startup companies' reliance upon venture capital, and could encourage them to innovate creatively on therapeutically significant, potentially higher risk development projects. Loan amounts up to $25 million would serve to advance drug candidates up to clinical investigation (IND stage); additional amounts would be required for early clinical trials.

CONCLUSION

Thank you for the opportunity to testify today. Antimicrobial resistance is a very real threat to public health and one that is only getting worse. I urge Congress to strongly consider the suggestions I, and others, have offered as steps toward managing emergence, transmission, and treatment of drug resistant organisms.

Senator BROWN. Thank you, Dr. Eisenstein. Mr. Noble, you, as a professional athlete now a college coach, what do you tell your players and other coaches to protect them from acquiring MRSA.

Mr. NOBLE. I think the big thing that we stress right now is getting to a doctor quickly. As fast as possible, have them culture something that looks like it could be an infection, kind of figure out what it is. Obviously, you know, wash your clothes, throw your towels in the hamper, make sure everything is clean.

In a locker room setting, it's dirty. Guys are athletes, football players, skin to skin contact, it's there. We've had kids every year that I've been at West Chester now that we've had one or two cases of MRSA.

The big thing really for me having had it and because of the delay that I had in getting treatment and as serious as it could have potentially gotten and it did get serious. I always tell the kids if you think you have an infection, get to your doctor right away. Go see the team doctor, your family doctor and get on it as quickly as possible.

Senator BROWN. Thank you. Dr. Graham, you've said that the use of antimicrobials apparently yields no appreciable economic benefits. Why does agriculture continue to use them and how do you change their minds?

Mr. GRAHAM. I think there's generally a fear that because they've been using these for a long time it's sort of a crutch. The economic study that I mentioned with swine, they basically showed that the better managed operations performed better than the operations that were using growth promoting antibiotics. I think it's this crutch. It's a low risk in their mind to their own operation or to the industries that are promoting this use.

I think it's more of a fear factor of being just not sure that they'll be able to improve management.

Senator BROWN. Does that study apply to, in your mind, poultry, pork, beef, if they're confined in large numbers in relatively small spaces or does the claim that there is no real savings, is that claim disputed by that kind of agriculture when it suggest they have to do a different kind of agriculture?

Mr. GRAHAM. Well, I was involved in the poultry study, where we looked at the economics of using growth promoting antibiotics. It was actually a 3-year study by Perdue, fourth largest producer of poultry in the United States. It was 3 years, 7 million broiler chickens involved.

During this research they looked at actually cleaning out the litter from the house. If they removed the litter from the house,

which when I worked with farmers in my dissertation research and they would actually clean the house about once every 5 years, a full cleaning. Now the reason they're doing that is because they're pinched.

They have been getting paid the same amount per pound of chicken for a long time. They don't have a lot of free time to spend cleaning the chicken houses. They're not cleaning the houses and so I think there's this crutch that's available which is this constant low dose of antibiotics that we feed the animals.

Senator BROWN. Thank you. Dr. Vogel, as we learned from Admiral Tollefson, a veterinarian herself, it's been 8 years since we passed legislation asking FDA to reassess the safety of using some antimicrobials with farm animals. Dr. Tollefson told us that FDA is still gathering data.

The STAAR Act that Senator Hatch and I have worked on contains a provision to improve data collection. In your assessment, at what point do we have enough data for FDA to determine that the use of antimicrobials in animal feed might be harmful to human health?

Mr. VOGEL. That's a good question but a difficult question to answer. It's very difficult to put a bright line on what type of data is needed for these various decisions. You'd have to examine what is the actual risk to human health in comparison to the benefits to animal health and welfare.

Each drug is different and acts in a different mechanism and can create different circumstances that need to be evaluated.

Senator BROWN. Dr. Brennan, are you familiar with Peter Pronovost's research in the use of a checklist? Do you know of his research, I assume?

Explain that to us, if you would, in what the Federal Government can do. I know that they've done it in Michigan and Rhode Island. Pretty much used his checklist to prevent hospital infections and other errors for physicians and for hospital personnel.

Run through that and its value in how we promote that through a system to cut down on medical errors and the kind of hospital infections that Mr. Noble and too many others have acquired.

Dr. BRENNAN. Well Senator, as I alluded to in my testimony, there is no single action that will prevent hospital acquired infections. It's really necessary to bundle a number of activities. Beginning with the decisionmaking process to use a device, the best practices to insert it, decisionmaking about the maintenance of the device and then further decisionmaking about removal of the device.

What the checklist does is it groups these bundles of evidenced-based activities or groups these activities into bundles so that they are addressed on a daily basis and that a decision is made in the most timely fashion to mitigate the risk. That is, improve the conditions around the site of the device by better site maintenance or make a timely decision to remove the device. These checklists have been demonstrated using these evidenced-based practices that are bundled together to reduce the incidence of ventilator associated pneumonies, catheter-related bloodstream infections and so on.

Senator BROWN. If these are as effective as I've been convinced and by reading Dr. Pogonandi's articles and so much that I've seen

without being an expert and surely on hospital administration. Why are more hospitals not using this checklist and adopting these kinds of practices?

Dr. BRENNAN. I think many hospitals, Senator, have begun to use the checklist. I do think that there's a need for deeper, cultural change in hospitals. I think that there is still a belief in many segments of the industry that these are the costs of doing business.

I think that slowly but surely we're demonstrating first in some hospital units and more often in many hospital units that at least some types of infection can be nearly eliminated. We've had the most success with central venous catheter bloodstream infections. Others I think are more intractable such as urinary tract infections and ventilator-associated pneumonies are particularly challenging.

I think that the belief has not penetrated our industry deeply enough to embrace this cultural change.

Senator BROWN. Ok. Thank you, Dr. Brennan.

Senator Hatch.

Senator HATCH. Well thank you. I appreciate the whole panel here today. Mr. Noble, I appreciate you and I am very empathetic toward what you've been through and what you and your family have had to endure. You know, people look up to you and I do certainly, and I'm grateful for your publicizing this important issue.

Did your physician or hospital ever determine the actual cause of how you contracted the bacterial infection?

Mr. NOBLE. That's kind of the tough thing with it, especially in my situation because I had had surgery and because I was in a locker room and a training room where MRSA is. We had five guys in Washington, the year I had it, contract MRSA mostly just in the skin. It never got as serious as mine.

Theirs were just in the skin, where as mine were in both knees. It was treated pretty quickly and it was after mine.

They were much more aggressive with the treatment. The doctors were never able to pinpoint exactly where I got it because of my situation—it was just in both. I was in a hospital setting and in a community setting, a locker room where you can get it.

Senator HATCH. Well thank you. Dr. Brennan, this has been alluded to, but States have begun to require hospitals to implement testing programs as a method to identify and appropriately care for patients with resistant infections. Is there room for the Federal Government to promote testing to provide consistency and a higher quality of care? If so, what do you envision that role to be?

Dr. BRENNAN. Senator, as you know many States have now adopted legislation requiring reporting and in some instances screening.

Senator HATCH. This legislation is pending in another six States as I understand it.

Dr. BRENNAN. Well, Senator, I believe that there are actually several other—there are a relatively small number of States that have actually begun to collect the data and only, I believe, two that have begun to report the data. I think there are many others that have actually adopted legislation. And still more that have bills pending.

Furthermore, there are some States that have gone on and adopted specific mandates about multi-drug resistant organisms

such as MRSA, for example and others. I think that what has been most striking to us in the field has been the migration toward the use of the National Health Care Safety Network at the CDC as a solution for the reporting mechanisms and surveillance mechanisms that can keep us informed about multi-drug resistance and about the performance of our hospitals. It enables us to have a benchmark for performance.

Seventeen States have now adopted NHSN out of the division for Healthcare Quality Promotion at CDC. Others are considering it. Pennsylvania has moved entirely toward that system as others have.

I think that that is an incredibly valuable national resource. It is one that I believe is not sufficiently supported. When it migrated from its predecessor system, the National Nosocomial Infections Surveillance System, there were only about 300 hospitals in it.

As recently as April 2007, there were only about 500 hospitals in it. Today there are 1,700. It's really growing exponentially as more and more States adopt this legislation. I fear that its capacity may be outstripped by this movement toward its use. I think that support of that will provide us great information on surveillance and benchmarking.

Senator HATCH. Thank you. Dr. Graham and Dr. Vogel, we appreciate your testimony and the advice that you've given us here today. Let me just ask one last question to Dr. Eisenstein. Your testimony acknowledged some of the important contributions that were included in the Food and Drug Administration Amendment Act of 2007 and suggests some others, including a new tax credit.

In terms of quick results and high impact for the cost, will you please highlight some of the incentives that would have the highest impact over the very short run?

Dr. EISENSTEIN. Well one of them I alluded to would be to have the FDA get even more energized toward the provisions of FDAAA to go back and re-examine the older antibiotics like vancomycin which has been the work horse for the agent that we're speaking about most today, namely MRSA. It turns out that because this drug was approved by the FDA over 50 years ago, about 50 years ago, the standards for what it needed to accomplish from an efficacy standpoint were essentially minimal. The understanding of resistance for vancomycin was quite antique by present standards.

New drugs that come out that are competing, if you will, for vancomycin have a very high hurdle to seem as if they are as good, if not better than this old drug. I would suggest that a very quick thing that can be done would just be to get the FDA to spend even more of its resources, I know they are precious. They can depend upon other groups like the CLSI, which is a not-for-profit group that examines break points very carefully and drug resistance very carefully. Use them as essentially the citizens group to enable them to make the expert decisions they need to make.

Senator HATCH. Well, thank you. Mr. Chairman, I appreciate your holding this hearing. I appreciate all of you coming here to testify. It means a lot to us.

Senator BROWN. Thank you, Senator Hatch.

Senator Sanders.

Senator SANDERS. Thank you, Mr. Chairman. This is an enormously important hearing. I apologize. I'm going to be busy running in and out.

Dr. Graham, I wonder if I could ask you a question. I was disturbed to read in your written testimony that the feeding of antibiotics to animals in North Carolina alone is estimated to exceed human consumptions of antibiotics nationwide. Not only does this seem to be a wasteful misuse of a precious resource, it appears to be very dangerous.

You said in your testimony that the practice of constantly feeding our livestock low doses of antibiotics for nontherapeutic purposes is facilitating the emergence of antibiotic-resistant infections. Could you talk a little bit more about how you came to that conclusion?

Mr. GRAHAM. Well in my personal research I focused on macrolides, lincosamides, streptogramin B resistance. That includes erythromycin, clindamycin and also quinupristin, dalfopristin. These are all important, clinical drugs.

Those drugs are also critical because the resistance, the genetic material that encodes resistance to those is linked. A lot of times it's linked on a certain type of DNA that can be transferred to other bacteria that aren't even related species or not even the same genera or family. We focused a lot on MRSA today. There are a lot of things that are limiting our options.

One of these is the loss of these drugs that I looked at and these resistance genes are present. When we found these resistant genes in bacteria that aren't necessarily disease causing organisms, which is something that doesn't get factored into risk assessments because they look at one specific bug. They look at one specific drug. It's this resistance gene that can be shared among a whole host of bacteria that's really critical.

That's one of the three antibiotics that I think should definitely be removed from food animal production. Of course there's a whole host of others, but that was really my focus.

Senator SANDERS. Let me just continue with Dr. Graham. You're working with the Pew Commission and the work you're doing is important and informative and it clearly is of great use to the public health sector. What I would like to know is that the Interagency Task Force on which Dr. Tenover and Rear Admiral Tollefson both serve, is supposed to be getting input from experts like you.

I have a simple question. That is, has anyone from the Task Force actually been in contact with you? The more important question, is the research that you're doing being utilized by the government in informing our infection, prevention and control efforts?

Mr. GRAHAM. Well, unfortunately in academia we work through peer-reviewed process and that's where most of my research is focused on getting peer-reviewed manuscripts published. Some of my colleagues may have been in contact with them. I personally have never received contact from them.

Senator SANDERS. But you are a leading expert on this area, are you not?

Mr. GRAHAM. I've been work——

Senator SANDERS. All modesty.

[Laughter.]

Mr. GRAHAM. Maybe.

[Laughter.]

Senator SANDERS. It does seem surprising that the government might not have reached out to you for your thoughts in my judgment.

Mr. GRAHAM. Yes, I think it is surprising.

Senator SANDERS. Mr. Chairman, thank you.

Senator BROWN. Thank you, Senator Sanders for your comments and questions. I have a couple more questions before adjourning.

Dr. Eisenstein, explain what gram negative bacteria are and why antibiotic development is especially challenged in this area. My understanding is that there's a growing number of resistant bugs that fall in this category including klebsiella, E. coli and acinetobacter. Do we need to consider different incentives for these types of infections?

Dr. EISENSTEIN. I think we need greater incentives for new agents against all of the bugs that you've described, Senator Brown. The difference between a gram positive of a gram negative organism is relatively straight forward. The gram negative has got an extra piece of armor on its outside, in simple terms.

That extra piece of armor also contains additionally powerful sump pumps that the gram positives don't contain. Given the extra armor plus the extra powerful sump pumps they're able to get antibiotics pumped out even more vividly than the gram positives can do. That's in part because gram negatives are the primary organism in our GI tract and in the sewer systems, if you will. They've therefore adapted over billions of years to develop the wherewithal to get rid of noxious products.

Senator BROWN. Is it safe to say the gram negatives do both more good and more bad?

Dr. EISENSTEIN. We would not. Yes, exactly right.

Senator BROWN. In verses terms——

Dr. EISENSTEIN. We would not be alive today if it weren't for the gram negatives in our GI tract. They make very important products for us like Vitamin K and other important products that we take advantage of. They're actually more bacteria in our body by an order of magnitude of tenfold than there are human cells in our body.

The other aspect to the use of antimicrobials is the careful, careful use, because we don't want to disturb that important flora. So it's not just resistance. It's also disturbing that balance of bacteria that live with us.

Going back to your question about the difficulty of coming up with new antimicrobial drugs. It's because these bacteria have the extra biological potency to get rid of agents that it becomes even more challenging to come up with new agents against them. The Infectious Diseases Society and in their Journals, Journal of Infectious Disease and Clinical Infectious Diseases, I cite in my document, point out some of the real issues that we have with many of these gram negative infections.

You've named some. I think acinetobacter has gotten particular attention because it has infected many of our brave service officers in the Middle East. They've gotten infected with this disease in a way that we have, in many cases, great difficulty in treating it.

Senator BROWN. Can you always determine if it's gram negative or gram positive?

Dr. EISENSTEIN. That's a fairly easy distinction. In fact it's the gram stand view.

Senator BROWN. Yes.

Dr. EISENSTEIN. Yes.

Senator BROWN. Ok. Thank you. One other question, Dr. Eisenstein. We talk about incentives for development. Can you discuss how development incentives may differ for small companies verses pharma-size companies?

Dr. EISENSTEIN. Yes. I actually had the experience of working in a big pharmaceutical company at Eli Lily, where I was head of infectious diseases. Now I work at a small company. Big companies essentially can bank roll a lot of their programs. What they do is look across the portfolio and decide what is the more likely area to have economic return.

Small companies, in contrast, don't have the luxury of having bank rolls. Their barrier to entry to get into the field is more difficult. Those incentives that enable a lowering event of the entry border is preferable for the small companies whereas those that allow greater economic value later in the course of the drug use.

For example, the extension of patent rights or market exclusivity actually benefits all. And, so far as market exclusivity can be used specifically for antimicrobials through the Orphan Drug Act or through some other parallel type program, that actually helps all manufacturers get more interest——

Senator BROWN. The extension is on the other end when the smaller companies need it in the front end.

Dr. EISENSTEIN. Right.

Senator BROWN. I'm looking for how we incent small companies that doesn't necessarily cost taxpayer dollars that are less crucial to large companies.

Dr. EISENSTEIN. Well the reason that even the patent extensions and marketing extensions help the small companies is that the product that they are now working on is viewed as of greater value by the bigger companies which will offer partner and sometimes buy the smaller companies or the products.

Senator BROWN. What I'm trying to get at, is there anything specific we can do that is unique to helping the small companies that where those barriers just seem a little bit too high to pursue some breakthrough in antimicrobial resistant drug.

Dr. EISENSTEIN. Well I think——

Senator BROWN. Certain antimicrobial.

Dr. EISENSTEIN. Yes, providing assistance to help finance some of the ongoing efforts and, as I said earlier, having even the present organization we have in place, namely the FDA to re-look the potency and resistance patterns of older antibiotics to demonstrate that these are actually not as powerful drugs as we sometimes presently think. Thereby enable physicians to recognize the better value of some of the newer drugs does have a value toward helping the smaller companies because their products, these newer products then become of greater value.

Senator BROWN. Thank you for that. Let me ask a related question. When I was in the House there was—we, in the 1990s, doubled the NIH budget, as you know.

Dr. EISENSTEIN. Yes.

Senator BROWN. Bipartisan agreement, Democratic President, Republican Congress. Every member of the Health Subcommittee, that on which I sat, seemed to have some relative or friend, not to sound a bit cynical, that could be helped by some major breakthrough that NIH might find. We didn't see the same congressional support by a long shot, on CDC because CDC is considered by many to help other people, not people that dress like this, but people that might be poor or because it's—but I don't think it's that agency. I think it's a public health agency that helps everyone.

When you talk about incenting pharma companies or smaller companies, talk if you would about where a billion dollars would go and whether it's best FDA would do the research—NIH. I hesitate a bit to ask the question whether NIH, FDA or CDC would be best at government research on finding out, on discovering some of these antibiotics and developing them?

Dr. EISENSTEIN. It's a very interesting question and has a complex answer. My own view, having been involved in academic research for many years and sat on NIH study sections, the most recent being less than a year ago where I was extraordinarily disappointed to see that we were only able to fund 11 percent of the extraordinarily powerful grants that were being performed by colleagues like Dr. Brennan and——

Senator BROWN. It was almost twice that 5 years ago.

Dr. EISENSTEIN. Yes, exactly. What this is doing and as a former chair of an academic department, I recognize this among my former colleagues, it's chasing some of our best minds out of the field. That's a great worry to me.

Senator BROWN. I'm going to pin you down. Who could do the best, understanding that with the fact that in this 2 hours we've been hearing this here. We've had this hearing. We spent $40 million on the War in Iraq and with the budget situation. We're not doing what we ought to do with NIH, CDC or FDA. Where would the money best be spent of those three agencies on something fairly narrow like finding antibiotics?

Dr. EISENSTEIN. I would put as a short-term investment, 35 cents on the dollar to the FDA so that they can have the resources needed to deal with break points. I would put 15 cents on the dollar to improve the epidemiologic assessments from States so that that can be best utilized and normalized and communicated. I would give 50 cents on the dollar to trying to invest more in the NIH. It's really investing in the infrastructure of U.S. academic research.

Senator BROWN. Ok. Thank you for the precise answer. Last question. Dr. Graham, unless Senator Sanders has another question, you mentioned drinking water and what we're finding in drinking water increasing. Are there any other places in our environment where antibiotics are showing up where they shouldn't be?

Mr. GRAHAM. Antibiotics or antibiotic-resistant bacteria?

Senator BROWN. Well, one may lead to the other certainly. Answer the question how you want.

Mr. GRAHAM. Ok. We find antimicrobials present in a lot of streams. USGS has done a report and they showed a high prevalence of streams with antibiotics, mainly looking at tetracycline, I believe.

As far as antimicrobial resistance we're, you know I think one of the things we think is that things at the farm stay at the farm. We know more and more that that's not the case with the E. coli in spinach, that sort of thing. I've seen studies where they're finding resistant bacteria, fecal organisms on vegetables and fruits.

We're really linked in this ecosystem so that you apply this waste untreated onto land. It ends up in our water supply, our ground water and surface water supply. Then that water is used as irrigation for our crops that we consume.

I've actually looked at flies on the Eastern Shore of Maryland. I've looked at resistance genes that are in the waste at the poultry farms. I've also identified the same resistance genes that flies are carrying around the environment.

There, I mean, it literally seems like they're everywhere just like, you know, we all carry a little bit of DDT in us. We're likely all carrying some resistant organism. Fortunately, most of us are healthy and not going to end up having to take antimicrobials. But there is, I guess, that chance.

Senator BROWN. Thank you. Thank you for the enthusiasm for what you do too.

Thank you all for testifying, both the first panel and the second panel. Your work is so important for all of us and your words today are so important too. Thank you very much.

The record will remain open for 2 weeks if any of you want to submit or the first panel wants to submit additional information. Senator Sanders and others, it's open for 2 weeks for us too, to ask questions and if you would respond to any Senator that does.

I thank you for being here. The committee is adjourned.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF SENATOR DURBIN

I would like to thank the HELP Committee for addressing the important issue of antimicrobial resistance and specifically the growing emergence of healthcare associated infections.

Though not a new issue, growing public attention in the past year and a half has raised public concerns around healthcare associated infections, like methicillin-resistant *Staphylococcus aureus* (MRSA). The Centers for Disease Control and Prevention (CDC) estimates that approximately 1.7 million healthcare associated infections (HAIs) occur in U.S. hospitals and are associated with 99,000 deaths, affecting 5 to 10 percent of hospitalized patients annually.

These infections are not only showing up in hospitals, they are a threat to our soldiers, to the safety of our community, and our entire healthcare system. Approximately half of the infections that are treated in a hospital are actually picked up in the community. Over the past year, schools in Illinois, Connecticut, Maryland, North Carolina, Ohio, Virginia and Kentucky have had to close to help contain the spread of an infection and others even had to report student deaths. Soldiers are increasingly coming back from Iraq with war wound infections and osteomyelitis caused by multidrug-resistant Acinetobacter species. In addition to the devastating impact on human lives, HAIs result in an estimated $20 billion of excess healthcare costs every year. Within the Medicare program alone, healthcare charges for Staph bloodstream infections exceeded $2.5 billion in 2005.

States are taking important steps to control infections. The State of Illinois has been aggressive in its efforts to identify the infection before it grows out of control. Illinois was the first State to require testing of all high-risk hospital patients and isolation of those who carry the bacteria called MRSA. With proactive testing and prevention methods a group of three hospitals near Chicago reduced MRSA infections by 70 percent over 2 years. Since then, 25 States have laws that require public reporting of infection rates.

The Federal Government needs to step up its commitment to controlling these infections. Since the rise in reported infections, the CDC has seen a dramatic increase in the number of hospitals submitting information to the National Healthcare Safety Network (NHSN). The NHSN is a secure, internet-based surveillance system that collects data from healthcare facilities on the emergence of infections and adherence to best practices in prevention of HAIs. The NHSN is an effective tool that should be sustained and expanded.

States are actively CDC's recommendations for communities and hospitals to help fight the spread of drug-resistant bugs. The CDC could do more and should do more to address the growing emergence of infections. I introduced the Community and Healthcare Associated Infections Reduction Act last year to establish a clearer leadership role for the Federal Government in improving the prevention, detection, and treatment of community and healthcare-associated infections. The bill doesn't reinvent the wheel, but instead builds on successes the healthcare community and government agencies have created.

My bill requires hospitals to report infection rates to the CDC's NHSN. More complete data will inform policies and practices to prevent and treat these dangerous infections. We also need comprehensive infection control programs. The bill commissions an updated, comprehensive look at best practices for hospitals on infection control. The bill also requires the Secretary to look into the creation of a Federal payment system to acknowledge and reward hospitals that are preventing infections. The bill would create a new public health campaign to increase awareness about reducing and preventing the spread of infections, especially in schools, locker rooms, and playgrounds—the areas where we know bacteria can thrive. Finally, the bill calls for greater coordination of and greater emphasis on research at the Federal level.

Healthcare-associated infections pose very real health risks and cost the healthcare system billions of dollars. But they are preventable, and with the proper attention and resources, we can control the spread of these infections. I look forward to working with my colleagues as the committee considers proposals to improve prevention, reporting, and research toward minimizing healthcare-associated infections.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY, SENATOR ENZI, SENATOR BROWN, AND SENATOR BURR BY FRED C. TENOVER, PH.D.

QUESTIONS OF SENATOR KENNEDY

Question 1. How might the data collection systems and agencies within CDC, FDA, and USDA be improved to more effectively monitor sources of antimicrobial resistance?

Answer 1. The National Antimicrobial Resistance Monitoring System (NARMS) was developed in 1996 to monitor changes in susceptibility of select foodborne bacteria to antimicrobial agents of human and veterinary importance and is a collaboration between three Federal agencies including FDA's Center for Veterinary Medicine (CVM), the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Agriculture (USDA). It is one of the key components of the FDA strategy to assess relationships between antimicrobial use in agriculture and subsequent human health consequences. NARMS surveillance and research data is valuable in identifying the source and magnitude of antimicrobial resistance in the food supply and is important for the development of public health recommendations for the use of antimicrobial drugs in humans and food animals. NARMS provides ongoing monitoring data on antimicrobial susceptibility/resistance patterns in select zoonotic foodborne bacteria, in particular *Salmonella*, *Campylobacter*, *E. coli* and *Enterococcus*.

With regard to expanding NARMS into other infection routes besides food, NARMS does not currently screen for *S. pneumoniae* or MRSA but is currently working with partners at the University of Maryland to conduct a small pilot study looking for MRSA in retail meats in the Washington, DC metro area. FDA/CDC is also meeting with FoodNet partners to explore the possibility of expanding MRSA testing to a larger collection of retail meats obtained through the NARMS retail program. Lastly, NARMS scientists have partnered with academic investigators at the University of Minnesota in another pilot study characterizing potential links between antimicrobial resistant *E. coli* recovered from foods and human extra-intestinal pathogenic *E. coli* infections (e.g., urinary tract infections, septicemia). Overall, the NARMS program is yielding information that is valuable in identifying the source and magnitude of antimicrobial resistance in the food supply and is important for the development of public health recommendations related to the use of antimicrobial drugs in humans and food animals.

For CDC, current surveillance systems for antimicrobial resistance are primarily with State health departments, hospitals, and public health clinics. There is a need to improve the systems for capturing timely and complete surveillance information. In general, there is also a need to expand the surveillance systems to include other potential emerging sources of resistant microorganisms and to collect isolates of bacteria, fungi, and other resistant microorganisms for characterization. Characteriza-

tion studies, such as defining the mechanisms of antimicrobial resistance and determining the strain types of the organisms for epidemiologic studies, are important activities that could be expanded. In addition, more comprehensive data on antimicrobial use are needed to understand the drivers of resistance. The current databases with this information are expensive to access, or are fragmented and in need of updates. These improvements would help CDC, working with other HHS Operating Divisions and academic partners, to design appropriate interventions to prevent the development of resistant organisms and control their spread.

Question 2. The NARMS program monitors antimicrobial resistance in enteric pathogens. In light of the significant and growing threats of other resistant pathogens like MRSA or *S. pneumoniae*, do you feel the scope of existing programs should be expanded to include other routes of infection such as through the skin, respiratory tract or urinary tract?

Answer 2. The surveillance data provided through NARMS, a collaborative effort of CDC, FDA, and USDA, continue to provide key information regarding the development and spread of antimicrobial resistance among enteric bacteria in humans, animals, and retail foods. Control efforts to interrupt the spread of resistant bacteria in the food supply may benefit from expanded surveillance for organisms including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* in food animals and retail meats. Such studies are currently under consideration by NARMS investigators.

Streptococcus pneumoniae is an example of a major human pathogen that is not transmitted through animals nor does it cause infection in animals; thus, it falls outside the scope of the NARMS program. *S. pneumoniae* infections, including respiratory tract infections, meningitis, and bacteremia, as well as invasive MRSA infections in humans are monitored through CDC's Emerging Infections Program. The Emerging Infections Program, an intensive surveillance system operating in 10 States, tracks serious human infections caused by resistant organisms and serves as a research platform that can evaluate the impact of prevention measures. Increased capacity of the current sites participating in the Emerging Infections Program would allow for assessments of the ability of new vaccines to prevent disease caused by emerging resistant strains of *Streptococcus pneumoniae* and to determine the effectiveness of new measures to control MRSA infections.

The need for such expansion is further illustrated by the recent detection of the first known cases of ciprofloxacin-resistant meningococcal disease reported in North America. The Emerging Infections Program provided CDC with strains from its surveillance sites to evaluate and describe the scope of the public health problem. This information allowed CDC to develop new recommendations for antimicrobials to protect individuals who come in contact with such cases.

Question 3. How can regulatory agencies such as the CDC, FDA, and Department of Agriculture (USDA) engage in additional data collection on how the use of antimicrobials in animal feeds might lead to antimicrobial resistance in human diseases? At what level (region, State, metropolitan area, farm, etc) is data collection on the use of antimicrobials in animal feeds necessary to effectively monitor and describe trends in antimicrobial resistance?

Answer 3. Minimizing the emergence of antimicrobial resistant bacteria in animals and the potential spread to humans is a complex problem requiring a coordinated, multifaceted approach. More than a dozen Federal agencies have an interest in the problem of antimicrobial resistance, and several of these agencies have responsibilities regarding the use of antimicrobials in agriculture. The strategy developed by FDA to address antimicrobial resistance is one component of more broad-reaching strategies being developed at the national level in the form of the Public Health Action Plan to Combat Antimicrobial Resistance.

CDC, FDA, and the Department of Agriculture (USDA) are currently collaborating on the operation and maintenance of the National Antimicrobial Resistance Monitoring System (NARMS). NARMS was developed in 1996 to monitor changes in susceptibility of select foodborne bacteria to antimicrobial agents of human and veterinary importance, including food animals and foods of animal origin. It is one of the key components of the FDA strategy to assess relationships between antimicrobial use in agriculture and subsequent human health consequences. NARMS surveillance and research data is valuable in identifying the source and magnitude of antimicrobial resistance in the food supply, and is important for the development of public health recommendations for the use of antimicrobial drugs in humans and food animals. NARMS provides ongoing monitoring data to physicians, veterinarians, and public health authorities on antimicrobial susceptibility/resistance patterns in

select zoonotic foodborne bacteria, in particular, *Salmonella*, *Campylobacter*, *E. coli* and *Enterococcus*.

CDC, FDA, and USDA NARMS scientists have been exploring additional avenues for data collection. They are currently working with partners at the University of Maryland to conduct a small pilot study looking for methicillin-resistant *Staphylococcus aureus* (MRSA) in retail meats in the Washington, DC metro area. FDA/CDC are also meeting with FoodNet partners to explore the possibility of expanding MRSA testing to a larger collection of retail meats obtained through the NARMS retail program. Lastly, NARMS scientists have partnered with academic investigators at the University of Minnesota in another pilot study characterizing potential links between antimicrobial resistant E. coli recovered from foods and human extra-intestinal pathogenic E. coli infections (e.g., urinary tract infections, septicemia). Overall, the NARMS program is yielding information that is valuable in identifying the source and magnitude of antimicrobial resistance in the food supply and is important for the development of public health recommendations related to the use of antimicrobial drugs in humans and food animals.

In regard to what level of use data collection is necessary to effectively monitor and ascertain potential trends in antimicrobial resistance, such use data needs to be at a level that will provide information relative to use in particular food animal species. Such species-specific use data, in conjunction with the data collected as part of the NARMS program, enables our epidemiologists to make associations between use patterns and emerging antimicrobial resistance trends.

Question 4. As you are aware, recent studies have shown an association between community-acquired strains of MRSA and colonization of swine and farmers in the Netherlands, Canada and now in the U.S. How are the FDA, CDC and USDA working together to understand and contain the spread of community acquired MRSA from farm animals such as pigs and cattle to humans?

Answer 4. CDC and others have investigated numerous outbreaks of community-associated MRSA infections in the United States, and in none of these investigations has animal exposure been identified as a risk factor for infection. Recent reports from the Netherlands and Canada suggest that human infections caused by MRSA strains of animal origin occur predominantly among persons with close proximity to colonized or infected animals. CDC has not identified the predominant strain identified in pigs in any human disease or colonization isolates in our CDC isolate database, suggesting this strain is not a prevalent cause of human infection in the United States. CDC works closely with its regulatory partners at FDA and USDA on issues affecting the safety of the U.S. food supply; further research is needed to understand the extent to which MRSA is present in food producing animals in the United States and the public health implications of this.

QUESTIONS OF SENATOR ENZI

Question 1. You talked extensively in your testimony about the CDC surveillance systems. Are there any gaps in your systems that are present because of barriers related to the CDC's authority?

Answer 1. CDC should expand its surveillance of resistant microorganisms (bacteria, fungi, viruses, and parasites) among multiple life stages, settings, and animals (domestically and internationally) to identify populations or communities that require interventions to reduce the development or spread of resistance, and to gather more nationally representative data. CDC relies on partners such as State health departments and hospitals to provide data on resistant infections and often such partners lack adequate resources to provide complete and timely data. The increasing availability of healthcare data in electronic form and recent advances in information technology provide new opportunities to accelerate the transition from manual healthcare-associated infections (HAI) case finding and reporting to computer-based algorithmic case detection and electronic reporting. Legislation that encourages collaboration among agencies and requires accountability for working together to ensure complementary systems in surveillance is helpful in achieving this aim. Privacy and confidentiality protections are a barrier that can have useful yet still protective legislative solutions. Linked authorization and appropriations for systems is important to have the ability to implement many solutions to barriers.

Question 2. Is the coordination of Federal entities currently producing the best information and resulting in the most appropriate actions that are necessary to take to help reduce antibiotic resistance? Are there any legislative barriers that prevent the agencies from sharing information or responding to the problem in a coordinated manner?

Answer 2. There is certainly an opportunity for greater data sharing among agencies to enhance efforts to monitor the spread of antimicrobial resistant microorganisms. For example, sharing of data between CDC and the Department of Defense on incidence of antimicrobial resistant strains of *N gonorrheae* could be very useful for selecting appropriate treatment regimens in the future. Limited public health infrastructure for detecting resistance and the heavy reliance on hospital microbiology laboratories around the United States to provide the antibiotic resistance data is a barrier. Additionally, confidentiality protections create barriers to sharing that need creative legislative solutions that both maintain protection and allow action.

QUESTIONS OF SENATOR BROWN

Question 1. CDC appoints a co-chair on the Interagency Task Force on Antimicrobial Resistance. Please describe the leadership chain and how the many participating agencies and the individuals representing them are held accountable for implementation of Action Items in their jurisdiction.

Answer 1. The CDC representative to the Interagency Task Force is the Director of the CDC Office of Antimicrobial Resistance, which is part of the Coordinating Center for Infectious Diseases at CDC. The Office of Antimicrobial Resistance consults with CDC leadership regarding issues of policy and clears all policy documents through the CDC Office of the Director. The Director of the CDC Office of Antimicrobial Resistance is responsible for monitoring and documenting progress on the Action Items for the Agency. Annual progress reports are posted on the CDC Antimicrobial Resistance Web site on behalf of the Interagency Task Force.

Question 2. Nearly 8 years ago, the Interagency Task Force put out an Action Plan identifying 13 (out of 84) elements as "top priority," critically necessary to address growing resistance. Shortly after, I introduced legislation to authorize such sums as necessary to implement these 13 top priority items. The bill didn't pass. How are these action items currently funded? According to HHS, in 2006, CDC spent $16.2 million; FDA $24 million; and NIH $220 million. In your professional judgment, please tell me what funding is necessary for each of your agencies to implement the Action Plan—especially the top priority action items. In addition, what funding is necessary for NIH?

Answer 2. CDC To fully combat the growing problem of antimicrobial resistance, and to fully implement the Action Plan, a significant increase in resources would be required. The increase in funding will provide resources for expansion and enhancement of networks for detection, monitoring and prevention of antimicrobial resistance, both domestically and internationally. For example, informatics will be used to expand current databases of both antimicrobial use and antimicrobial resistance patterns, and expand web based reporting capabilities. Antimicrobial use will be improved in multiple settings and populations through prevention activities. CDC will conduct new research and demonstration projects, and develop software for data and trend analysis. Reference laboratories will be expanded and rapid diagnostic methods developed to determine the susceptibility of microorganisms to new anti-infective agents. Laboratory enhancements will include the purchase of state-of-the-art equipment. Finally, the increase in funding will provide expanded support for the Antimicrobial Resistance Task Force.

NIH: The National Institute of Allergy and Infectious Diseases (NIAID) supports a broad research portfolio dedicated to antimicrobial resistance that includes innovative research on new potential therapeutics and vaccines, as well as efforts to reduce the pressure on the existing arsenal of antimicrobial drugs. The research priorities outlined in the Interagency Task Force on Antimicrobial *Resistance Public Health Action Plan to Combat Antimicrobial Resistance* are actively being addressed through NIAID-supported research grants and contracts. The *Action Plan*, which is updated annually, is currently in the process of being revised to ensure that the document is appropriately focused on current priorities. In December 2007, the Task Force held a public meeting and received input from experts about pressing antimicrobial resistance needs; these issues are being considered by the CDC, NIH, Food and Drug Administration and other Task Force members as they update the *Action Plan*.

FDA: Implementation of the action items, both top priority action items and others, are funded through the respective agencies' appropriations. There is no dedicated funding for the Interagency Task Force or the Public Health Action Plan.

Question 3. In the late 1990s, the Office of Technology Assessment (OTA), the Institutes of Medicine (IOM) and the GAO issued reports to Congress on the growing problem of antimicrobial resistance. The reports focused on a number of shortcomings of our Federal response to antimicrobial resistance. Specifically, it cited the

need for antibiotic development, enhanced surveillance and data collection. Please discuss current data collection related to or specifically addressing antimicrobial resistance in this country and in other countries—how does the U.S. data effort compare to others, especially European countries? Are we doing a better job than our European counterparts collecting such data?

Answer 3. The European Community has established a system for monitoring both antimicrobial resistance rates among bacterial species [European Antimicrobial Resistance Surveillance System (EARSS)] and antimicrobial use. Annual reports are published by EARSS showing resistance rates for a wide array of bacterial species in most of the countries in the European Union. Comparable data from the United States (i.e., population based data) are available only for a few bacterial species. The European Union also publishes extensive data on antimicrobial use in humans and animals by country. The United Kingdom has a national system for MRSA, and has made significant investments in this system.

The United States does not produce comparable data to those listed above. The United States has systems such as CDC's Emerging Infections Program, the National Healthcare Safety Network (NHSN), and NARMS that collect some bacteria and specific infection data. These systems have the potential to be national systems with the appropriate investments, and could be expanded to include additional bacteria and to have a national scope. In contrast to systems in Europe, the United States has limited access to comprehensive and timely data on antimicrobial use.

Question 4. What more does CDC need to do to address antimicrobial resistance? What are the barriers to doing more?

Answer 4. CDC should expand its surveillance of resistant microorganisms (bacteria, fungi, viruses, and parasites) among multiple life stages, settings, and animals (domestically and internationally) to identify populations or communities that require interventions to reduce the development or spread of resistance. For example, to reduce the potential for widespread failure of primary therapy for gonorrhea in the future, surveillance for cephalosporin-resistant *Neisseria gonorrhoeae* should extend beyond men in public health clinics to include the men and women in the private sector and military personnel. CDC also needs to improve prevention and control activities in all healthcare settings such as outpatient centers, hospitals and long-term care facilities to stop transmission of resistant microorganisms and to reduce inappropriate antimicrobial use. Finally, CDC needs to enhance the surveillance infrastructure at both the local, State, and Federal levels to improve antimicrobial resistance activities, and to enhance laboratory capacity and expand research. Current investments limit the capacity to appropriately respond to the emerging problem.

Question 5. Last year, I introduced S. 2313, the Strategies to Address Antimicrobial Resistance (STAAR) Act, a bill targeting the problem of antimicrobial resistance. Can CDC tell me how this legislation will make an impact on addressing antimicrobial resistance?

Answer 5. CDC applauds efforts to raise awareness about the problem of antimicrobial resistance and to reduce the development and spread of resistant microorganisms. It is important that the provisions of The STAAR Act compliment the many current activities and programs which address microbial resistance.

Question 6. Within the STAAR Act, can you explain how you think the provision on Clinical Research & Public Health Network will compliment the current surveillance activities and discuss the importance of isolate collection? In short, will these proposed activities better prepare physicians to be on the look out for emerging resistance issues and help contain them before they spread to other States?

Answer 6. The proposed mandate for the Clinical Research & Public Health Network is very broad. Hopefully, such an activity would be designed to enhance and compliment the existing CDC activities of the Emerging Infections Program, NARMS, the Prevention EpiCenters, and other existing surveillance systems and prevention efforts rather than replace these long standing activities. Integrating and leveraging the surveillance and research while maintaining existing expertise and depth can be useful.

Question 7. Does CDC have access to the antimicrobial resistance data that FDA collects? Do you have access to the data collected by Medicare and the VA? In your perspective, do you believe more reliable and comparative animal and human usage data would be of value to CDC's public health mission? If so, please explain.

Answer 7. Data collected by CDC, FDA, and USDA as part of the NARMS programs is shared among the three agencies. CDC has partnered with several VA medical centers to collect limited antimicrobial resistance data. However, data are

not shared in any consistent manner beyond those specific programs. Better access to antimicrobial use data from humans and animals would be a tremendous help to CDC's activities to monitor and control the development and spread of antimicrobial resistant organisms by indicating where selective pressure is highest.

QUESTIONS OF SENATOR BURR

Question 1. How does CDC currently decide which organisms to monitor for antimicrobial resistance and how does the agency conduct surveillance of organisms of concern, such as campylobacter, E. coli, gram negative and gram positive organisms, HIV, influenza, malaria, tuberculosis and others? Are these surveillance activities conducted by State and local public health departments?

Answer 1. CDC and the Council of State and Territorial Epidemiologists provide guidance under the Nationally Notifiable Disease Surveillance System and State health departments are responsible for determining which microbial species are to be reported by physicians and laboratories in their respective States and territories. These data contribute to CDC's overall picture of the burden of antimicrobial resistance. The selection of which microorganisms to monitor for resistance at CDC is based on CDC's estimation of the potential public health impact of the development of resistance on human and animal health. It also is impacted by CDC's need to measure the effectiveness of intervention programs that are undertaken. For example, the introduction of the pneumococcal conjugate vaccine to decrease invasive pneumococcal infections in children required a monitoring system to be in place to measure the effectiveness of this multimillion dollar public health initiative. The ABCs program, an active laboratory- and population-based surveillance system for invasive bacterial pathogens of public health importance that is part of CDC's Emerging Infections Program, serves that purpose and continues to monitor the development and spread of novel strains of pneumococci that cause invasive pneumococcal disease in the United States. ABCs also provides an infrastructure for further public health research, such as monitoring the impact of the next generation pneumococcal vaccine on newly emerging resistant strains not covered by the first vaccine and whether new control measures introduced in several States can reduce MRSA disease.

Question 2. How do CDC and NIH decide what research to fund on prevention, control and treatment of resistant organisms? Aren't there research funds available that academic centers or public health departments can apply for? Does CDC have a position on the Brown-Hatch legislation and the required establishment of 10 new research centers on antimicrobial resistance? How does this change what is already occurring?

Answer 2. To assess scientific opportunities and priorities, the National Institutes of Health (N1H) receive input from a range of sources, including ad hoc advisory groups, focus groups, conferences, and informal discussions with outside scientists. Further, each Institute and Center (IC) of the NIH has advisory bodies and a main advisory Council that provide recommendations on broad research priorities and directions, providing the perspective of the outside community. Scientific priorities, especially in emerging areas, can be reflected in new research initiatives that an IC issues to solicit grant applications or contract proposals to address specific scientific questions. In addition, through investigator-initiated research, scientists in the extramural community can identify scientific opportunities that they feel are important to a particular field. Whether research is solicited or investigator-initiated, the most important factor in determining funding decisions is scientific merit of a proposal or application, as judged by peer reviewers.

The National Institute of Allergy and Infectious Diseases, a component of the NIH, conducts and supports broad research on antimicrobial resistance. This research includes innovative research on new potential therapeutics and vaccines, as well as efforts to reduce the pressure on the existing arsenal of antimicrobial drugs. For example, in 2007, NIAID awarded two contracts totaling $19 million over 5 years to support multisite, Phase II/III clinical trials to study whether selected oral, off-patent antibiotics can effectively treat skin and soft tissue infection caused by community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Should the data from these studies demonstrate that off-patent antibiotics are effective, final option drugs such as vancomycin and linezolid could be preserved for treatment of healthcare associated MRSA. These contracts were awarded to two groups of researchers qualified to address the questions within this specific disease area. These researchers, and the multiple sites associated with them for these studies, form a "functional network," an approach that provides NIAID with a flexible structure in which to address specific scientific questions of highest priority.

NIAID has announced a fiscal year 2009 initiative, "Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance," that is soliciting proposals for research to treat a variety of important bacterial infections with strategies such as shorter courses of antimicrobials drugs and different dosages/frequencies of drugs. NIAID anticipates the release of a similar initiative in fiscal year 2010.

CDC bases funding activities on the Action Plan to Combat Antimicrobial Resistance. Academic centers and public health departments can apply for funding. The proposed mandate for the Clinical Research & Public Health Network is very broad. Hopefully, such an activity would be designed to enhance and compliment the existing CDC activities of the Emerging Infections Program, NARMS, the Prevention EpiCenters, and other existing surveillance systems and prevention efforts rather than replace these long standing activities. Integrating and leveraging the surveillance and research while maintaining existing expertise and depth can be useful.

Question 3. How much is CDC currently spending on antimicrobial resistance research and surveillance activities each year?

Answer 3. In 2008, CDC's Office of Antimicrobial Resistance obligated $16.3 million to antimicrobial resistance activities. In addition, divisions within the Coordinating Center for Infectious Diseases spent an additional $6.7 million dollars to support antimicrobial resistance activities.

Question 4. When we talk about antimicrobial resistance, are we capturing antiviral resistance? If not, do you see this as a separate policy issue that should be dealt with differently?

Answer 4. Resistance to the antiviral agents used to treat Human Immunodeficiency Virus infections, influenza viruses, and some hepatitis viruses are captured currently by CDC surveillance systems. Resistance to other antiviral agents is not monitored.

Question 5. In your testimony, you talked about a partnership between CDC and the VA, which led to a 60 percent reduction in the rate of MRSA infections in VA medical centers after a series of infection control procedures were implemented. Please tell us more about those procedures and how other hospitals and community settings, like gyms, can be encouraged to follow suit.

Answer 5. CDC has collaborated with the VA to demonstrate the preventability of healthcare-associated MRSA infections for several years. In 2001, CDC funded the Veteran's Affairs Pittsburgh Healthcare System (VAPHS) to perform an MRSA infection prevention demonstration project. This collaboration, using a prevention strategy consistent with CDC's guideline for control of multidrug resistant organisms (MDROs), began a pilot study in a single patient care unit within the hospital. After a post-intervention reduction in MRSA infection rates of over 60 percent was observed in that unit, the intervention was implemented in a second unit with similar results. Finally, the intervention was implemented across the entire hospital, and an overall 60 percent decrease in the hospital-wide MRSA incidence was observed. The Department of Veteran's Health Affairs (VHA) issued a directive to all VHA hospitals nationwide to implement MRSA prevention programs using the VAPHS intervention as a model. In addition, the Agency for Healthcare Research and Quality and the Robert Wood Johnson Foundation have provided funding for hospitals in five States to use innovative methods to facilitate implementation of MRSA prevention programs modeled closely after the VAPHS demonstration project, and the Maryland Patient Safety Center has implemented a voluntary MRSA prevention initiative involving 29 healthcare facilities using the VAPHS intervention as a model. CDC is helping to measure the impact of several of these initiatives, and preliminary data from some of the early reporters show successes similar to what was observed following the VAPHS intervention, providing encouraging evidence that implementing CDC recommendations can result in control of MRSA.

CDC also has recommendations to prevent transmission of MRSA in community settings. CDC has partnered with the National Collegiate Athletic Association (NCAA), the National Federation of High School Associations, the National Athletic Trainers' Association (NATA), and others to develop informational materials and to educate athletes and trainers about community associated MRSA and its prevention, and is currently developing educational materials for mothers. With appropriate investments, these strategies can be implemented on a national scale.

Question 6. I understand a revised Public Health Action Plan is going to be released for public comment this fall. Can you please make sure we are made aware of this updated action plan?

Answer 6. CDC will provide the committee with the updated action plan.

DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS),
FOOD AND DRUG ADMINISTRATION (FDA),
ROCKVILLE, MD 20857,
September 19, 2008.

Hon. EDWARD M. KENNEDY, *Chairman,*
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510–6300.

DEAR MR. CHAIRMAN: Thank you for providing the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the June 24, 2008, hearing entitled, "Emergence of the Superbug: Antimicrobial Resistance in the U.S.," before the Senate Committee on Health, Education, Labor, and Pensions. RADM Linda R. Tollefson, D.V.M., M.P.H., Assistant Commissioner for Science, testified on behalf of FDA. We are responding to your July 17, 2008, e-mail transmitting questions for the record.

We have restated your questions below in bold, followed by our response.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY, SENATOR BROWN, AND SENATOR BURR BY THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

QUESTIONS OF SENATOR KENNEDY

Question 1. As you mentioned, the FDA has only restricted the use of one class of antimicrobial, fluoroquinolones, for subtherapeutic doses in poultry feed. Do you believe that other classes of antimicrobials used in subtherapeutic doses in animals should be reviewed for the risks that they pose to human health, in food, the environment and other avenues of potential risk? How are risks of penicillin and other older antibiotics being assessed?

Answer 1. For clarification, FDA has only restricted the use of fluoroquinolones for therapeutic uses in poultry. These fluoroquinolones were never approved for use at subtherapeutic doses. The approved application for sarafloxacin for use in chickens and turkeys was voluntarily withdrawn by the pharmaceutical sponsor. The approved application for enrofloxacin for use in chickens and turkeys was withdrawn following statutory due process procedures for withdrawal of an approval of a New Animal Drug Application. Fluoroquinolones are approved for other food-producing species; however, they are on the FDA list of drugs that are prohibited from extra-label use in food-producing species. This means that fluoroquinolones may not be used for extra-label use in feed or otherwise, e.g. in water.

FDA monitors all new animal drugs to ensure that the approved uses are safe and effective in accordance with the requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). The Agency has the authority to take action to withdraw an approval on various grounds, including that experience or scientific data show that the approved new animal drug is unsafe.

For penicillin-containing products, FDA reviewed all information contained in the administrative files, looking specifically for microbial food safety information that can be used to assess any potential human health risks. Additionally, FDA searched and reviewed scientific literature for microbial food safety information for penicillin-containing products. The basic tenets of the qualitative risk assessment process described in Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (GFI #152 or Guidance) (copy enclosed), were applied by review scientists to perform this assessment. A similar review process is being applied to other "older" approved antimicrobial products (e.g., tetracyclines).

Question 2. Do you feel FDA Guidance for Industry #152 provides a sufficient framework for addressing all of the public health risks associated with antimicrobial drugs in animal feeds, including environmental risks?

Answer 2. Yes, however, GFI #152 was designed to primarily address the foodborne pathway and does not specifically address environmental risks. FDA believes that the most likely pathway for the transference of antimicrobial resistance in bacteria from animals to humans is through foodborne exposures. GFI #152 is a non-binding guidance document that provides an approach for the industry to format, organize, and present data and other information to FDA for evaluation. The Guidance provides suggestions for some risk mitigations that might be considered. The Guidance does not bind or constrain FDA in making a determination whether a particular animal drug meets the food safety standard of a reasonable certainty of no harm. As new scientific information causes FDA to consider new or different

approaches to assessing the microbial safety of new animal drugs, FDA can change the Guidance through its administrative procedures outlined in Good Guidance Practice regulations.

GFI #152 provides a framework for sponsors of antimicrobial new animal drugs to follow when providing information to FDA on microbial food safety. GFI #152 was designed to address public health risks associated with antimicrobial drugs primarily through food exposure. However, as other avenues of potential public health risk are demonstrated, FDA may ask sponsors for additional data and information when it is applicable and appropriate.

Since 2001, FDA has reviewed a variety of antimicrobial animal drugs for numerous intended uses. Among these drugs, a number of risk mitigations have been implemented. These include modifying the conditions of use of the product and applying certain label restrictions such as requiring veterinary prescription status.

Question 3. Does the FDA currently have the authority to collect the antimicrobial drug use data needed to manage the risk of antimicrobial resistance, such as geographic location and actual mechanism of use by producers?

Answer 3. FDA has the statutory authority to promulgate regulations requiring sponsors of approved new animal drugs to submit reports of data relating to experience with those new animal drugs. This includes experience with extra-label uses of the drug, and other data or information the sponsor receives or otherwise obtains with respect to the drug as necessary to determine or facilitate a determination of whether grounds to withdraw the approval of a new animal drug exist. In addition, the act authorizes FDA to issue an order requiring a sponsor to submit such reports for those same purposes. Current FDA regulations at Title 21, *Code of the Federal Regulations* (CFR) section 514.80, require the sponsor to submit total quantity marketed data annually (semi-annually for the first 2 years post-approval) for each new animal drug application.

Question 4. On July 3, FDA issued a prohibition order on extra-label use of cephalosporin drugs. The order states that "the surveillance data cited [in the order] supports the finding that certain cephalosporin use in animals is likely contributing to an increase in cephalosporin-resistant human pathogens." In my understanding, the extra-label uses of cephalosporin are not very different from that of labeled uses—which include different species or dosing times from on-label uses. Is FDA concerned about on-label uses as well? If so, what is FDA doing to understand risks to humans from all cephalosporin use?

Answer 4. FDA believes that the approved cephalosporins are safe for on-label uses with respect to microbial food safety. Human food safety concerns associated with the approved uses of cephalosporins in food-producing animals were evaluated as part of the new animal drug approval process. In contrast, we do not have safety information relative to extra-label uses. Given the trends of increasing resistance cited in the July 3 order, FDA determined that steps were needed to help curtail further escalation of cephalosporin resistance. As discussed in the July 3 order of prohibition, FDA believes there is sufficient evidence to support the conclusion that the extra-label use of these drugs is contributing to resistance emergence and thus presents a risk to public health. Based on a number of requests to extend the comment period and effective date received since publication of the July 3 order, FDA has extended the comment period until November 1, 2008, and has delayed the effective date until November 30, 2008. Although FDA does not have specific concerns about the approved on-label uses of cephalosporins at this time, FDA is continuing to monitor resistance trends through the National Antimicrobial Resistance Monitoring System.

Question 5. As you are aware, recent studies have shown an association between community-acquired strains of MRSA and colonization in swine and farmers in the Netherlands, Canada, and now in the United States. What steps will the FDA take to determine the prevalence of MRSA on U.S. farms, in farm workers, and in the community at large?

Answer 5. Methicillin-resistant *S. aureus* (MRSA) was first reported in 1961, soon after the antimicrobial methicillin was introduced into human medicine to treat penicillin-resistant staphylococci. MRSA has since emerged as an important human pathogen world wide, with some epidemic strains spreading between hospitals, countries and more recently in people who have not been hospitalized (community acquired MRSA or CA-MRSA). More recently, there is concern in the veterinary medicine and food safety arenas with regards to MRSA as a possible zoonosis (i.e., a disease that may be transmitted from animals to humans), in particular those strains belonging to clonal lineage ST398. FDA scientists have been following the

emergence of MRSA clonal lineage ST398 from humans and animals in Central Europe and Canada and are monitoring the situation very closely.

MRSA infections in domestic animals have been reported among horses, pigs, cattle, sheep, cats, dogs and rabbits as well as being reported as an emerging problem in veterinary teaching facilities. Pig-to-farmer transmission of MRSA ST398 has been documented in the Netherlands and a high prevalence of ST398 was also found in slaughtered pigs in Denmark, and in humans, horses, dogs and pigs in Austria and Germany. Researchers from the University, of Iowa recently presented data at the 2008 International Conference on Emerging Infectious Diseases which indicated that MRSA was present among several swine farms in Iowa. This data has yet to be published in a peer reviewed scientific journal, however, a recent study from Canada reported on the prevalence of MRSA colonization in pigs and people that work with pigs on South-western Ontario pig farms.[1] Both human-to-animal and animal-to-human transmission of MRSA are known to be possible; however, it has not yet been adequately determined whether animals are an important primary source of MRSA infections for populations other than high-risk exposure groups (e.g. swine farmers and veterinarians), or if MRSA is colonized in animals after contact with human carriers.

The National Antimicrobial Resistance Monitoring System (NARMS) is one of the key components of FDA's Center for Veterinary Medicine (CVM) strategy to assess relationships between antimicrobial use in agriculture and subsequent human health consequences. NARMS surveillance and research data is valuable in identifying the source and magnitude of antimicrobial resistance in the food supply and is important for the development of public health recommendations for the use of antimicrobial drugs in humans and food animals. NARMS provides ongoing monitoring data on antimicrobial susceptibility/resistance patterns in select zoonotic foodborne bacteria, in particular *Salmonella*, *Campylobacter*, *E. coli* and *Enterococcus*. NARMS does not currently screen for MRSA but is currently working with partners at the University of Maryland to conduct a small pilot study looking for MRSA in retail meats in the Washington, DC metropolitan area. Overall, 700 total samples will be tested: 300 of ground pork, 200 of ground beef, and 200 of ground turkey. Of the 249 retail meats tested to date, no MRSA have been detected. FDA is also meeting with FoodNet partners to explore the possibility of expanding MRSA testing to a larger collection of retail meats obtained through the NARMS retail program.

It has come to my attention that the fuel ethanol industry uses human therapeutic antibiotics during the fermentation process. I have been informed that FDA has found residues of these antibiotics in "distiller's grains," a bioproduct of fuel ethanol production which is sold as animal feed throughout the United States.

Question 6a. FDA issued a letter in 1993 approving the use of virginiamycin in alcohol fermentations at an amount no greater than 6 parts per million with residuals in the distiller's grains at a level no greater than 0.5 parts per million. What are the levels of virginiamycin or other antibiotics found at fuel ethanol plants and in grain?

Answer 6a. FDA has been proactive in issuing field assignments to collect distillers' grain samples and test for the presence of antibiotics; however, FDA will not have data on antibiotic residue levels in distillers' grains until the ongoing assay method validation is completed.

Question 6b. Has FDA taken action to prevent contamination of distiller's grains with antibiotic residues?

Answer 6b. The Agency has been very proactive in working with and educating the ethanol industry about animal feed requirements. To that end, during 2007/2008 FDA spoke at several industry meetings including the Renewable Fuel Association's National Ethanol Conference, the International Fuel Ethanol Workshop and the Association of American Feed Control Officials (AAFCO) BioFuel Symposium. Additionally, FDA is a member of several distillers' grain's taskforces including the National Grain and Feed Association (NGFA) and AAFCO as well as a member of the Department of Energy's (DOE) interagency working group on biochemical conversion platform.

Recently, FDA has worked with the Environmental Protection Agency to make clear FDA's regulatory authority over the use of these antimicrobials during ethanol production when the distillers' grains are used as an animal feed ingredient.

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[1] Khanna, T., et al. 2007. Methicillin-resistant *Staphylococcus aureus* colonization in pigs and pig farmers, Veterinary Microbiology, doi:10.1016/j.vetmic.2007.10.006.

FDA has been in contact with individual firms to advise them that food additive petitions are needed for antibiotics used in ethanol production when the distillers grains are used as a livestock feed.

Question 6c. What are the implications of unregulated antibiotic use in fuel ethanol production for animal and human health? Could these unknown doses of antibiotics be confounding research on human safety aspects of antibiotic use in animals?

Answer 6c. The use of antibiotics in fuel ethanol production is being regulated under the provisions of the FD&C Act as food additives. The animal and human health implications of antibiotic residues resulting from such use will be addressed in food additive petitions to the Agency. As ethanol production increases so does the amount of distillers' grain available as an animal feed ingredient. In order to use these supplies, distillers' grains are now expanding from the cattle market to the swine, poultry, fish, etc. markets. Additionally, the use rate of distillers' grains in animal diets has increased. At one time, an animal's ration incorporated approximately 10 percent distillers' grain. Currently, academic and industrial research is supporting levels as high as 50 percent. At this time, FDA has requested firms to address the impact of the higher use levels on potential exposure antibiotic residues.

QUESTIONS OF SENATOR BROWN

Question 1. FDA appoints a co-chair on the Interagency Task Force on Antimicrobial Resistance. Please describe the leadership chain and how the many participating agencies and the individuals representing them are held accountable for implementation of Action Items in their jurisdiction.

Answer 1. Each agency develops and internally approves the work products resulting from the Public Health Action Plan to Combat Antibiotic Resistance. If more than one agency works on a project, simultaneous clearance takes place within each of the agencies. FDA established the Antimicrobial Resistance Steering Committee, chaired by Dr. Tollefson, to coordinate FDA's activities and track action items. FDA centers and the Office of the Commissioner are represented on the steering committee. Greater than 90 percent of the action items represent work that is core to the mission of each of the agencies.

Question 2. Nearly 8 years ago, the Interagency Task Force put out an Action Plan identifying thirteen (out of 84) elements as "top priority," critically necessary to address growing resistance. Shortly after, I introduced legislation to authorize such sums as necessary to implement these 13 top priority items. The bill didn't pass. How are these action items currently funded? According to HHS, in 2006, CDC spent $16.2 million; FDA $24 million; and NIH $220 million. In your professional judgment, please tell me what funding is necessary for each of your agencies to implement the Action Plan—especially the top priority action items. In addition, what funding is necessary for NIH?

Answer 2. Work on the action items, both top priority action items and others, are funded through the respective agencies' appropriations.

Question 3. In the late 1990s, the Office of Technology Assessment (OTA), the Institutes of Medicine (IOM) and the GAO issued reports to Congress on the growing problem of antimicrobial resistance. The reports focused on a number of shortcomings of our Federal response to antimicrobial resistance. Specifically, it cited the need for antibiotic development, enhanced surveillance and data collection.

Answer 3. The Task Force is aware of these reports on the threat of antimicrobial resistance and took each of them into consideration when drafting the original Public Health Action Plan to Combat Antimicrobial Resistance (Action Plan). The reports were also very influential in selecting the four focus areas of the Action Plan: Surveillance, Prevention and Control, Research, and Product Development.

Question 4. Please discuss current data collection related to or specifically addressing antimicrobial resistance in this country and in other countries—how does the U.S. data effort compare to others, especially European countries? Are we doing a better job than our European counterparts collecting such data?

Answer 4. There are several data collection, or surveillance and monitoring, efforts in the United States focused on hospital infections, community acquired infections, and agriculture or food- producing animal-related enteric infections. The National Antimicrobial Resistance Monitoring System (NARMS), for example, was modeled after the Danish system for monitoring antimicrobial resistance, called DANMAP. NARMS monitors antimicrobial resistance in isolates of enteric bacteria from ill humans, healthy animals presented for slaughter, and retail meat. Several other European countries, as well as Canada, Australia and New Zealand, collect

information on antimicrobial resistance. We work very closely with these countries to harmonize as much as possible the methods used to isolate and test the bacteria and the reporting of the data.

Question 5. It's my understanding that FDA currently collects human and animal drug distribution data, including for antibiotics. My bill, the STAAR Act, would change the date this information is submitted to FDA—from anniversary of product approval to a calendar year and in a format that allows comparison of data. Also, the bill requires the Federal Government to explore opportunities to obtain data from private vendors. It is my understanding that other countries purchase data to be used in research. What does FDA do with the data currently collected? Do you have recommendations regarding ways to improve this data collection? Is the data shared with the Interagency Task Force? Does it help us understand the relationship between use and resistance? Are summaries of this information available for research purposes?

Answer 5. With regard to the data for human drugs, there are two routes through which we have access to these data. First, all holders of approved new drug applications (NDAs) are required to include distribution data in the annual reports to their NDAs. They are required to include quantities of product distributed for both domestic and foreign use. These submissions are not shared with parties outside FDA without permission from the NDA holder. We use these data as the need arises, but do not generally use it to help us understand the relationship between use and resistance.

Secondly, FDA has access to drug distribution data through a number of commercial external vendors:

Outpatient Drug Use—(1) Vendor: Verispan, Database: Vector One (contains prescription-level and patient-level data); (2) Vendor: Verispan, Database: Physician Drug and Diagnosis Audit (contains physician survey data); (3) Vendor: IMS Health, Database: IMS National Sales Perspectives, Retail and Non-Retail

Inpatient Drug Use—Vendor: Premier, Database: RxMarket Advisor

These databases have proven to be useful in assessing safety signals with marketed drugs. They can be used to determine the number of prescriptions dispensed as well as the number of patients exposed to a particular drug. They can also be used to determine prescribing habits, such as which physician specialty prescribes the drug most and for what diagnoses, and to determine patient demographics such as age and gender. Sales data are used to determine estimated usage of a particular product by patients in the United States. They can also be used to determine market share in cases of withdrawal or drug shortage. Finally, these databases can be used for pharmacoeconomic analyses as well as to assess the impact of labeling changes and to monitor changes in usage over time for a particular drug.

Reports from these databases cannot be shared outside FDA (even with other agencies within HHS) without permission from the vendor. It is rare that information from these databases is made available to the public by FDA, and when it is, it is only done so with permission from the vendor, and it is presented at a high level (i.e., no detailed data).

FDA's Center for Drug Evaluation and Research has generally not used drug distribution data for research regarding antimicrobial resistance, and due to the confidential nature of the data, we have not made this information available for research outside the Agency.

Question 6. As I mentioned at the hearing, when I was in the House, I made sure language was Included in the fiscal year 2001 Appropriation bill requesting that FDA review the safety of non-therapeutic use of antibiotics on farms. In 2004, letters were sent from FDA to manufacturers of penicillin and other drugs requesting more information because the FDA reassessed their safety and found that the use of these drugs for growth promotion, feed efficiency, and weight gain posed a high risk of producing resistant organisms and potential harm to human health. At the hearing, you said that some companies responded to that request and that some didn't and that the research is ongoing. Can you outline for me specifically what kind of research is ongoing and for those companies that did not send you that information, what is being done to get that information? Also, please give me a specific date for when this assessment will be completed.

Answer 6. FDA has completed its review of the approved new animal drug applications for the use of penicillin in animal feed. FDA reviewed all information contained in the administrative files, looking specifically for microbial food safety information that can be used to assess any potential human health risks. Additionally, FDA searched and reviewed scientific literature for microbial food safety information for penicillin-containing products. FDA review scientists applied the basic te-

nets of the qualitative risk assessment process described in GFI #152 to perform this assessment. A similar review process is being applied to other "older" approved antimicrobial products (e.g., tetracyclines). At this time, we do not have a projected date for a report of our review. FDA continues to have safety concerns regarding the non-therapeutic use of antimicrobial drugs in food-producing animals and is committed to pursuing the appropriate action to address those concerns.

Question 7. The public health community has been concerned about the resistance implications of veterinary drugs for decades now. I understand that certain classes of antibiotics pose more of a resistance threat than others. Which classes of antibiotics approved for use in animal agriculture have been reviewed in the last 10 years for their impacts on the development of antibiotic resistant disease? What is the status of those reviews? Have any drugs or drug classes been taken off the market as the result of the reviews?

Answer 7. FDA is most concerned about those antimicrobial new animal drugs or classes of drugs that are approved for use in food-producing animals and are also important human medical therapies. In the past 10 years, FDA has conducted antimicrobial resistance-related reviews on a number of approved antimicrobial new animal drugs or classes of drugs including fluoroquinolones, streptogramins, penicillins, tetracyclines, and cephalosporins.

FDA's review of data regarding resistance to the fluoroquinolone and glycopeptides classes of drugs led the Agency to issue an order in May 1997 prohibiting the extra-label use of those classes of drugs in food-producing animals. FDA subsequently conducted an assessment of two specific fluoroquinolone drugs, enrofloxacin and sarafloxacin, approved for use in poultry. Based on concerns raised by this assessment, sarafloxacin was voluntarily withdrawn by the pharmaceutical sponsor. FDA issued a notice of opportunity for a hearing in October 2000 proposing to withdraw the approved application for enrofloxacin for use in chickens and turkeys. The final decision to withdraw the approval was issued in August 2005 following completion of the statutorily defined due process procedures.

In November 2004, FDA completed a draft risk assessment on the potential impact that food-animal use of streptogramin antimicrobial drugs on the resistance to chemically similar streptogramins used to treat human enterococcal infections. CVM conducted a thorough review and analysis of all public comments submitted on the draft risk assessment and concluded that a number of significant data gaps existed that prevented finalization of the assessment. Therefore, CVM decided to continue to monitor the scientific literature, the results of surveillance studies, the usage patterns of streptogramin drugs in hospital and health care settings, and other relevant data that may affect the findings of the risk assessment.CVM will revisit the risk assessment at a time dictated by the availability of new data and scientific developments in streptogramin resistance.

On July 3, 2008, FDA issued an order prohibiting the extra-label use of cephalosporin antimicrobial drugs in food-producing animals. We issued this order based on evidence that extra-label use of these drugs in food-producing animals will likely cause an adverse event in humans and, as such, presents a risk to the public health.

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) amended the FD&C Act to permit licensed veterinarians to prescribe extra-label uses of approved animal and human drugs in animals. AMDUCA also provided that FDA may issue a prohibition order if it determined that extra-label use of a drug in animals presents a risk to the public health. As explained in the July 3, 2008, final rule, CVM made the decision to prohibit the extra-label use of cephalosporins in food-producing animals based on information supporting the conclusion that such uses are likely contributing to the emergence of cephalosporin-resistant zoonotic foodborne pathogens. Based on a number of requests to extend the comment period and effective date received since publication of the July 3 order, FDA has extended the comment period until November 1, 2008, and has delayed the effective date until November 30, 2008.

As discussed in the response to Question 6, FDA has completed its review of the approved new animal drug applications for the use of penicillin in animal feed. In addition, similar reviews are being conducted on other "older" approved antimicrobial products (e.g., tetracyclines).

Question 8. The Center for Veterinary Medicine (CVM) has a 3 million line item in its budget to reexamine the resistance implications of already approved antibiotics. What specific activities at CVM have been supported by that budget line item? Has the CVM initiated action to take any drugs off the market as a result of those reviews?

Answer 8. The review of already approved antibiotics is important to FDA and these resources have been devoted toward this effort. FDA has developed a broad-based approach utilizing a strategic framework in place, the interagency Public Health Action Plan to Combat Antimicrobial Resistance, tracking resistance patterns through NARMS and participating in international activities. The analysis of previously approved applications not only includes the activities just mentioned but also the review of relevant published literature, interactions with scientists in the field, and input from the public. Including all these facets in our review provides the best possible process for obtaining the scientific information necessary to ensure safe antimicrobial new animal drugs are on the market. Please see response to Question 7 for a description of actions initiated by CVM as a result of reviews conducted on already approved antibiotic products.

Question 9. FDA currently requires that holders of approved new animal drug applications report quantities of drugs distributed on an annual basis. Do the current reporting requirements for drug distribution data meet the current needs of FDA to adequately track, evaluate and control the development of antimicrobial resistance related to veterinary drug use? If not, what additional data are needed and how, could the reporting requirements be modified to meet the FDA's needs?

Answer 9. FDA receives limited information on the total quantity of animal drug products sold as part of Drug Experience Reports (DERs) that are required to be submitted annually for new animal drug applications. More detailed information relative to the quantity of antimicrobial drugs sold that more closely correlates with actual amounts used in particular animal species would be helpful in conjunction with surveillance data for tracking trends in antimicrobial resistance development. Estimates of antimicrobial drug usage in animals is difficult data to collect because many drugs are approved and labeled for use in multiple species for a variety of purposes. Additionally, many drugs come in multi-dose vials and thus while we might know how much drug was sold it is difficult to associate this amount of drug with the specific number of animals in which it was actually used.

Antimicrobial drug usage data is important for investigating potential causes of emerging trends in antimicrobial resistance associated with use in animals. Such data enables our epidemiologists to make associations between use patterns and emerging trends.

Question 10. Does the FDA currently have the authority to collect the antimicrobial drug use data needed to manage the risk of antimicrobial resistance?

Answer 10. FDA has the statutory authority to promulgate regulations requiring sponsors of approved new animal drugs to submit reports of data relating to experience with those new animal drugs. This includes experience with extra-label uses of the drug, and other data or information the sponsor receives or otherwise obtains with respect to the drug as necessary to determine or facilitate a determination of whether grounds to withdraw the approval of a new animal drug exist. In addition, the Act authorizes FDA to issue an order requiring a sponsor to submit such reports for those same purposes. Current FDA regulations at 21 CFR §514.80 require the sponsor to submit total quantity marketed data annually (semi-annually for the first 2 years post-approval) for each new animal drug application.

QUESTIONS OF SENATOR BURR

Question 1. How does the FDA approve an antibiotic for use in food animals? Many people believe the FDA does not consider the impact on human health, but 1 know that is completely incorrect.

Answer 1. FDA approves antimicrobial new animal drugs only after a thorough scientific review permits the Agency to conclude that the drug is safe and effective. For antimicrobial drugs intended for use in food-producing animals, this includes a determination that food derived from treated animals is safe for humans.

Antimicrobial drugs are evaluated for their effectiveness in the animal for their intended uses. These studies provide substantial evidence of the drug's effectiveness. Effectiveness studies are generally conducted at different locations to account for variability among animals and geography throughout the United States. Further, experimental studies are conducted to determine the safety of the animal drug to the animal. The animal drug is evaluated through an environmental assessment under the provisions of the National Environmental Policy Act.

With respect to human health, the safety of the animal drug is assessed in traditional, nonclinical toxicology studies that address both its acute and chronic health effects, leading to the establishment of acceptable drug residue levels in animal-derived food products. Additionally, microbial food safety (antimicrobial resistance development) and effects of antibiotic residues on human intestinal bacteria are care-

fully evaluated through a process that relies on risk assessment and/or experimental data.

FDA communicates its findings at the time of approval: (1) through publication in the Federal Register as a final rule (with subsequent codification in the CFRs); (2) through a Freedom of Information Summary readily available to the public, describing the information FDA considered in making its decision; and (3) through the labeling, providing important information and direction about the safe and effective use of the drug to the user.

Question 2. Does FDA have a position on the legislation introduced by Mr. Brown and Mr. Hatch? Would this legislation make the current interagency task force more effective or less effective?

Answer 2. The administration has not taken a position on the legislation.

Question 3. The Brown-Hatch legislation calls for FDA to consult with other Federal agencies before acting upon an antibiotic submission. Does FDA currently consult with other Federal agencies or outside bodies when reviewing an antibiotic drug?

Answer 3. FDA often consults with external advisory committees for advice related to the review of applications for antibacterial drugs. We now bring most NDAs for antibacterial new molecular entities before FDA's Anti-Infective Drugs Advisory Committee (Advisory Committee) as well as other applications that present unusual or difficult issues. In addition to asking this Advisory Committee for advice on specific new drug applications, we also bring more general issues to the Advisory Committee for discussion. These general issues have included antimicrobial resistance and clinical development of drugs for specific indications such as community acquired pneumonia.

FDA's advisory committees are generally the means by which FDA gets external advice on drug applications. We generally do not consult with other Federal agencies on individual drug approvals; however, we sometimes include individuals from other Federal agencies on our advisory committee panels.

In addition to public Advisory Committee meetings, we have discussed antibacterial development issues in other public meetings. We have cohosted workshops on topics such as drug development issues that relate to antibacterial resistance and the development of drugs for the treatment of community acquired pneumonia. We also recently convened a public hearing in which we solicited feedback from the public regarding the use of the provisions of the Orphan Drug Act for the development of drugs for serious and life threatening infectious diseases, such as diseases due to gram-negative bacteria and other diseases due to antimicrobial-resistant bacteria.

Thank you again for the opportunity to testify. Please let us know if you have any further questions or concerns.

STEPHEN R. MASON,
Acting Assistant Commissioner for Legislation.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY, SENATOR BROWN, AND SENATOR BURR BY PATRICK J. BRENNAN, M.D.

QUESTION OF SENATOR KENNEDY

Question. In your testimony, you cited several practices that can reduce or eliminate many routes of infection in a hospital environment. Would Federal regulations or a mandate of certain guidelines be beneficial to hospitals in helping them reduce infection rates, or does the unique environment of each hospital prevent standardized guidelines from being effective across the Nation?

Answer. Many guidelines, particularly those from CDC and its Healthcare Infection Control Practices Advisory Committee (HICPAC), are already widely utilized in healthcare settings throughout the United States. Additional guidelines from other professional organizations such as The Society for Healthcare Epidemiology of America (SHEA) are also integrated into current practices. An additional layer of regulatory responsibility for infection control practices is imposed by other Federal agencies such as OSHA and, increasingly, by CMS.

What is uniquely valuable in CDC/HICPAC guidelines is the emphasis on rigorous and ongoing evaluation of both infection control practices and infectious disease outcomes by each institution. This approach facilitates each healthcare facility's ability to direct its response to its local infection problems and allows for selection of appropriate interventions from among the practices recommended in each guideline. To the extent that new Federal legislation would promote the use of guidelines in this way, especially if it were to direct much needed resources to infection prevention

and control programs at the local (both State and institutional) level, such legislation might be useful. However, new legislative mandates that focus only on reporting without providing appropriate resources and flexibility for adaptation to local needs and priorities, could have unintended and deleterious consequences by diverting resources away from critical infection prevention and control efforts based on locally determined needs.

QUESTION OF SENATOR BROWN

Question. The IOM report from 1998 reported that the "most critical issues concern the expansion, coordination, and improvement of the diverse elements of surveillance." The report went on to say that investments in research can make a difference. Your organization has endorsed the STAAR Act. As State epidemiologists, would you explain how you think the provision on Clinical Research & Public Health Network will compliment the current surveillance activities and discuss the importance of isolate collection? In short, will these proposed activities better prepare physicians to be on the look out for emerging resistance issues and help contain them before they spread to other States?

Answer. The majority of SHEA members work in both academic and voluntary private and public hospitals, although we collaborate closely with our colleagues in public health epidemiology at the State and local level. Although the CDC and some State health departments have already established sentinel monitoring systems for antimicrobial resistance, there are geographical and infrastructure gaps that prevent a true nationwide network that is nimble and consistent. We concur with our colleagues in the Infectious Diseases Society of America (IDSA) that additional resources need to be directed to surveillance of antimicrobial resistance. The Clinical Research & Public Health Network provision in the STAAR Act would anchor its 10 network sites in existing centers but focus on overcoming the geographical, technological and infrastructure gaps that currently exist. As the details of the Network are clarified it is important to emphasize that such a network not be duplicative or replace existing activities managed by the CDC.

We note that this surveillance effort needs to be at both a national and a global level. Numerous antibiotic-resistant pathogens have first appeared outside the United States and subsequently been introduced into the U.S. healthcare system. CDC's Morbidity and Mortality Reports (MMWR) have been the primary information source for physicians about the importation of such pathogens. Other outbreaks appear to start locally and may be spread from one healthcare facility to another by shared patients and/or healthcare workers. Hence, surveillance and expedited sharing of information needs to be supported at the international, national, State, and local level. To encourage frank reporting and sharing of data which may be perceived as adversely affecting a facility's reputation or engendering liability, local, State and Federal laws should protect the confidential sharing of such information through public health agencies at all levels of government.

QUESTIONS OF SENATOR BURR

Question 1. In your testimony, you emphasized the importance of accurate measurement of hospital acquired infections and the impact of preventive strategies. I agree that data collection and transparency can spur progress. How well are we doing at that? Is there a need for more guidance?

Answer 1. Accurate measurement of healthcare associated infections is the most important tool available for identifying what problems exist (and therefore where to focus improvement work) and for measuring improvement over time. This type of measurement is most useful to individual institutions working on reducing healthcare associated infections, but shared information can be useful on a statewide or regional or even national level to understand trends over time, which can inform resource allocation decisionmaking and our understanding of how preventive strategies are most effectively deployed. Many hospitals have used this type of measurement to identify problems with central line associated bloodstream infections, ventilator-associated pneumonias, and other healthcare associated infections, and to measure the success of their interventions. Ultimately, development of measurement strategies that extend beyond acute care facilities to allow measurement of healthcare-associated infections associated with other types of healthcare will enhance our ability to address local needs.

Use of data collected through surveillance programs being used to develop internal infection prevention strategies for public reporting has become more common in recent years. The impact of using the data in this way is less direct, but may have helped in standardizing some data collections methods, and to identify regional problems. Although the experience is still early, a number of model programs devel-

oped by States have improved both transparency and accuracy of data regarding healthcare associated infections. Importantly, in contrast to several years ago, most infection control programs have come to welcome the advent of public reporting when instituted with appropriate selection of indicators, training, and scale-up. Programs that were ill-conceived or over-reaching in their requirements have been abandoned and replaced by programs that are more carefully structured in their requirements. Model programs already established in several States provide useful examples for other States and the Federal Government in developing new programs. There is national momentum towards transparency in this area that we expect to continue. More than 40 States have considered legislation regarding public reporting and 17 have adopted NHSN as a mandatory reporting tool. We expect more States to move in this direction without further Federal guidance. Our society in collaboration with other stakeholders have provided templates for model programs of public reporting as well as a toolkit for implementation of such programs (accessible at the following links): http://www.shea-online.org/Assets/files/Essentials_of_Public_Reporting_Tool_Kit.pdf; http://www.shea-online.org/Assets/files/Model_Legislation_-APIC_IDSA_SHEA.pdf.

Question 2. How do hospitals and other health care providers currently decide which organisms to monitor for antimicrobial resistance and how do they participate in the surveillance of organisms of concern?

Answer 2. As noted previously, current CDC/HICPAC guidelines provide a template for assessment of current antimicrobial resistance problems by each institution. Working collaboratively with local microbiology and pharmacy professionals, infection control programs monitor trends in both resistance and antibiotic utilization in their healthcare facility. Using information gained from initial and ongoing assessment, programs develop local priorities, design programs, and allocate resources so that they most effectively target resistant organisms that represent the greatest local threats. Control of antimicrobial resistance in any institution rests on this pillar of ongoing surveillance and is achieved by a combination of infection prevention strategies such as hand hygiene, patient isolation and the careful management of medical devices, and, increasingly, through programs that enhance antimicrobial stewardship.

SHEA and IDSA jointly published a paper (attached) addressing antimicrobial stewardship in 2008 which offers further insight to our society's perspectives on this issue.

Question 3. When we talk about antimicrobial resistance, are we capturing antiviral resistance? If not, do you see this as a separate policy issue that should be dealt with differently?

Answer 3. Although most hospital-based laboratories and clinical reference laboratories perform antibiotic resistance testing, viral resistance testing is a more specialized procedure usually confined to academic or research laboratories. For many viruses, there are no specific antiviral therapies, so antiviral resistance is, in general, a much less common problem than antibacterial resistance. From the public health viewpoint, the viral pathogens of major interest in terms of resistance are the influenza viruses and HIV. CDC collaborates with the World Health Organization (WHO) to monitor influenza virus resistance on an ongoing basis and disseminate this information to physicians and public health officials. In addition, CDC and a number of research laboratories monitor trends in HIV resistance on a global and national level. Importantly, HIV resistance testing through genotyping and phenotyping is widely available through commercial laboratories in the United States and is an accepted standard of practice when initiating or changing therapies for patients with HIV disease.

Question 4. In our world of limited resources, tell us where you think we could get the biggest "bang for our buck" in addressing antimicrobial resistance. Should we be focusing more on developing new antimicrobial drugs and vaccines? Or on educating health care providers and institutions on how best to use the ones we have?

Answer 4. It is critically important that we pursue both drug development and education and dissemination of evidence-based practices to address antimicrobial resistance. Innovative ways to ensure that currently available antimicrobial agents are used carefully and appropriately (i.e., stewardship) are needed to maximize their effectiveness for as long as possible. In addition, we must face the reality that microbes will continue to develop resistance to the drugs to which they are exposed. The rapid rate of microbial evolution ensures that, as antimicrobial agents are used, resistance will emerge. Pathways for the development of antimicrobial resistance have even been found in primitive societies where antibiotics have never been used.

At the same time, there is evidence that inappropriate use of antimicrobial agents (due to inappropriate patient demand, efforts to promote animal growth, or simply courses of antibiotics that are too long, too broad, or not effective) can increase the speed at which such resistance emerges. It's important to recognize that even appropriate use of antimicrobial agents increases the development of resistance, by allowing the growth of resistant organisms.

To some extent, we are reaping the fruits of our own success in treating previously fatal infectious diseases. But ironically, it is often the same patients—often with chronic diseases, or suppressed immune systems, who survive infection with antimicrobial susceptible organisms, which are ultimately most vulnerable to antimicrobial resistant pathogens. While clinician and patient education on the challenges of antimicrobial resistance and guidance on the most appropriate use of currently available agents are clearly important, there is an urgent need for new antimicrobial agents to address the certain continued evolution of antimicrobial resistance.

THE SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA (SHEA),
ROSLYN, VA 22209.

DEAR CHAIRMAN WAXMAN: The Society for Healthcare Epidemiology of America (SHEA) is pleased to respond to your request for information on estimates of the number of reasonably preventable deaths and cases of health care-associated infections (HAIs) in U.S. hospitals, particularly ventilator-associated pneumonia (VAP) and bloodstream infections (BSI). The enclosed report was developed for the Committee on Oversight and Government Reform by SHEA through the support of The Center for Evidence-based Practice at the University of Pennsylvania Health System.

Two-thirds of the deaths from HAIs are estimated to be due to bloodstream infections (BSI) and ventilator-associated pneumonia (VAP). In 2002, there were 1.75 million estimated HAIs and 99,000 deaths estimated to be attributable to them. It is important to note that a limitation of the data is that current estimates may be lower. From 1975 to 2002 there was a decreasing trend in HAI incidence.

In order to arrive at our estimates we used the range of HAI reductions in U.S. studies of quality interventions to prevent these occurrences multiplied by the 2002 estimate of HAIs and resulting deaths. The estimates are as follows:

- Bloodstream infections: 18 percent–82 percent of infections preventable, 5,520–25,145 preventable deaths per year;
- Ventilator-associated pneumonia: 46 percent–55 percent of infections preventable, 16,545–19,782 preventable deaths per year;
- Urinary tract infections: 17 percent–69 percent of infections preventable, 2,225–9,031 preventable deaths per year; and
- Surgical site infections: 28 percent–54 percent of infections preventable, 2,297–4,431 preventable deaths per year.

There is considerable uncertainty in these figures because of the numerous assumptions used in their development. Policy decisions should take into account the sources of uncertainty which are more fully addressed in the attached report. Thank you for the opportunity to respond to the Committee on Oversight and Government Reform.

Sincerely yours,

PATRICK J. BRENNAN, M.D.,
President.

GUIDELINES—INFECTIOUS DISEASES SOCIETY OF AMERICA AND THE SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA.—GUIDELINES FOR DEVELOPING AN INSTITUTIONAL PROGRAM TO ENHANCE ANTIMICROBIAL STEWARDSHIP, *see www.premierinc.com/safety/topics/guidelines/downloads/CID-Guideline-Antibiotic-Stewardship__b.pdf.*

PENN CENTER FOR EVIDENCE-BASED PRACTICE ADVISORY

MORTALITY FROM REASONABLY-PREVENTABLE HOSPITAL-ACQUIRED INFECTIONS

(Craig A. Umscheid, MD, MSCE; Matthew D. Mitchell, PhD; Rajender Agarwal, MD, MPH; Kendal Williams, MD, MPH, and Patrick J. Brennan, MD, for the **Society for Healthcare Epidemiology of America**)*

SUMMARY

- Survey data from the National Nosocomial Infections Surveillance (NNIS) system, National Hospital Discharge Summary, and American Hospital Association report the incidence of hospital-acquired infections (HAIs) and the mortality resulting from them.
  - In 2002, there were 1.74 million HAIs and 99,000 attributable deaths.
  - Two-thirds of those deaths are the result of bloodstream infections and ventilator-associated pneumonia.
  - There was a decreasing trend in HAI incidence from 1975 to 2002.
- An Agency for Healthcare Research and Quality (AHRQ) report published in 2007 surveyed the evidence on various interventions to reduce HAIs.
  - The AHRQ reviewers found that the quality of evidence was low, and that there was little consistency in patient populations and interventions examined. Therefore, they did not combine the results of the studies into a single numeric result estimating the ability of interventions to reduce HAIs.
- We used the 2002 estimate of HAIs and resulting deaths from the NNIS survey and the range of HAI reductions observed in the AHRQ report to calculate the number of preventable HAIs and HAI deaths per year:
  - Bloodstream infections: 18 percent–82 percent of infections preventable, 5,520–25,145 preventable deaths per year;
  - Ventilator-associated pneumonia: 46 percent–55 percent of infections preventable, 13,667–25,537 preventable deaths per year;
  - Urinary tract infections: 17 percent–69 percent of infections preventable, 2,225–9,031 preventable deaths per year; and
  - Surgical site infections: 26 percent–54 percent of infections preventable, 2,133–4,431 preventable deaths per year.
- There is considerable uncertainty in these figures because of the numerous assumptions going into them. One should not base policy decisions on these figures without understanding the sources of uncertainty.

BACKGROUND

To inform policy discussions regarding the reduction of infections in hospitals, the Center for Evidence-based Practice at the University of Pennsylvania Health System was asked to estimate the number of annual deaths in U.S. hospitals from reasonably-preventable cases of hospital-associated infections (HAIs), particularly bloodstream infections (BSI) and ventilator-associated pneumonia (VAP).

METHODS

An accurate estimation of this figure requires accurate estimates of two underlying figures: the current total of annual deaths from HAIs and the proportion of these deaths that are "reasonably preventable." Uncertainty in either of these components will necessarily lead to uncertainty in the final estimate.

A best-evidence approach was used to obtain the source data for this calculation. To estimate the number of HAIs and resulting mortality, we used estimates from the National Nosocomial Infections Surveillance (NNIS) system, National Hospital Discharge Summary, and American Hospital Association as reported by Klevens and colleagues.[1] To estimate the proportion of HAIs that could be prevented, we used the estimates of HAI risk reductions resulting from quality improvement strategies

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as reported in an Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) report.[2] Given the limited quality of the studies reviewed by the AHRQ report, we only used HAI risk reductions reported from U.S. studies that were graded as good quality by AHRQ, and that examined risk reductions in BSI, VAP, urinary tract infections (UTI) and surgical site infections (SSI). When there were fewer than three studies that met these criteria, we also included studies graded as moderate quality.

Because the patient populations and interventions tested in the published studies of HAI prevention varied from study to study, it was not appropriate to combine the risk reductions into a single summary estimate. Thus, to calculate a range of possible risk reductions for each HAI, we simply used the highest and lowest infection reductions for each HAI as listed in the AHRQ report. We then multiplied this range of risk reduction for each HAI by the frequency of that HAI as reported by the NNIS survey to calculate a range for the number of preventable infections for each HAI. To estimate a range for the number of preventable deaths for each HAI, we multiplied the risk reduction for each HAI by the reported frequency of deaths for that HAI.

NUMBER OF ANNUAL DEATHS

A comprehensive estimate of annual incidence of and mortality from hospital-acquired infections was reported by Klevens and colleagues of the Centers for Disease Control and Prevention (CDC) in 2007.[1] (Table 1) This estimate was based on broad surveys of U.S. hospitals so the risk of uncertainty from measuring an unrepresentative sample is low. However, the survey data is from 2002, so changes in infection rates and mortality resulting from improved care practices implemented between 2002 and today are not captured in these figures. If care has improved since that time, the current number of infections and deaths will be lower than observed in 2002. That would continue the trend observed since 1975–76, when the total number of hospital-associated infections estimated by the CDC's SENIC project was 2.15 million.[3] Infection-related deaths were not estimated in that project.

The survey data show that BSI and VAP cause more than two-thirds of the deaths resulting from HAIs, and that they are five times more deadly than the other infections. Thus it may make sense to target these two types of infections first for reduction measures.

Table 1.—Hospital-Acquired Infections in 2002

Type of infection	No. of infections (2002)	Deaths from infections (2002)	Percent of fatal infections
BSI	248,678	30,665	12.3
VAP	250,205	35,967	14.4
UTI	561,667	13,088	2.3
SSI	290,485	8,205	2.8
Other	386,090	11,062	2.9
Total	1,737,125	98,987	5.7

Data from Klevens (1).

PROPORTION OF DEATHS THAT ARE PREVENTABLE

We based our estimates of the preventability of infection-related deaths on the evidence tables of the AHRQ EPC report.[2] An earlier review by Harbarth and colleagues,[4] done in much less detail, has similar findings.

Description of Studies Included in the AHRQ Report

The quality of the evidence base reviewed in the AHRQ report was poor. For example, half of the BSI studies met none or one of the reviewers' three internal validity standards. The AHRQ report divided the before-after studies into "good," "moderate," and "poor" quality categories (Table 2) but did not explain how the categories were defined. They did not grade the quality of controlled and interrupted time series trials.

The AHRQ investigators reported that there was little consistency among patient groups studied or among interventions tested. Therefore they could not perform any quantitative synthesis of the data, and *they did not attempt to make a summary estimate of the proportion of infections or deaths that could be considered preventable.*

The highest quality studies in the AHRQ report examined interventions to reduce BSI, VAP, UTI and SSI. For prevention of other HAIs, the evidence bases were even weaker and any numeric conclusions are even more speculative.

Table 2.—Description of Infection Prevention Studies Examined in AHRQ Report

Infection type	N	Controlled trials	Time series	Simple before-after studies		
				Good	Moderate	Poor
BSI	19	2	1	6	2	8
VAP	12	0	0	3	4	5
UTI	10	3	0	0	6	1
SSI	28	4	2	1	6	15

Not all studies in this table were used to calculate results, since they did not all report infection results.
Data from AHRQ EPC report (2).

Estimates of Preventable Deaths

Our estimates for the ranges of potential reductions in HAIs are found in the fifth column of Table 3 and the resulting estimates of preventable infections and deaths are found in the seventh and last columns of Table 3 respectively.

There is nothing novel about trying to estimate the number of infections that could be prevented or lives that could be saved if hospitals followed best practices in infection control. The SENIC project made such an estimate in 1975. They considered 30 to 35 percent of most HAIs preventable with effective surveillance and control programs, and 22 percent of pneumonia cases preventable. In a 1985 follow-up survey, they found that only a fraction of those infections were actually being prevented, because many hospitals still had not implemented recommended infection control measures.[5] This was still the case in the present decade.[6] Our estimated ranges of potential reductions in HAIs is in line with the estimates in Kaye's review.[7]

Table 3.—Estimates of Preventable Infections and Deaths

Infection type	No. of HAIs[1]	No. Deaths[1]	Case fatality rate [in percent]	Reduction in infection risk with QI programs[2] [in percent]	Projected no. of infections with institution of QI programs	Estimated no. of preventable infections	Projected no. of deaths with institution of QI programs	Estimated no. of preventable deaths
BSI	248,678	30,665	12.3	18–82	44,762–203,916	44,762–203,916	5,520–25,145	5,520–25,145
VAP	250,205	35,967	14.4	38–71	72,559–155,127	95,078–177,646	10,430–22,300	13,667–25,537
UTI	561,667	13,088	2.3	17–69	174,117–466,184	95,483–387,550	4,057–10,863	2,225–9,031
SSI	290,485	8,205	2.8	26–54	133,623–204,959	75,526–156,862	3,774–6,072	2,133–4,431

HAI—hospital-acquired infection.
QI—quality improvement.
[1] NNIS 2002 estimates.
[2] Range from U.S.-based QI studies of good or moderate quality in AHRQ report.

LIMITATIONS

There is considerable uncertainty in our estimate of preventable HAI-related deaths. Uncertainty stems from both the component numbers and the calculation itself. Here we discuss some of those sources of uncertainty.

Number of Deaths Caused by HAIs

While our estimate of the number of annual deaths caused by HAIs is based on a broad national survey, that survey data is more than 5 years old. It does not reflect improvements in infection control practice that hospitals have implemented since the time of the survey. The true number of annual HAI deaths at present may be lower. The estimate of HAI-related deaths is also uncertain because there is no definite way to attribute a death to HAI. Patient deaths frequently have multiple causes, and there exists a blurred line between a patient whose death was caused by an HAI and a patient with an HAI whose death was due to another cause.

Proportion of HAIs That Are Preventable

The key uncertainty in the estimate of preventable HAIs is the limited quality of the HAI reduction studies. In particular, none of the studies are randomized, and few of the studies are controlled, so the validity of the risk reductions reported are limited, and may be exaggerated. For example, most of the studies are of a simple before-after study design, comparing outcomes after the HAI intervention was implemented in a patient population with results from the same population during a time period prior to the HAI intervention. This study design cannot control for other changes in patient care that took place between the control period and the experimental period, making it difficult to attribute the results reported in the study to the study intervention rather than to random variation, patient selection, or other uncontrolled variables, like changes in staffing structures or the implementation of other quality/safety initiatives.

In addition, some of the published studies date back a decade or more, so the infection control practices used in them may have already been implemented at some hospitals, making large HAI reductions less likely in today's hospitals. Another source of uncertainty is generalizing from the results of specialized study populations like the ICU population to more general populations like a general hospital ward.

Number of HAI-caused Deaths That Are Preventable

The key uncertainty here is the fact that we are not estimating preventable deaths from studies that have directly measured death as an outcome. Instead, we are extrapolating reductions in death from the above estimates of reductions in HAIs, and these above estimates have their own limitations. In addition, in multiplying the estimated fraction of HAIs that are preventable by the fatality rate for a given HAI, we assume that the fatality rate for preventable infections is the same as the rate for those infections that weren't prevented. The true effect on deaths could be larger or smaller, depending on the extent to which preventive measures affect the severity of HAIs and the extent to which preventive measures work for the kinds of patients who are more susceptible to fatal HAIs.

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EVIDENCE TABLES

Table 4.—BSI Prevention Studies Reviewed by AHRQ Suggest an 18 to 82 Percent Reduction in BSIs Depending on the Intervention and Population Examined

Author, Year	Study Design	Setting	Intervention	Comparison	Risk before intervention	Risk after intervention	Risk Reduction [in percent]
Provonost, 2006	Interrupted time series.	ICU patients (United States).	***Preventive:*** Hand hygiene; maximum sterile barrier; insertion site selection; chlorhexidine disinfection; removal of unnecessary catheters; ***QI:*** Clinician education, audit and feedback, clinician reminder, organizational change.	Previous care	7.7 per 1,000 catheter days.	1.4 per 1,000 catheter days.	82
Higuera, 2005	Before-after study	ICU patients (Mexico).	***Preventive:*** Hand Hygiene; ***QI:*** Clinician education, audit and feedback, organizational change.	Previous care	46.3 per 1,000 catheter days.	19.5 per 1,000 catheter days.	58
Berenholtz, 2004	Controlled before-after study.	ICU patients (United States).	***Intervention: /Preventive:*** Hand hygiene, maximum sterile barrier, insertion site selection, chlorhexidine disinfection, removal of unnecessary catheters; ***QI:*** Clinician education, audit and feedback; ***Control:*** Clinician education only.	Previous care	Intervention 11.3 per 1,000 catheter days. Control 5.7 per 1,000 catheter days.	Intervention 0 per 1,000 catheter days. Control 1.6 per 1,000 catheter days.	100 82
Coopersmith, 2004	Before-after study	ICU patients (United States).	***Preventive:*** Hand Hygiene, maximum sterile barrier, insertion site selection; ***QI:*** Clinician education.	Previous care	3.4 per 1,000 catheter days.	2.8 per 1,000 catheter days.	18
Warren, 2004	Before-after study	ICU patients (United States).	***Preventive:*** Hand hygiene, maximum sterile barrier, insertion site selection; ***QI:*** Clinician education, audit and feedback.	Previous care	9.4 per 1,000 catheter days.	5.5 per 1,000 catheter days.	42

Evidence Tables

Table 4.—BSI Prevention Studies Reviewed by AHRQ Suggest an 18 to 82 Percent Reduction in BSIs Depending on the Intervention and Population Examined

Author, Year	Study Design	Setting	Intervention	Comparison	Risk before intervention	Risk after intervention	Risk Reduction [in percent]
Warren, 2003	Before-after study	ICU patients (United States).	***Preventive:*** Maximum sterile barrier; insertion site selection; ***QI:*** Clinician education, audit and feedback.	Previous care	4.9 per 1,000 catheter days.	2.1 per 1,000 catheter days.	57
Coopersmith, 2002	Before-after study	ICU patients (United States).	***Preventive:*** Hand hygiene; ***QI:*** Clinician education, audit and feedback.	Previous care	10.8 per 1,000 catheter days.	3.7 per 1,000 catheter days.	66
Eggiman, 2000	Controlled Before-after study.	ICU patients (Switzerland).	***Intervention:/Preventive:*** Hand hygiene, maximum sterile barrier, chlorhexidine disinfection, removal of unnecessary catheters; ***QI:*** Clinician education; ***Control:*** No additional measures.	Previous care	Intervention (MICU) 11.3 per 1,000 catheter days. Control (SICU) 10.3 per 1,000 catheter days.	Intervention 3.8 per 1,000 catheter days. Control 11.6 per 1,000 catheter days.	–13 (increase)
Sherertz, 2000	Before-after study	ICU patients (United States).	***Preventive:*** Hand hygiene, maximum sterile barrier; ***QI:*** Clinician education.	Previous care	4.51 per 1,000 catheter days.	2.92 per 1,000 catheter days.	35

Table 5.—VAP Prevention Studies Reviewed by AHRQ Suggest a 38 to 71 Percent Reduction in VAPs Depending on the Intervention and Population Examined

Author, Year	Study Design	Setting	Intervention	Comparison	Risk before intervention	Risk after intervention	Risk Reduction [in percent]
Good quality:							
Babcock, 2004.	Before-after study	ICU patients (United States).	***Preventive:*** Hand hygiene; HOB >30°, daily interruption of sedation; ***QI:*** Clinician education.	Previous care	8.75 per 1,000 ventilator days	4.74 per 1,000 ventilator days	46
Zack, 2002 ...	Before-after study	ICU patients (United States).	***Preventive:*** HOB >30°; ***QI:*** Clinician education.	Previous care	12.6 per 1,000 ventilator days	12.6 per 1,000 ventilator days	55
Moderate quality:							
Rosenthall, 2006.	Before-after study	ICU patients (Argentina).	***Preventive:*** Hand hygiene; ***QI:*** Clinician education, audit & feedback.	Previous care	51.3 per 1,000 ventilator days	35.5 per 1,000 ventilator days	31
Salahuddin, 2004.	Before-after study	ICU patients (Pakistan).	***Preventive:*** Hand hygiene, HOB>30°; ***QI:*** Clinician education, audit & feedback.	Previous care	13.2 per 1,000 ventilator days	6.5 per 1,000 ventilator days	51
Lai, 2003	Before-after study	ICU patients (United States).	***Preventive:*** HOB>30°; ***QI:*** Clinician education, audit & feedback.	Previous care	SICU: 45.1 per 1,000 ventilator days. MICU: 22.4 per 1,000 ventilator days.	SICU: 27.9 per 1,000 ventilator days. MICU: 11.6 per 1,000 ventilator days.	38 48
Kelleghan, 1993.	Before-after study	Not reported (United States).	***Preventive:*** Hand hygiene, HOB>30°; ***QI:*** Clinician education, audit & feedback.	Previous care	17 per 1,000 ventilator days	5 per 1,000 ventilator days ...	71

Evidence Tables

Table 6.—UTI Prevention Studies Reviewed by AHRQ Suggest a 17 to 69 Percent Reduction in UTIs Depending on the Intervention and Population Examined

Author, Year	Study Design	Setting	Intervention	Comparison	Risk before intervention	Risk after intervention	Risk Reduction [in percent]
Good quality:							
Huang, 2004	Before-after study	ICU patients (Taiwan)	***Preventive:*** Removal of unnecessary urinary catheters; ***QI***: Clinician reminder.	Previous care	11.5 per 1,000 catheter days	8.3 per 1,000 catheter days ..	29
Greco, 1991 ..	Before-after study	ICU patients (Italy)	***Preventive:*** Aseptic insertion and catheter care; ***QI:*** Audit and feedback, clinician education, clinician reminder.	Previous care	12.9 per 100 catheters	11.9 per 100 catheters	8
Moderate quality:							
Topal, 2005 ..	Before-after study	Ward patients (United States).	***Preventive:*** Reduction in placement of catheters, removal of unecessary catheters; ***QI:*** Clinician education, clinician reminder, organizational change.	Previous care	36 per 1,000 catheter days ...	11 per 1,000 catheter days ...	69
Rosenthal, 2004	Before-after study	ICU patients (Argentina).	***Preventive:*** Hand hygiene, aseptic catheter care; ***QI:*** Audit and feedback, clinician education.	Previous care	21.3 per 1,000 catheter days	12.4 per 1,000 catheter days	42
Dumigan, 1998	Before-after study	ICU patients (United States).	***Preventive:*** Aseptic insertion and cathter care, removal of unecessary catheters; ***QI:*** Clinician education, organizational change.	Previous care	SICU: 10.3 per 1,000 catheter days.	8.6 per 1,000 catheter days ..	17
					MICU: 15.8 per 1,000 catheter days.	11.2 per 1,000 catheter days	29
					CICU: 15.1 per catheter days	8.3 per 1,000 catheter days ..	45

Table 7.—SSI Prevention Studies Reviewed by AHRQ suggest a 26 to 54 Percent Reduction in SSIs Depending on the Intervention and Population Examined

Author, Year	Study Design	Setting	Intervention	Comparison	Risk before intervention [in percent]	Risk after intervention [in percent]	Risk Reduction [in percent]
Good quality:							
Van Kasteren, 2005.	Interrupted time series	Not reported (Netherlands).	***Preventive:*** Appropriate use of perioperative antibiotics; ***QI:*** Audit and feedback, clinician education, clinician reminder.	Previous care	5.4	4.6	15
Gastmeier, 2002.	Controlled study	ICU (Germany)	***Preventive:*** Hand hygiene, appropriate use of perioperative antibiotics, decreasing use of preoperative shaving, improving perioperative glucose control; ***QI:*** Audit and feedback, clinician education.	Previous care	2.2	1.6	26
Weinberg, 2001.	Interrupted time series	Not reported (Columbia).	***Preventive:*** Appropriate use of perioperative antibiotics; ***QI:*** Audit and feedback, organizational change.	Previous care	Hospital A: 10.5 Hospital B: 6.1	0 4.4	100 28
Greco, 1991 ..	Before-after study	ICU (Italy)	***Preventive:*** Appropriate use of perioperative antibiotics, decreasing use of preoperative shaving; ***QI:*** Audit and feedback, clinician education, clinician reminder.	Previous care	7.8	6.2	21

Table 7.—SSI Prevention Studies Reviewed by AHRQ suggest a 26 to 54 Percent Reduction in SSIs Depending on the Intervention and Population Examined

Author, Year	Study Design	Setting	Intervention	Comparison	Risk before intervention [in percent]	Risk after intervention [in percent]	Risk Reduction [in percent]
Moderate quality:							
Dellinger, 2005.	Before-after study	Not reported (United States).	***Preventive:*** Appropriate use of perioperative antibiotics, decreasing use of peroperative shaving, improving perioperative glucose control; ***QI:*** Audit and feedback, clinician education, clinician reminder.	Previous care	2.3	1.7	26
Borer, 2004 ..	Before-after study	Operating room (Israel).	***Preventive:*** Hand hygiene, appropriate use of perioperative antibiotics, decreasing use of preoperative shaving, improving perioperative glucose control; ***QI:*** Clinician education.	Previous care	4.2	0	100
Lutarewych, 2004.	Before-after study	Not reported (United States).	***Preventive:*** Improving perioperative glucose control; ***QI:*** Audit and feedback, clinician education, patient education.	Previous care	7.58	3.47	54
Rao, 2004	Before-after study	Not reported (United States).	***Preventive:*** Appropriate use of perioperative antibiotics, decreasing use of preoperative shaving, improving perioperative glucose control; ***QI:*** Clinician education, clinician reminder.	Previous care	2.1	1.5	29
Won, 2004	Before-after study	Not reported (Taiwan)	***Preventive:*** Hand hygiene; ***QI:*** Clinician education, audit and feedback.	Previous care	0.33 per 1,000 patient days ..	0.84 per 1,000 patient days ..	-154 (increase)

Larsen, 1989	Before-after study	Operating room (United States).	***Preventive:*** Appropriate use of perioperative antibiotics; ***QI:*** Audit and feedback, clinician reminder.	Previous care	1.1	0.7	36

RESPONSE TO QUESTIONS OF SENATOR KENNEDY AND SENATOR BURR BY JAY P. GRAHAM, PH.D., MBA

QUESTIONS OF SENATOR KENNEDY

Question 1. Dr. Graham, you mentioned the public health risks associated with antimicrobial resistance in many classes of antimicrobials. Would a review of previously approved labeled subtherapeutic doses of antimicrobials under a risk assessment framework such as FDA Guidance #152 effectively determine which antimicrobial uses pose a risk to human health?

Answer 1. FDA Guidance #152 does not sufficiently address the potential spread of resistance genes and resistance determinants. Guidance #152 focuses solely on foodborne pathogens and disregards resistance in other human pathogens. For example, resistance genes that encode resistance to macrolides, lincosamides and streptogramins (e.g., erythromycin, clindamycin and quinupristin-dalfopristin, respectively) are relatively mobile, since they are commonly found on conjugative transposons. These transposons can transfer resistance to different genera of bacteria, many of which are human commensals. Guidance #152 should consider the medical implications of increasing the reservoir of specific resistance genes that are augmented by the use of subtherapeutic doses of antimicrobials.

Question 2. Is Guidance #152 stringent enough to adequately assess the full risk to human health posed by non-therapeutic uses of antibiotics on farms, including risks in addition to food safety such as environmental contamination?

Answer 2. No. Historically, research has focused on occupational and food-borne exposure pathways. Environmental pathways of exposure, however, are increasingly documented as surveillance of infectious diseases improves. The spread of resistance could occur in a number of ways: (1) crops fertilized with manure or irrigated with water contaminated by land-disposed manure; (2) aerosolized particles of waste emitted from confinement or waste storage facilities, or emanating from fields fertilized with manure or trucks transporting live animals for processing; (3) runoff of waste into groundwater and surface water; and (4) contamination and carriage by other organisms (e.g., flies). All of these pathways have been documented in the peer-reviewed literature. For example, antimicrobial-resistant enteric bacteria have been found in surface water and groundwater supplies near confined animal feeding operations. And, groundwater makes up 40 percent of the water used for public water supplies and provides drinking water for more than 97 percent of rural U.S. populations.

Question 3. You mentioned that your studies have shown that animal producers would not experience a significant increase in costs if they ceased using subtherapeutic doses of antimicrobials. Are alternative treatments, such as probiotics, diet acidification, enzymes, or immune system modulators including antibodies and spray-dried plasma cost effective when compared with subtherapeutic antimicrobials?

Answer 3. The research that I referenced in the hearing was based on data published by the Perdue Company, in which a non-randomized controlled trial of growth promoting antibiotic use was conducted with 7 million broiler chickens to evaluate the impact of removing growth promoting antibiotics (GPAs). The company did not look at alternative treatments in this study; it just looked at the results of removing growth promoting antibiotics from feed. The results of the economic analysis showed that positive production changes were associated with GPA use, but were insufficient to offset the cost of the antibiotics. Interestingly, the Perdue study showed that mortality rates dropped following a full clean-out of the poultry houses. There are likely alternative treatments that could replace subtherapeutic antimicrobials, however, it appears that improved hygiene and management could suffice (Graham et al. 2007; Miller et al., 2003).

Question 4. Is there a connection between MRSA outbreaks and the use of subtherapeutic doses of antimicrobials in animal feeds?

Answer 4. Research in Denmark showed that MRSA on pig farms was associated with use of tetracycline in the feed. However, more research in the United States is needed to better understand what is driving MRSA at U.S. swine operations.

Question 5. On July 3, FDA issued a prohibition order on extra-label use of cephalosporin drugs. The order states that "the surveillance data . . . supports the finding that certain cephalosporin use in animals is likely contributing to an increase in cephalosporin-resistant human pathogens." In my understanding, the extra-label uses of cephalosporin are not very different from that of labeled uses—

which include different species or dosing times from on-label uses. Do you think there should be a concern about on-label uses of cephalosporins as well?

Answer 5. Yes, I do think there should be concern about the on-label uses of cephalosporins. Of particular concern are the increasingly isolated plasmidencoded resistance genes associated with cephalosporin resistance (Li et al., 2007). There are 12 other antimicrobials that are still effective for bovine respiratory disease, so it doesn't seem appropriate to approve cefquinome for on-label uses, when this is so important in human medicine. Bacteria from agricultural settings can make their way to clinical settings and the complexity of the spread of resistance should be more fully integrated into the FDA risk assessment of Guidance #152.

QUESTIONS OF SENATOR BURR

Question 1. How did the Pew Commission come up with the definition for non-therapeutic? Mr. Vogel said the AVMA considers "therapeutic use" to be disease control, prevention and treatment. The AVMA definition is consistent with the FDA, 0IE, Codex and other international authorities. Can you please explain your definition and why it is different?

Answer 1. The Pew Commission used information from the World Health Organization (WHO) and consulted with officials at the Centers for Disease Control and Prevention (CDC) to establish the definition for non-therapeutic. The Commissioners wanted to craft a more narrow definition to help reduce the potential spread and impact of antimicrobial resistance in human medicine. The current definitions have not reduced drug-resistant infections, and it is, in fact, a growing problem. Pew also based its definition on peer-reviewed studies and a commissioned technical report on farm animal production and antimicrobial resistance (available at: http:/Awmf.ncifap.org/reports/). The Commission was also able to draw upon the expertise of three of its members: Drs. Mary Wilson, James Merchant, and Michael Blackwell. Dr. Wilson is a faculty member at the Harvard School of Public Health and has more than 30 years experience in infectious diseases. Dr. Merchant is a medical doctor and a Doctor of Public Health. He recently retired as Dean of the College of Public Health at the University of Iowa. Dr. Blackwell is a veterinarian and recently retired as Dean of the College of Veterinary Medicine at the University of Tennessee/Knoxville. He has a Masters of Public Health and served as Assistant Surgeon General of the United States. Pew decided on a definition for therapeutic that is more in line with human usage and more protective of the public's health.

Currently, there is unrestricted access for purchasing antimicrobials for use in animal agriculture, which can be bought in feed stores, online or directly from distributors; no prescription or veterinarian oversight is needed. Some antimicrobials, such as penicillins and tetracyclines, are used routinely, without any sign of disease. It is important to know how antimicrobials are used (i.e. how much goes for routine use in the absence of disease?) so that we can determine the level to which this use is leading to an increase in drug-resistant infections in humans.

Question 2. Your written testimony states that "in North Carolina alone, the use of antimicrobials as a feed supplement has been estimated to exceed all U.S. antimicrobial use in human medicine." Who has estimated that? And were you aware that, according to the N.C. Dept. of Agriculture, in 2007 8.9 billion chickens and 10.1 million pigs were born in N.C.? In comparison, the U.S. population is 304 million people.

Answer 2. The State and county estimates of antibiotics in agricultural feed and animal waste were derived using data from the U.S. Department of Agriculture's 2002 Census of Agriculture, along with per-animal estimates of antibiotic feed-additive use developed by the Union of Concerned Scientists (UCS) for broiler chickens, hogs and beef cattle. The UCS estimates were used because they are the most detailed and transparent figures on antibiotic use now available. The report referenced can be found at:http://www.edf.org/documents/4301__AgEstimates.pdf.

I understand that it is difficult to believe that more antimicrobials go to food animals in North Carolina than are used in all of human medicine in the United States. However, food animals are fed a constant, low-dose of antimicrobials, and humans are not. For example, 1 billion chickens consume roughly 5 million tons of feed (a five-pound chicken consumes roughly 10 pounds of feed). Each ton of feed has 0.22–0.44 pounds (100–200 grams) of antimicrobials. Thus 5 million tons of feed multiplied by the 0.22–0.44 lbs of antimicrobials is equal to 1.1–2.2 million pounds of antimicrobials. This calculation is just for 1 billion poultry, so it easy to see how the low doses of antimicrobials on a per-animal basis can at first appear deceptively small.

Question 3. I have an article written by an N.C. State University researcher stating "there is a fallacy that more than 70 percent of the life-saving antibiotics and related drugs produced are used in food animal production . . . The reality is that, annually, humans and our pets consume 10 times more antibiotics per pound of body mass than food animals do." Who is right? You or him?

Answer 3. An important point is being overlooked here: The issue is not the amount of use "per pound of body mass" but total drug use. Of the total amount of antimicrobials used, including humans, pets, and food animals, the best estimates we have available report that the majority of antimicrobials are used at subtherapeutic concentrations to raise food animals. These constant low doses of antimicrobials are a major driver in the development of drug-resistant bacteria, and a number of studies have shown this. These bacteria then end up in our food supply and in our environment.

Question 4. Are you not concerned with the 143 percent increase in the quantity of antimicrobials used for therapeutic purposes in Denmark post-ban? Isn't this a case of chopping off your nose to spite your face?

Answer 4. This is a skewed way of looking at the results of the ban. Total consumption of antimicrobial drugs by food animals in Denmark declined after the ban, by 36 percent between 1996 and 2003. After the ban in Norway, antimicrobial use in food animals dropped 45 percent between1995 and 2003. In Sweden, total antimicrobial use in food animals in 2003 amounted to only one-third of the amounts used in 1984—a 35-ton decrease. Termination of antimicrobials for growth promotion was only a temporary risk factor for increased use of therapeutic antimicrobials in food animals in Sweden and Denmark; however, an exception might be use in weaning piglets in Denmark.

In Denmark, there is a program (VetStat) that monitors all veterinary use of medicines for animals. It is based on reporting from the pharmacies and from veterinary practitioners and contains detailed information, such as animal species, reason for prescription, and dosage on each prescription. In Denmark, antimicrobial drugs can be obtained only by prescription and only at pharmacies. We need something similar in the United States to protect the public's health.

Question 5. Please cite the science that illustrates the risk to public health that antibiotic use in food animals creates.

Answer 5. World Health Organization Strategy for Containment of Antimicrobial Resistance. 2001. (Available at:http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf).

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Question 6. What proof do you have that public health in the EU has benefited from the ban of antibiotic growth promoters in animals?

Answer 6. One of the most important issues regarding antimicrobial resistance is that the principle of proof requires that resistance has already emerged, by which time the "genie is out of the bottle." Another important fact is that all use of antimicrobials leads to the development of resistance in bacteria. The number of drug-resistant bacteria and resistance genes in our food supply and in the environment is an important part of the risk of exposure for humans. Adopting precautionary measures, as the EU has done, reduced the opportunities to find out how risky this practice is. The benefit of the ban in Europe is that policymakers there reduced the human health risk by reducing the prevalence of resistant bacteria in Europe's food supply. Even when transmission to humans is infrequent, amplifying resistant bacteria still makes transmission via food and other pathways more likely (Turnidge, 2004).

Question 7. While antibiotic resistance is a public health threat, does your report include an estimate of how much of the total human burden is caused by antibiotic use in humans and how much by use in animals?

Answer 7. The antimicrobial resistant bacteria that we select in food animal production are often indistinguishable from those that we select from other uses (e.g., hospital use). Therefore, once resistant bacteria are disseminated into the human population from their point of origin, it is nearly impossible to attribute them to a particular source. In contrast to hospital-selected resistant bacteria, many of those

selected in the food animal setting are distributed into the community on food animal products such as meat and poultry. Peer-reviewed studies of meat and poultry products have shown that they are regularly contaminated with antibiotic resistant bacteria. Most of our U.S. population is exposed to meat and poultry products, whereas only those entering hospitals have direct exposure to the antibiotic resistant bacteria that are selected in that setting. Thus, while it is currently impossible to determine what percentage of antimicrobial resistant infections in humans can be traced to food animals, the science points to a substantial proportion of these human diseases being attributable to antimicrobial use in food animal production. Thus, as Smith et al. (2005) conclude, a large number of people exposed to a low risk may generate more cases than a small number of people exposed to a high risk. Evidence for the increasing prevalence of community sources of multidrug resistance is found in a study of incoming patients at a tertiary care hospital in Boston: From 1998/9 to 2002/3, the likelihood of multidrug resistance in *E. coli* increased from 2 percent to almost 20 percent (Pop-Vicas, 2005).

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AMERICAN VETERINARY MEDICAL ASSOCIATION,
July 31, 2008.

DEAR MEMBERS OF THE SENATE HEALTH, EDUCATION, LABOR, AND PENSIONS COMMITTEE: Thank you for the opportunity to respond to your questions concerning the use of antimicrobials in food animals.

However, I cannot respond to the questions regarding "non-therapeutic" use in that same terminology. The term "non-therapeutic" has no meaning in Federal regulation or common usage. The Food and Drug Administration approves antimicrobials for four purposes: disease treatment, disease prevention, disease control, and growth promotion/feed efficiency. The FDA does not approve antimicrobials for "non-therapeutic" uses. Also, the various organizations and people who use the term "non-therapeutic" use it inconsistently to mean different things. For example, the Pew Commission on Industrial Farm Animal Production (PCIFAP) provides an unclear definition of "non-therapeutic" that is different from that found in S. 549, the Preservation of Antibiotics for Medical Treatment Act of 2007 (PAMTA). Additionally, the definitions include terms that themselves are undefined such as "routine preventive uses and other routine uses." As a result, the language is not commonly understood. The use of exclusionary terms, such as "non-therapeutic," that are ill-defined and not commonly understood, is confusing. We caution against the use of the term "non-therapeutic" for the sake of clear communication and understanding.

Instead we urge that FDA terminology, which appears on labeled uses of antimicrobials, be used. Specifically, these terms are: "treatment," "prevention," "control," or "growth promotion/feed efficiency." Alternatively, use the classifications of the Codex Alimentarius Commission (an organization of the World Health Organization and the Food and Agricultural Organization of the United Nations) and the American Veterinary Medical Association. Both organizations classify treatment, prevention, and control of disease as therapeutic uses.

In the responses below, I do not use "non-therapeutic" terminology for clarity.

LYLE VOGEL, D.V.M., M.P.H., DACVPM,
Assistant Executive Vice President.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY, SENATOR BROWN, AND SENATOR BURR BY LYLE VOGEL, D.V.M., M.P.H., DACVPM

QUESTIONS OF SENATOR KENNEDY

Question 1. Dr. Vogel, you mentioned in your testimony that the AVMA has "a great interest in the prevention, control, and treatment of disease." How would a reduction in the use of antimicrobials for non-treatment or non-therapeutic purposes, such as "feed efficiency," prevent veterinarians from using their discretion to prescribe antimicrobials for sick animals or a sick herd when an infection is diagnosed.

Answer 1. We will presume that this question pertains to antimicrobials that are labeled for feed efficiency or growth promotion. While often used under the supervision or guidance of a veterinarian, the use of antimicrobials for feed efficiency or growth promotion does not require a veterinary prescription. As a result, legislative restrictions on such uses have no direct effect on the ability for veterinarians to prescribe antimicrobials for therapeutic uses, such as treatment of "sick" animals, control of disease within a "sick" herd, and prevention of disease when animals are at high risk of becoming ill.

However, if our presumption is incorrect and the question also pertains to antimicrobials that are labeled for prevention of disease (as does PAMTA), then the veterinarian's ability to prevent disease in herds or flocks will be seriously compromised. If veterinarians are required to wait until animals are sick and dying from disease, then this will significantly and adversely affect health plans established by veterinarians. If veterinarians cannot use antimicrobials until animals are sick and dying from disease, animal welfare will be greatly harmed.

The Danish experience has shown us that the use of antimicrobials for growth promotion had the added benefit of preventing or controlling disease.

Question 2. How have European countries dealt with the ramifications of the EU ban on antimicrobial use for growth promotion?

Answer 2. Based upon reports from Denmark (the most complete data that is available for evaluating trends of antimicrobial use), the ban on antimicrobial use for growth promotion has caused a substantial increase in therapeutic use of antimicrobials to maintain food animal health. While the total quantity of antimicrobials used in food animals decreased, the therapeutic use increased greatly The total quantity of antibiotics used in food animals decreased by 24 percent between 1997 (160 tons) (the year closest to the start of the ban in 1998) and 2007 (121.1 tons), while therapeutic use increased by 152 percent (from 57.3 tons in 1996 to 121.1 tons in 2007) (1996 is the year closest to start of the ban in 1998 for which therapeutic use data is available).

The antimicrobials now being used for therapy are in classes such as tetracyclines that are also used in humans. This compares to previously used drugs such as avilamycin, salinomycin, monensin, flavomycin, and bacitracin that are not used in human medicine or are not important for human medicine. Tetracycline use in food animals has increased from 12,900 kg of active compound in 1996 to 32,650 in 2006 (153 percent increase), 13-lactamase sensitive penicillins from 7,200 to 22,600 (214 percent increase), cephalosporins and other penicillins from 5,800 to 11,550 (99 percent increase), macrolides from 11,400 to 22,050 (93 percent increase), and sulfonamides + trimethoprim from 4,800 to 13,800 (188 percent increase). Hence, as a result of the ban, we have seen a significant increase in the use of classes of antibiotics that are used in humans.

During this same period of time, resistance to tetracycline of *Salmonella* Typhimurium isolated from clinically ill humans in Denmark increased from 18 percent in 1997 to 53 percent in 2006, and resistance of *Salmonella* Typhimurium isolates to ampicillin increased from 11 percent to 56 percent. Resistance of *Campylobacter jejuni* to tetracycline increased from 3 percent to 7 percent. It is unknown if these increases are associated with the increased food animal use of the antibiotics or increased use of antibiotics in humans themselves. Tetracycline resistance of *Enterococus faecium*, *Enterococcus faecalis*, and *Escherichia coli* from healthy humans stayed the same for the first two organisms and decreased for *E. coli*.

In the early years, swine producers substituted zinc oxide to deal with the ramifications of discontinuing antimicrobial growth promoters. However, because of potential adverse environmental impact, the use of zinc oxide was stopped.

The swine producers also delayed weaning piglets so they were older and better able to adjust to a non-milk diet. While successful, later weaning has created other health risks. For example, piglets are now subjected to prolonged exposure to pathogens from the sow. This occurs while protection from maternal antibodies received

through nursing is waning, resulting in increased risk of disease. Increased quantities of antimicrobials are now used to prevent disease in piglets. In addition to the disease concerns, delayed weaning also impacts efficiency of production.

Question 3. Since there are alternatives to non-treatment uses of antimicrobials such as certain minerals, enzymes or probiotics, is the issue with restricting non-treatment uses of antimicrobials a matter of animal health, or mainly about costs and expenses?

Answer 3. The use of alternatives including vaccines and probiotics, are always strongly encouraged as a part of the AVMA judicious use guidelines, regardless of costs and expenses.

While I am not an expert in the effectiveness of these alternatives, my impression is that there is not a good science-base that demonstrates predictable efficacy of these alternatives. As mentioned above, Denmark initially used zinc oxide as an alternative, but withdrew it because of potential environmental impacts.

Question 4. How often do producers use antibiotics without a prescription?

Answer 4. Currently, there is no accurate system to obtain information on the quantity of use of over-the-counter antibiotics by producers. While there have been estimates of veterinary and human use of antimicrobials, the estimates vary greatly. Also, there is not a system to determine use by producers or any other specific group of individuals. This is one of the many reasons why we discourage broad based bans on antimicrobial use in food animals. Without further information, there is no way of determining public health impact based upon a specific use. Thus, we encourage further evaluation, research, monitoring and surveillance of antimicrobial use.

The USDA National Animal Health Monitoring System (NAHMS) provides some information that addresses the question in terms of frequency of use and involvement of veterinarians.

The Feedlot '99—Part III: Health Management and Biosecurity in U.S. Feedlots, 1999, provides the following information:

- Antimicrobials are added to feed or water of feedlot cattle for a number of purposes, such as a therapeutic response to an outbreak of respiratory disease, disease prevention, to aid in controlling liver abcessation, or to increase average daily gains and/or improve dry matter conversion.
- Nearly 17 percent of feedlots used no antimicrobials in feed or water. (83.2 percent did use antimicrobials in feed or water for some purpose.)
- Tetracyclines were fed between 4 and 12 days, on average, whereas tylosin was fed for a longer time period, likely because the desired purpose differs depending on which antimicrobials were administered. Tetracyclines are often used to treat or prevent outbreaks of respiratory disease, while tylosin is fed to reduce the occurrence of liver abscessation. Tylosin is fed on average 138–145 days.
- Almost all feedlots (99.8 percent) used an injectable antimicrobial as part of an initial therapeutic regimen for an animal believed to be suffering from a respiratory disease.

The Swine 2006 Report (Part I: Reference of Swine Health and Management Practices in the United States, 2006 and Part II: Reference of Swine Health and Health Management Practices in the United States, 2006) provides the following information:

- Nursery pigs
  - Approximately 8 of 10 sites (79.6 percent) used antibiotics in feed as a preventive practice for nursery pigs. 40.4 percent of the sites used injectable antibiotics. On the nursery pig sites that used antibiotics in the specified way (in feed or injectable), 89.5 percent of the nursery pigs received antibiotics in the feed and 64.7 percent of the nursery pigs received injectable antibiotics.
  - The most common reason for giving antimicrobials in feed was disease prevention (50.9 percent of sites). The second most common reason was for disease or parasite treatment (39.3 percent of sites). The third most common reason was for growth promotion (24.5 percent of the sites).
  - Antimicrobials were administered via feed to nursery-age pigs for growth promotion for an average of 32.4 days, for disease prevention—28.6 days, enteric disease treatment—26.1 days, and respiratory disease treatment—20.3 days.
  - Regarding treatment for disease of nursery-age pigs, the percentage of sites where the owner of the operation was the primary decisionmaker regarding antimicrobial use in sick nursery-age pigs decreased as size of site increased. The owner of the operation was the primary decisionmaker in 75.8 percent of the small sites and 35.0 percent of the large sites. The local veterinary practitioner was the primary decisionmaker for treatment of sick nursery-age pigs in 6.1 percent of the small sites and 14.2 percent of the large sites. The company veterinarian or com-

pany nutritionist was the primary decisionmaker in 4.4 percent of the small sites and 20.0 percent of the large sites. A consulting or second-opinion veterinarian was the primary decisionmaker in 0.3 percent of the small sites and 5.2 percent of the large sites.

• 8.2 percent of the sites did not use antimicrobials for growth- promotion in nursery-age pigs. Of those that did use antimicrobial growth promoters, the primary decisionmaker was the owner in 75.7 percent of the small sites and 37.4 percent of the large sites. The local veterinary practitioner was the primary-decision maker at 3.2 percent of the small sites and 17.9 percent of the large sites. The company veterinarian or company nutritionist was the primary decisionmaker at 6.7 percent of the small sites and 34.7 percent of the large sites. A consulting or second-opinion veterinarian was the primary decisionmaker at 0 percent of the small sites and 3.3 percent of the large sites.

• Grower/finisher pigs

• 68.1 percent of grower/finisher sites used antibiotics in feed as a preventive practice. 38.8 percent of the sites used injectable antibiotics. On the grower/finisher pig sites that used antibiotics in the specified way (in feed or injectable), 78.2 percent of the grower/finisher pigs received antibiotics in the feed and 52.7 percent of the grower/finisher pigs received injectable antibiotics.

• The most common reason for giving antimicrobials in feed was for growth promotion (55.1 percent of sites). The second most common reason was for disease treatment (46.1 percent of sites). The third most common reason was for disease prevention (37.5 percent of the sites).

• Antimicrobials were administered via feed to grower/finisher pigs for growth promotion for an average of 62.3 days, for disease prevention—38.4 days, enteric disease treatment—40.8 days, and respiratory disease treatment—27.3 days.

• Regarding treatment for disease of grower/finisher pigs, the percentage of sites where the owner of the operation was the primary decisionmaker regarding antimicrobial use in sick nursery-age pigs decreased as size of site increased. The owner of the operation was the primary decisionmaker in 67.9 percent of the small sites and 29.0 percent of the large sites. The local veterinary practitioner was the primary decisionmaker for treatment of sick grower/finisher pigs in 7.5 percent of the small sites and 11.0 percent of the large sites. The company veterinarian or company nutritionist was the primary decisionmaker in 6.6 percent of the small sites and 28.8 percent of the large sites. A consulting or second-opinion veterinarian was the primary decisionmaker in 2.7 percent of the small sites and 3.8 percent of the large sites.

• 6.7 percent of the sites did not use antimicrobials for growth-promotion in grower/finisher pigs. Of those that did use antimicrobial growth promoters, the primary decisionmaker was the owner in 67.0 percent of the small sites and 33.9 percent of the large sites. The local veterinary practitioner was the primary-decision maker at 3.8 percent of the small sites and 7.5 percent of the large sites. The company veterinarian or company nutritionist was the primary decisionmaker at 12.9 percent of the small sites and 49.9 percent of the large sites. A consulting or second-opinion veterinarian was the primary decisionmaker at 1.2 percent of the small sites and 1.2 percent of the large sites.

• Piglets

• 60.0 percent of piglet sites used antibiotics in feed as a preventive practice before or at weaning. 51.4 percent of the sites used injectable antibiotics. On the piglet sites that used antibiotics in the specified way (in feed or injectable), 30.8 percent of the piglets received antibiotics in the feed and 68.7 percent of the piglets received injectable antibiotics.

• Sows

• 47.7 percent of sow sites used antibiotics in feed as a preventive practice. 40.8 percent of the sites used injectable antibiotics. On the sow sites that used antibiotics in the specified way (in feed or injectable), 46.1 percent of the sows received antibiotics in the feed and 51.9 percent of the sows received injectable antibiotics.

• Boars

• 34.5 percent of boar sites used antibiotics in feed as a preventive practice. 23.2 percent of the sites used injectable antibiotics. On the boar sites that used antibiotics in the specified way (in feed or injectable), 41.1 percent of the boars received antibiotics in the feed and 32.0 percent of the boars received injectable antibiotics.

Question 4. Without directly consulting with a veterinarian?

Answer 4. Veterinarians strongly encourage a Veterinarian-Client-Patient Relationship (VCPR) (required for any veterinary prescription drug) and veterinary consultation when implementing any treatment regimen.

NAHMS also provides some information for this question. For example, Beef '97—Part II: Reference of 1997 Cow-Calf Health and Health Management Practices reports that the veterinarian is a key information resource for cow-calf producers. The veterinarian may provide many services to operations such as diagnosis and care of sick animals, disease prevention, consultation on production practices, and financial analysis. Veterinarians were most commonly used for disease diagnosis and treatment (42.0 percent of operations) and 39.1 percent of producers consulted a veterinarian for disease prevention information. There were differences in the use of veterinary services by herd size, both in terms of overall use and also what services the veterinarians were being asked to provide. There was more overall use of veterinary services in larger operations (83.4 percent) compared to the smallest operations (48.6 percent).

Feedlot '99—Part I: Baseline Reference of Feedlot Management Practices, 1999, reports that all large operations and nearly all (96.5 percent) small operations used the services of a veterinarian. Large operations were more likely to use a veterinarian that made regular or routine visits or employ a full-time veterinarian on staff than small operations. Conversely, small operations were more likely to use a veterinarian when the need for one arose. Veterinarian recommendations had strong or moderate influence on selection of an antimicrobial for nearly 100 percent of feedlots. Veterinarian recommendations and laboratory test results were more likely to strongly influence selection of antimicrobials on large feedlots than small feedlots. Almost three out of four feedlots provided formal training in areas related to antimicrobial use.

The USDA Swine 2006 reports that a higher percentage of large and medium sites (88.1 and 85.0 percent, respectively) used a veterinarian during the previous year compared to small sites (60.8 percent). Nearly 5 of 10 large sites (46.8 percent) used an on-staff veterinarian. A similar percentage of large sites (42.5 percent) used a local practitioner. Overall, approximately half of the sites (49.5 percent) used a local veterinarian during the previous 12 months. About one of four sites (24.7 percent) were visited by a veterinarian five or more times. Producers used the services of a veterinarian for many purposes during the previous 12 months. A higher percentage of large sites used a veterinarian for blood testing, production record analysis, employee education, and quality assurance compared to small sites. For sites that had at least one veterinary visit during the previous 12 months, the highest percentage of sites used a veterinarian to treat individual pigs (63.8 percent). These are followed by vaccination consultation (48.6 percent), quality assurance (47.9 percent), blood testing (47.6 percent), nutritional consultation (19.8 percent), environmental consultation (19.0 percent), and employee training/education (18.0 percent).

Question 5. Are antibiotics easy to purchase without a prescription?

Answer 5. The older antimicrobials are available in medicated feeds that can be purchased without a veterinary prescription. These are called over-the-counter or OTC drugs. A newer category of drugs, the Veterinary Feed Directive (VFD) Drug category, was created by the Animal Drug Availability Act of 1996 to provide veterinary control for certain animal pharmaceuticals for use in feed that are not suitable for OTC status. Any animal feed bearing or containing a VFD drug shall be fed to animals only by or upon a lawful VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice.

QUESTIONS OF SENATOR BROWN

Question 1. Given your comments on the need for more data, do you support the collection and review of safety and use data for non-therapeutic uses of antimicrobials?

Answer 1. We support the collection and review of data for all uses of antimicrobials and other pharmaceuticals in humans and animals to protect both human and animal health. We hope that the collection is done correctly so the data is meaningful and not a waste of resources. We urge that such data be collected in concert with other data that is necessary to explain or inform fluctuations in use, e.g., disease prevalence, populations of animals, etc. An example is the USDA program, Collaboration for Animal Health, Food Safety and Epidemiology, that is attempting to study the use of antimicrobials on farm correlated with disease occurrence, and the effects of antimicrobial use on antimicrobial resistance as measured both on the farm and during processing of the meat from the specific farm. Unfortunately, the program has not received adequate funding. We urge for adequate funding.

We also support adequate funding and improvement of food safety programs such as FoodNet and the National Antimicrobial Resistance Monitoring System (NARMS). It is unfortunate that reporting by NARMS is not timelier. For example,

the most recent Centers for Disease Control and Prevention NARMS report that is available to the public is for 2004—4 years ago.

Question 2. Do you believe that we should be reassessing all previously approved antimicrobials through the science-based risk assessment outlined in Guidance #152?

Answer 2. No, not ALL previously approved antimicrobials need to be reassessed, only the priority antimicrobials (antimicrobials important to humans) that have not had a risk assessment performed by FDA or academicians. Some have already been concluded. If FDA is expected to perform the reassessments, the Agency must be given adequate resources to perform the reassessment so that this effort does not detract from its many other priority missions.

The priority for reassessment must be established based on the potential for a negative impact on human health. A drug, such as bacitracin, that is not classified as an important human antibiotic by either the World Health Organization or the FDA should not be reassessed. Also, there is no need to reassess bambermycin or ionophores because they are not used in humans. FDA has already performed a risk assessment of virginiamycin. Academicians have performed risk assessments on other antimicrobials such as the macrolides. These assessments do not need to be repeated unless new information becomes available. Finally, we understand that the FDA is reassessing the penicillins and tetracyclines and are waiting for the report of the FDA findings.

Reassessment of all previously approved antimicrobials may or may not provide useful information. However, it will require additional FDA resources and has the potential to divert current resources away from the development and approval of new antimicrobials based on the current system of science based risk assessments that evaluate human risks.

Question 3. If yes, and if such a review were to show that there was a potential risk to humans, should we restrict the non-therapeutic use of antimicrobials in animals?

Answer 3. Any restrictions on antimicrobial use should be based on a carefully constructed, science-based risk Assessment that thoroughly weighs risks and benefits to both humans and animals. Restrictions should also be focused upon specific antimicrobials and specific uses of the antimicrobials supported by scientific data that demonstrates a significant public health risk.

AVMA policy supports this approach: "Risk analysis should continue to evaluate the risks and benefits to animal health and welfare in addition to the risks and benefits to human health attributed to [antimicrobial] uses in animals." Because veterinarians are ethically charged with promoting public health in addition to protecting animal health and welfare, we participate in the prevention of both human and animal disease. The public health community and physicians do not need to consider the risks to animal health and welfare and therefore are free to recommend precautionary restrictions on animal drugs based on theoretical or minimal risks to human health. However veterinarians must balance the need for animal health and welfare with the need of human health. Sometimes we believe that the balance should fall in favor of animal health and welfare if the decision will result in a small or insignificant impact on human health but a large or significant impact on animal health and welfare.

But if the human health impact is significant, then we are supportive of measures to mitigate the risk to human health. Those risk management measures can include any of the following: FDA advisory committee review of an existing approval or application for a new animal drug approval; post-approval monitoring through systems such as NARMS; limitations on the extent of use (e.g., individual animals only for short duration of use); targeted extra-label use restrictions; antimicrobial use through prescription or Veterinary Feed Directive Drugs only; and finally non-approval or withdrawal of a previously approved antimicrobial.

Question 4. The AVMA policy states that "regulatory action should be transparent and based on scientific risk analysis." Does AVMA consider Guidance #152 a scientifically sound framework for making decisions about the safety of new animal antimicrobials?

Answer 4. Yes, the AVMA supports the use of Guidance for Industry #152 as a scientifically sound framework for evaluating the safety of new applications for approval and the safety of previously approved antimicrobials.

We support GFI #152 while recognizing that it is very conservative in ensuring the protection of human health without consideration of benefits to animal health and welfare. We also recognize that the ranking of antimicrobial drugs according to their importance in human medicine adds additional difficulty for approving animal

drugs because the ranking design includes treatment of human diseases that are not in any manner associated with food animals. These diseases include gonorrhea, tuberculosis caused by *Mycobacterium tuberculosis*, neurosyphillis, meningitis, neutropenic fever, and Legionnaire's disease. Antibiotics used to treat these diseases in humans are ranked critically important which creates additional barriers to approval of drugs for animals even though the pathogens that cause the human disease are not present in animals.

In addition, we also recognize that the design of GFI #152 makes it extremely difficult or impossible for FDA to approve antibiotics that are used in humans for use in feed or water for treatment or other use in groups of animals. This is because the extent-of-use limitations table assigns a high ranking for intended administration to flocks or herds of animals regardless if the duration of use is short (less than 6 days) or long (more than 21 days).

QUESTIONS OF SENATOR BURR

Question 1. Can you please give us some more detail on what happened in Denmark after the government banned the use of antimicrobials for growth promotion?

Answer 1. The ban on antibiotic growth promoters in Denmark resulted in an increase in disease and death in swine herds, especially in newly weaned pigs, and an increase in the use of antimicrobials for therapeutic uses in swine herds. At the weaning stage, farmers noted an increase in piglet diarrhea, higher mortality rates, decreased weight gains, and greater weight variations. Initially, farmers generally reported few health problems in the finishing stage of pork production. Some farms noticed negative impacts in average daily gain and mortality. Many farms adjusted production practices to address these negative impacts, but some farmers have not been able to make the adjustments.

There is little evidence to demonstrate a general decline in antimicrobial resistance in humans, and there is no evidence of an improvement in clinical outcomes of antimicrobial treatment of humans, the desired effect of the antibiotic ban in Denmark. If the measure of success is resistance in humans, then the results have been mixed and disappointing.

In fact, resistance in humans to some of the banned drugs has increased dramatically. For example, when resistance is measured by using the same resistance definition as is used by CDC, the resistance of *Enterococcus faecium* from healthy humans to quinupristin/dalfopristin (Synercid®) increased from 29 percent in 1997 to 35 percent in 2004, 54 percent in 2005, and 37.5 percent in 2006. The animal equivalent drug (virginiamycin) was banned in Denmark in 1998. While virginiamycin is still approved and used in the United States, the level of resistance in humans (3.7 percent) in the United States is 10 times less than in Denmark.

In another situation, resistance of *Enterococcus faecium* to vancomycin in healthy humans has remained at 0 percent. This may be associated with the ban on the use of avoparcin in animals. (Avoparcin has never been approved for use in the United States). Alternatively, this may also be associated with a different pattern of vancomycin use in human medicine in Denmark.

Question 2. Wasn't there a significant increase in the quantities of antimicrobials used for therapeutic purposes?

Answer 2. Yes, the increase in disease, or the need to prevent disease that was previously prevented by antimicrobial growth promoters has resulted in a 152 percent increase in the quantity of antimicrobials used for therapeutic purposes. Unfortunately, the antimicrobials now used are at higher doses and in classes that are also used in humans, such as tetracyclines.[1]

Question 3. What is the difference between what Denmark and other EU countries have done compared to what Senator Kennedy proposes in his legislation?

Answer 3. Even though the results of the Danish experience with antimicrobial growth promotant drug bans is very mixed, proposals within the United States, such as PAMTA, go beyond the Danish example by proposing to ban uses for the prevention and control of disease, in addition to uses to promote growth and feed efficiency. Evidence shows that the Danish ban (and a ban in the United States, if instituted) will cause animal health and welfare problems.

Question 4. Many people have never spoken to animal producers to understand what non-therapeutic uses of antibiotics means. Can you please explain why animal producers use antibiotics for non-therapeutic uses and what "non-therapeutic uses" means exactly?

Answer 4. The terms non-treatment or non-therapeutic have no true definition and often cause confusion. Treatment, control, and prevention of disease are classi-

fied as therapeutic uses by the FDA, AVMA and Codex Alimentarius Commission (an organization of the World Health Organization and the Food and Agricultural Organization of the United Nations). The use of exclusionary terms, such as non-therapeutic, that are ill-defined and have no clear definition only serves to further confuse the issue. We caution against the use of these terms, as it is defined by some groups, because it could potentially disallow veterinary discretion in control or prevention of disease and consequently interfere with the practice of veterinary medicine.

In addition to treatment, control, and prevention of disease, the FDA also approves antimicrobials for growth promotion or feed efficiency. The antimicrobials that have been approved for growth promotion or feed efficiency are sometimes not in the same classes as antimicrobials that are used in human medicine and thus do not contribute to human resistance concerns. In addition, antimicrobials approved for growth promotion or feed efficiency have been shown to have health-promoting effects.

Question 5. Have non-therapeutic uses of antimicrobials negatively impacted human health?

Answer 5. We don't know if growth promotion and feed efficiency use has impacted human health but we believe that any impact is minimal if it exists. Because the human health impact is not known is the reason why we recommend that risk assessments be performed to aid the risk management decision process.

It is clear that any use of antimicrobials, whether in humans or animals, can foster resistance. However, what is not clear is whether resistance in animals results in an impact on human health. While there has been much speculation, there has been little evidence indicating a negative impact on human health as a result of antimicrobial use in animals. And the Danish experience has not demonstrated an improvement in human health that resulted from the ban. However, there is a fair amount of evidence indicating that broad based bans on antimicrobial use has resulted in significant declines in animal health and could potentially harm human health.

Information from resistance monitoring systems, such as NARMS, indicates that there is not a public health crisis associated with resistant pathogens that may originate in animals. For example, NARMS data, when combined with FoodNet data, demonstrates that the case rate of human infections with multidrug resistant *Salmonella* spp. has decreased 49 percent between the NARMS baseline years of 1996–98 and 2004 (the most current, publicly available human data from NARMS). In addition, there has been a 65 percent reduction in the case rate of penta-resistant *Salmonella* Typhimurium infections. Non-typhi *Salmonella* spp. are one-half as likely to be resistant in 2004 than in 1996. Resistance of *Enterococcus faecium* to quinupristin/dalfopristin (Synercid®) decreased from 20.9 percent in 2001 to 3.7 percent in 2004. As mentioned earlier, the resistance rate in 2004 is 10 times less than the resistance rate in Denmark, where the animal equivalent antimicrobial, virginiamycin, has been banned for 10 years. Resistance of *E. faecium* to other antimicrobials or antimicrobial classes, such as vancomycin and aminoglycosides, also decreased from 2001 to 2004. *Escherichia coli* 0157 is one-third as likely to be resistant in 2004 compared to 1996.

Several risk assessments have been performed that demonstrate a very low risk to human health from the use of antimicrobials in food animals, and some of the models predict an increased human health burden if antimicrobial use is withdrawn. The unique farm-to-patient risk assessment performed by Hurd demonstrates that the use of tylosin and tilmicosin in food animals presents a very low risk of human treatment failure because of macrolide resistance, with an approximate annual probability of less than 1 in 10 million with *Campylobacter* infections and approximately 1 in 3 billion *E. faecium* infections.[2] Cox performed a quantitative human health risks and benefits assessment for virginiamycin and concluded that there would be a significant human health risk if virginiamycin use is withdrawn. There would be 6,660 excess cases per year of campylobacteriosis, which far outweighs the 0.27 per year reduction of cases of streptogramin-resistant and vancomycin-resistant *E. faecium* (VREF) resulting from the withdrawal.[3] Cox also performed a risk assessment regarding macrolide and fluoroquinolone use and concluded that withdrawal is estimated to cause significantly more illness days than it would prevent.[11] Cox also examined the impact of the use of penicillin-based drugs in food animals on penicillin/aminopenicillin resistant enterococcal infections and concluded that not more than 0.04 excess mortalities per year (under conservative assumptions) to 0.18 excess mortalities per year (under very conservative assumptions) might be prevented in the whole U.S. population by discontinuing current use of penicillin-based drugs in food animals. The true risk could be as low as

zero.[4] This equates to one potentially preventable mortality in the U.S. population roughly every 7–25 years. Alban's risk assessment concluded that the risk associated with veterinary use of macrolides in Danish pigs resulted in a low risk to human health.[5] Others have estimated that risk management strategies that focus on eliminating resistance are expected to create <1 percent of the public health benefit of strategies that focus on reducing microbial loads in animals or on foods.[6] Programs such as farm-to-fork pathogen reduction are much more effective than antimicrobial restrictions or bans in mitigating human health risks. In another paper, the authors concluded, "We came to some surprising conclusions that were robust to many uncertainties. Among these were that antimicrobials that benefit animal health may benefit human health, while regulatory interventions that seek to reduce antimicrobial resistance in animals may unintentionally increase illness rates (and hence antimicrobial use and resistance rates) in humans. . . . In conclusion, our analysis suggests that the precautionary-principle approach to regulatory risk management may itself be too risky."[7]

Question 6. Please explain how a veterinarian prescribes antibiotics.

Answer 6. Dispensing or prescribing a prescription product (including antimicrobials) requires a veterinarian-client-patient relationship (VCPR). The VCPR is the basis for interaction among veterinarians, their clients, and their patients. Veterinary prescription drugs are to be used or prescribed only within the context of a VCPR.

The veterinarian must have sufficient knowledge of the animal(s) to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), or by medically appropriate and timely visits to the premises where the animal(s) are kept.

Veterinarians making treatment decisions must use sound clinical judgment and current medical information and must be in compliance with Federal, State, and local laws and regulations. The veterinarian must also include consideration of: judicious use principles; food safety and public health; and producer education as a part of the treatment plan.

After considerations have been made for both animal and human health impact, veterinary authorization is required prior to dispensing of the prescription product.

Question 7. What happens if a veterinarian is complicit in an off-label use of animal drugs? Are there penalties for this? Who enforces these rules? In recent years have there been any enforcement actions taken? What were the outcomes?

Answer 7. The Animal Medicinal Drug Use Clarification Act[8] (AMDUCA) made extra-label drug use (ELDU) (off-label use) legal when the ELDU regulations are followed by the veterinarian. Without a valid veterinarian-client-patient relationship (VCPR), extra-label use of any pharmaceutical is unethical and is illegal under Federal law. Given the numerous animal species and diversity of disease conditions that affect animals, the indications for FDA approved drugs are severely limited. The numbers of FDA approved drugs are inadequate to meet veterinary medical needs, placing both animal health and potentially human health at significant risk. As a result, extra label drug use is a medically necessary provision authorized by the U.S. Congress through AMDUCA to relieve the pain and suffering of millions of animals. The ELDU of medicated feeds is strictly prohibited. The FDA, in conjunction with the State boards of veterinary medicine (which license veterinarians), enforce ELDU and prescribing regulations. Penalties for violation of these regulations range from investigations and warning letters to suspension and loss of licensure. There is also the potential for civil and criminal penalties for violation of these regulations. However, AVMA does not enforce ELDU regulations and therefore does not have record of enforcement actions or outcomes of any violations.

ENDNOTES

1. DANMAP 2006. Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. Available at www.danmap.org.

2. Hurd S. et al. Public Health Consequences of Macrolide Use in Food Animals: A Deterministic Risk Assessment. J Food Protection 2004; 67:980–992.

3. Cox LA. Potential human health benefits of antibiotics used in food animals: a case study of virginiamycin. Environ Int 2005; 31:549–63.

4. Cox LA. et al. Human Health Risk Assessment of Penicillin/Aminopenicillin Resistance in Enterococci Due to Penicillin Use in Food Animals. 2008. In Press.

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7. Cox LA. et al. Quantifying Human Health Risks from Animal Antimicrobials. Interfaces. 2007; 37:22–38.
8. **Animal Medicinal Drug Use Clarification Act (AMDUCA) Compliance in Drug Use**—The therapeutic administration of any approved dosage form drug in a manner that is not in accordance with the drug's labeling requires additional management. AMDUCA regulations are in force for all approved therapeutic dosage form drugs if administered in a manner not in accordance with the drug's labeling. For such usage, the FDA specifies that the following criteria must be met:

- Make a careful diagnosis and evaluation of the conditions for which the drug is to be used.
- There is no approved animal drug that is labeled for such use, or that contains the same active ingredient in the required dosage form and concentration. Alternatively, an approved animal drug exists, but a veterinarian finds, within the context of a veterinarian/client/patient relationship, that the approved drug is clinically ineffective for its intended use.
- Assure that the identity of the treated animal(s) is carefully maintained.
- Establish a substantially extended withdrawal period supported by appropriate scientific information prior to marketing milk, meat, eggs, or other edible products from the treated animal(s).

CUBIST PHARMACEUTICALS, INC.,
LEXINGTON, MA 02421,
July 30, 2008.

Hon. EDWARD M. KENNEDY, *Chairman,*
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510.

ATTN: Laura Kwinn, Ph.D.

DEAR CHAIRMAN KENNEDY: Thank you for convening the June 24, 2008 hearing on "Emergence of the Superbug: Antimicrobial Resistance in the U.S." and for inviting me to participate as a witness.

As you know, antimicrobial resistance presents a serious threat to the public health which must be immediately addressed. Cubist appreciates your leadership in this area and your willingness to work with all stakeholders to find the appropriate legislative solutions.

Enclosed, please find my answers to the questions for the record. I look forward to continuing the dialogue with you and your staff and I am happy to provide additional materials as needed. Please feel free to contact me at any time.

BARRY I. EISENTEIN, M.D.,
Senior Vice President,
Scientific Affairs Cubist Pharmaceuticals.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY, SENATOR BROWN, SENATOR BURR, AND SENATOR HATCH BY BARRY I. EISENSTEIN, M.D.

QUESTION OF SENATOR KENNEDY

Question. You mentioned Federal incentives to increase research into biodefense agents such as Project Bioshield and the Biomedical Advanced Research and Development Authority. Do you think research into development of new antimicrobials should be included in those programs?

Answer. Antimicrobials are clearly an important category of therapeutic countermeasures against select agents such as anthrax. The Biomedical Advanced Research and Development Authority (BARDA) provides Federal funding for the development of new vaccines, diagnostics and therapeutics to combat health threats. BARDA also manages Project Bioshield, which focuses on advanced development for bioterrorism countermeasures through expedited procedures and guarantee purchase agreements. These initiatives serve as existing opportunities that should be explored in

regards to spurring new antimicrobial research and development, as antimicrobial resistance is a clear public health threat.

QUESTION OF SENATOR BROWN

Question. Fifteen years ago, the Office of Technology Assessment urged Congress to develop new antibiotics specifically to treat infections caused by antibiotic-resistant bacteria. Not much has happened since then to address this growing problem. Can you discuss how development incentives may differ for small companies versus big PhRMA companies?

Answer. As you may know, I was part of the expert panel of consultants involved in this Office of Technology Assessment report. Large pharmaceutical companies generally have a scope of resources and a stable risk profile that can tolerate the high-cost, high-risk research targeted to relatively small populations, such as antimicrobial research and development. Investigative and small biomedical companies operate in an arena far more challenging: these emerging companies have no revenue stream; depend on venture funding with pre-established investment windows; and face large intellectual property and scientific start-up costs. Incentives which would lower these barriers to entry in order to attract private funding are integral for small companies. Tools such as research and development tax credits, orphan drug tax credits, orphan product designations, net operation loss carry-forwards and priority review vouchers can act to help infuse capital into early- and mid-market companies. Incentives that allow greater economic value later in the course of drug development life, such as extension of patent rights and market exclusivity, will benefit large companies.

Regulatory hurdles also exist; the removal of which may spur innovation and interest in the antimicrobial field for both small and large companies. As you may know, the effectiveness of older antibiotics were reviewed and approved with technology that is now 50 years old. Reviewing these older lines of antibiotics to examine their modern effectiveness would help new antibiotic products gain a greater appreciation, and thus assist innovative small and large companies.

Specifically, older antibiotics reflect standards of measuring antibiotic resistance which are decades old and now outdated. Newer compounds must meet more rigorous tests of resistance but must still compete against the older, already approved drugs. This compromises patient safety since the effectiveness of older antimicrobials is called into question, but also puts newer compounds at a competitive disadvantage—they face higher barriers to market entry. Periodic review by the FDA of the "breakpoint" (labeled concentration at which a compound is considered resistant) for older compounds will benefit patients as well as ensure a fair playing field for approval of newer antibiotics.

In addition to the outdated "breakpoints" of these older compounds, approval standards necessary to demonstrate safety and effectiveness for older antimicrobials were less rigorous than modern standards, allowing approval of a broad array of indications for older antibiotics with comparatively less scientific data. New antibiotics cannot be approved for a broad array of indications without meeting significantly more rigorous scientific standards, making these drugs appear, by comparison to older drugs, to be weaker, less potent, and less broadly effective. Clinical guidelines often follow approved, labeled indications to set standards of care, thus the commercial opportunities for newer compounds are more limited and lead to lower returns on investment. This is particularly true in light of current "antibiotic stewardship" practices which conserve use of new antimicrobials to delay emergence of resistance. Adherence to exacting scientific standards is, of course, appropriate. These standards should be applied to new drugs as well as older compounds, not only for the purposes of commercial fairness, but also to ensure patients are receiving the most effective drugs available.

QUESTION OF SENATOR BURR

Question. In your testimony, you identified some possible incentives to encourage the development of antimicrobial products by pharmaceutical and biotech companies. You mentioned encouraging HHS and individual hospitals to stockpile antimicrobials. You also suggested guaranteed market contracts similar to Project Bioshield. In the Bioshield arena, we learned there needed to be a stronger emphasis on advanced development, which is why we created the Biomedical Advanced Research and Development Authority (BARDA). You suggested small contracts of $50 million could provide the incentive necessary for antimicrobial R&D. That figure seems low to me. From a business standpoint, how much impact can a $50 million development contract have? Are there other things that provide an even greater disincentive for companies that we need to focus on?

Answer. Contracts of $50 million would be at the lower end of the spectrum for small and mid-sized biopharmaceutical companies; such sums would provide a small, but not substantial, incentive for research and development. Additionally, the earlier such an investment is made, the greater the potential benefits to a start-up company without marketed products or revenue. As I have witnessed first hand, antimicrobial R&D is an expensive endeavor and the marketplace is challenging even for successful products.

Again, the current regulatory environment may provide the greatest disincentive to antimicrobial development as it tilts the playing field toward older, less-effective products. The Infectious Disease Society of America as well as the Clinical Laboratory Standards Institute determined that the labels of many older antibiotics are outdated and fail to reflect current anti-infective resistance. Additionally, these labels reflect approval for indications that may not be appropriate under today's scientific standards. I strongly agree with these findings and feel these outmoded labels give a false sense of confidence to physicians and the public. FDA recently addressed these concerns by partially lowering the breakpoint for vancomycin—but the persistent loss of drug potency requires continued review by the FDA.

QUESTION OF SENATOR HATCH

Question. Dr. Eisenstein, you discussed in your testimony your concerns regarding the lack of Medicare coverage for home infusion of intravenous antibiotics. In some instances, Medicare beneficiaries either stay in the hospital longer in order to continue receiving their IV antibiotics or they travel to the hospital for daily infusions. Both scenarios cause difficulties for Medicare beneficiaries and encourage additional spending in the Medicare program. Additionally, if the Medicare beneficiary has Methicillin-resistant Staphylococcus aureus, better known as MRSA, shouldn't we be discharging these patients from the hospital as soon as possible to reduce the spread of MRSA to other patients?

Answer. In general, yes, we should be discharging patients from the hospital ASAP. Medicare coverage of home infusion services would allow patients to receive a daily dose of IV antibiotics safely and effectively at home. Home infusion, a medical service carried by many private insurers, has been found to be easier and more convenient for patients, safer for patients and hospital providers, and good public health policy as it removes infected patients from the hospital and reduces the risk of its spread. Home infusion can also be far less costly for patients and payers. In fact, many private health plans, including those provided to Senators and their staff through the Federal Employees Health Benefits program, recognize the benefits of home infusion and provide comprehensive coverage and reimbursement for all necessary home infusion components.

Unfortunately, Medicare—unlike the overwhelming majority of other health plans—provides fragmented and limited coverage and reimbursement for home infusion. Some parts of Medicare, like Part C, do a good job of providing coverage and reimbursement for all the component parts of medical treatment necessary for a comprehensive home infusion benefit, including the drug/ingredient supplies; and the administration service fee to the provider. Medicare Part B, however, pays for some but not all of these components. Missing from Medicare Part B reimbursement is the fee for the administration service. This situation is akin to Medicare paying for a topical anesthetic for the removal of a skin mole in a doctor's office but not paying for the doctor to actually perform the service.

The lack of an administration fee for home infusion services under Medicare Part B is a significant problem that Congress should remedy. In fact, included in the 2008 MedPAC Report to Congress this March, MedPAC identified "hospital discharge problems" for those patients requiring on-going IV antibiotic infusions.

In such situations, patients are often kept in the inpatient setting longer than necessary simply to assure continued IV antibiotic treatment—an obvious cost to Medicare. Other patients who are discharged from inpatient care may be required to return to the hospital outpatient department for daily IV antibiotic infusions because there is no coverage of the administration fee under the home infusion benefit. Daily back and forth travel to the hospital is often inconvenient and even impossible for Medicare beneficiaries living in rural areas. Finally, as your questions note, keeping infected patients in the inpatient setting or having them return for daily infusions increases the risk of spread of MRSA infection to other patients.

If home infusion of IV antibiotics were comprehensively covered under Medicare Part B, including the administration service fee, this would make financial sense for the Medicare program, it would be more convenient for beneficiaries (particularly those in rural areas), and it would be safer for other patients.

[Whereupon, at 12:38 p.m. the hearing was adjourned.]

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