DEPARTMENT OF HEALTH & HUMAN SERVICES

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BEFORE THE

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HEARING ON

ANTIMICROBIAL RESISTANCE IN THE U. S.

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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 two 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 U.S. 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, Georgia, to obtain input from outside consultants for revising and updating the Action Plan. The consultants, including a diverse group of experts from the U.S. and six other countries, reviewed the 2001 Action Plan in detail and participated in discussions on updating the Action Plan for the next five 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 of 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 enterohermorrhagic *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.