DEPARTMENT OF HEALTH & HUMAN SERVICES

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INTRODUCTION

Good morning, Mr. Chairman and Members of the Subcommittee. I am Bernadette Dunham, D.V.M., Ph.D., Director of the Food and Drug Administration's (FDA or the Agency) Center for Veterinary Medicine (CVM), which is a part of the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss FDA's role with regard to antimicrobial resistance.

Preserving the effectiveness of current antimicrobials, and encouraging the continued development of new ones, are 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 associated with bacterial pathogens displaying resistance to at least one antimicrobial 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. The problem is not limited to hospitals. Resistant infections impact clinicians practicing in every field of medicine, including veterinarians. Community-acquired infections are also frequently resistant to multiple antimicrobial drugs, 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 contaminated 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. The term "antimicrobial" refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites (such as malaria). The term "antibacterial" refers to drugs with activity against bacteria in particular. Another term commonly used to describe an antibacterial drug is "antibiotic." This 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 are synthetic compounds; i.e., they are not produced by microorganisms. Though these do not meet the technical definition of antibiotics, they are referred to as antibiotics in common usage.

Antimicrobial resistance is the ability of bacteria or other microbes to resist the effects of a drug. Antimicrobial 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.

Many factors contribute to the spread of antimicrobial resistance. In some cases, doctors prescribe antimicrobials too frequently or inappropriately. Sometimes patients do not complete the prescribed course of an antimicrobial, making it more likely that surviving

microbes will develop resistance. Antimicrobial use in animals may contribute to the emergence of resistant microorganisms that can infect people. Through international trade and travel, resistant microbes can spread quickly worldwide.

Antimicrobial agents have been used in human and veterinary medicine for more than 50 years, with tremendous benefits to both human and animal health. Many infections that were fatal, or left individuals with severe disabilities, are now treatable or preventable. However, because resistance to antimicrobial drugs is expected to occur with their use, it is essential that such drugs be regulated and used judiciously to delay the development of resistance. Misuse and overuse of these drugs contribute to an even more rapid development of resistance. After several decades of successful antimicrobial 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 are emerging because of the combined impact of the various uses of antimicrobial drugs, including their use in humans and animals. All of these pathways are not yet 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

To address these challenges, the U.S. Interagency Task Force on Antimicrobial Resistance was created in 1999 to develop a national plan to combat antimicrobial resistance. FDA co-chairs the task force, along with the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH).

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" (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 antibacterial drugs can help reduce the incidence of antimicrobial resistance. In 2003, FDA partnered with CDC on its launch of its *Get Smart: Know When Antibiotics Work* campaign. The goal of the campaign is 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 labeling regulations for the appropriate use of systemic antibacterial drugs in humans. CVM has developed, in conjunction with stakeholders, in-depth antimicrobial prudent use principles for beef, dairy, swine, poultry, and more recently, aquatic veterinarians.

Measures that reduce the need for antimicrobial use also serve to reduce the emergence of antimicrobial-resistant microorganisms. Prevention of bacterial 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 antimicrobials. Prevention of viral infections through the use of vaccines can also indirectly help reduce antibiotic use and minimize the emergence of antibiotic-resistant microorganisms. For example, viral infections, such as respiratory infections due to influenza, often lead to unnecessary antimicrobial use and are sometimes complicated by 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 antimicrobial 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 antimicrobials 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 of the Action Plan 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 antimicrobial resistance (e.g., MRSA), thereby reducing the need for antimicrobials and the occurrence of antimicrobial resistant strains.

The task force is currently 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, product development, education, and research.

- **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, including new drugs and vaccines, and improved, more timely tests for infectious diseases.
- **Education:** Facilitating the safe and effective use of antimicrobials and thus prolonging the life of these products by helping improve the quantity and quality of information available to consumers and health professionals regarding antimicrobial 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 Veterinary Medicine (CVM)

CVM is addressing potential human health risks associated with the use of antimicrobial drugs in food-producing animals. CVM's 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. CVM is actively conducting research to advance our understanding of antimicrobial resistance mechanisms and to support our regulatory decisions. The Agency also continues to participate in public meetings with stakeholders to provide educational outreach activities and 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 CVM's strategy to assess relationships between antimicrobial use in agriculture and subsequent human health consequences is the National Antimicrobial Resistance Monitoring System (NARMS). CVM is the lead coordinator of 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 provide regulatory officials and the veterinary medical community with critical information to help assess the risk associated with antimicrobial use in food animal production.

As part of the new animal drug approval process, CVM developed and implemented an approach for assessing antimicrobial resistance concerns associated with the use of

antimicrobial drugs intended for use in food-producing animals. This approach uses risk assessment methodologies to assess the potential human health impact from the proposed antimicrobial use in animals and outlines risk management strategies that may be applied. 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 provides recommendations to drug sponsors on the use of a qualitative risk assessment approach for evaluating 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.

CVM is also applying the basic principles of this approach to an ongoing review of currently approved antimicrobial drugs. While potential public health concerns must be addressed, it is critical that veterinarians continue to have access to effective antimicrobial drugs for the treatment, control, and prevention of disease in animals.

CVM continues to collaborate with veterinary and animal producer associations to develop and distribute guidelines on the judicious use of antimicrobial drugs in food-producing animals.

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 systemic antibacterial drugs in humans. The regulations encourage healthcare professionals to prescribe these antibacterial drugs only when clinically necessary and to counsel patients about the proper use of such drugs and the importance of taking them as directed.

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 antimicrobials can contribute to the development of antimicrobial 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 antimicrobial 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 antimicrobial 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. Since October 2007, CDER has issued

four such guidance documents. In January of this year, FDA co-sponsored a workshop with the Infectious Diseases Society of America to discuss clinical trial designs for community acquired pneumonia (CAP). The Agency also convened an advisory committee meeting in April 2008 to get additional advice and the Agency is now 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.

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 other 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 antimicrobial 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 antimicrobial 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 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 the Food and Drug Administration Amendments Act of 2007 (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 to consider "which serious and life threatening infectious diseases, such as diseases due to gram-negative bacteria and other diseases due to antibiotic-resistant bacteria, [would] 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 antimicrobial resistance by reducing or even nearly eliminating some types of infections. Other vaccines contribute by reducing the need for use of antimicrobials. CBER has initiated a new research program to facilitate vaccine development to prevent 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 antimicrobial-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 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. CDRH also recently cleared 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 stool specimens to aid in the diagnosis of diseases caused by enterohermorrhagic *E. coli* infections.

CONCLUSION

In conclusion, I would like to note that USDA and FDA are cosponsoring a meeting this afternoon to discuss agenda items and to present draft U.S. positions on them for the upcoming second session of the Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance (AMR) to be held in Korea, October 20-24, 2008. The public meeting will be held at CVM's Rockville, Maryland, offices between 1:00 and 3:00 pm today. This AMR Task Force was established in 2006 to develop science-based guidance to be used to assess the risks to human health associated with the presence in food and feed, including aquaculture, and the transmission through food and feed of antimicrobial resistant microorganisms and genes. FDA will continue to work with Federal, State, local and foreign government officials, medical professionals including the veterinary community, the regulated industry and all of FDA's stakeholders, in developing sound strategies to address and advance both human and animal health.

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