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Statement of FDA Principal Deputy Commissioner
Joshua M. Sharfstein (2010)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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STATEMENT OF

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FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

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COMMITTEE ON ENERGY AND COMMERCE

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INTRODUCTION

Good afternoon, Chairman Pallone and Members of the Subcommittee, I am Dr. Joshua M. Sharfstein, Principal Deputy Commissioner of the Food and Drug Administration (FDA or the Agency), which is an agency of the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss FDA's role with regard to antimicrobial resistance. We appreciate your leadership on this important public health matter.

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. A 2004 report from the Infectious Diseases Society of America (IDSA) noted that "About 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." 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. Clinicians practicing in every field of medicine, including my own field of pediatrics, encounter resistant infections frequently. So, too, do veterinarians. Community-acquired infections are 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resistance, describe FDA's actions to combat resistance and promote product development, and discuss the newly released draft guidance entitled, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals."

As I will discuss in more detail later, in the draft guidance, FDA concludes that the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health. Developing strategies for reducing antimicrobial resistance is critically important for protecting both public and animal health.

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 contributes 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.

New classes or modifications of older classes of antimicrobials over the past six decades have been matched slowly but surely by the development of new bacterial resistance mechanisms. As of today, antimicrobial resistance mechanisms have been reported in the scientific literature 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

The U.S. Interagency Task Force on Antimicrobial Resistance (Task Force) 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.

The Task Force also includes the Agency for Healthcare Research and Quality, Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, the United States 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.

In 2001, the Task Force published the "Public Health Action Plan to Combat Antimicrobial Resistance" (Action Plan). The Action Plan has four major components: surveillance, prevention and control, research, and product development. The Interagency Task Force has been working on a revised Action Plan. The revised Action Plan, which is currently undergoing interagency review, will provide more specific action items than the 2001 Action Plan and will include goal dates for completing many of the action items.

ANTIBIOTIC REDUCTION IN HUMAN MEDICINE

The issue of antimicrobial resistance is being addressed on a number of fronts. My colleague from CDC will discuss the data associated with human resistance as it relates to antimicrobial

use in food-producing animals and on his agency's leadership in efforts to fight resistance in human medicine. As a pediatrician, I remember when CDC and the American Academy of Pediatrics published principles in 1998 (Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz, B. *Pediatrics*. 1998;101:163-165) for the judicious use of antibiotics in common pediatric infections: the common cold, otitis media, acute sinusitis, and pharyngitis. Children often have a high number (3-8) of viral upper respiratory infections each year and it is important to not be using antibiotics for viral infections which will not respond to them but will increase the child's probability of having a resistant organism when they do have an infection due to a bacteria. Otitis media, or ear infections, are one of the most common infections of childhood where an antibiotic may be needed. By three years of age, greater than 80% of children have had at least one episode of acute otitis media and 46% have had three or more episodes of ear infections. Judicious use of antibiotics helps decrease the probability that this common infection will be caused by an organism that is resistant to the more commonly used antibiotics (Feigin & Cherry: 1998). This initiative has been successful in reducing antibiotic prescription rates. Pediatricians are now using more discretion when administering antibiotics to their patients. A recent study in the Journal of the American Medical Association, which utilized national databases, reported that antibiotic prescription rates for children under five years of age with respiratory tract infections (including infections such as the common cold) decreased by 41% between 1995-1996 and 2005-2006 (JAMA 2009;302:758-66).

FDA'S ACTIVITIES TO COMBAT ANTIMICROBIAL RESISTANCE

Many Centers at FDA are addressing the public health concern about antimicrobial resistance. For example, research and regulatory efforts at the Center for Biologics Evaluation and Research (CBER) have contributed to the development and continued availability of effective vaccines

which have eliminated or markedly decreased antimicrobial resistance by reducing or nearly eliminating some types of infections. Additionally, the Center for Devices and Radiological Health (CDRH) leads several efforts to clarify regulatory requirements for both industry and the scientific community on clearance of diagnostic tests for use in antimicrobial resistance initiatives.

Since today's hearing focuses specifically on the use of antimicrobials in animal agriculture, my testimony will highlight the efforts at the Center for Veterinary Medicine (CVM). I will also provide a brief update to Dr. Janet Woodcock's recent testimony before this Subcommittee about the initiatives at the Center for Drug Evaluation and Research (CDER).

Center for Veterinary Medicine (CVM)

FDA's strategy for addressing the antimicrobial resistance issue starts with surveillance through the National Antimicrobial Resistance Monitoring System (NARMS). NARMS is a multi-faceted system that monitors trends in the prevalence of antimicrobial-resistance among bacteria isolated from humans, retail meats, and food animals. CVM is the lead coordinator of NARMS and collaborates with CDC, the United States Department of Agriculture's (USDA) Agricultural Research Service and State public health laboratories. NARMS data are critical for monitoring antimicrobial drug resistance among Salmonella and other enteric bacterial organisms from human and animal populations, as well as retail meats. Such data provide important information to regulatory officials, physicians, and veterinarians for assessing trends and identifying appropriate risk mitigating measures. Additionally, NARMS provides a national source of enteric bacterial isolates that are invaluable for conducting antimicrobial resistance research.

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." (To view FDA guidance documents, please visit *http://www.fda.gov/RegulatoryInformation/Guidances/default.htm*). 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.

FDA believes the approach outlined in Guidance #152 for evaluating the safety of antimicrobial drugs as part of the drug approval process is scientifically sound and is protective of the public health. However, many antimicrobial drug products, approved prior to the implementation of Guidance #152 in 2003, have not been evaluated under the current processes for assessing safety with respect to antimicrobial resistance. Of particular concern are those antimicrobials that are considered medically important drugs (i.e., those drugs or classes of drugs that are important in human medicine) and are approved for use in food-producing animals for production or growth-enhancing purposes.

Judicious Use Guidance for Antimicrobials in Food-Producing Animals

To address this concern, CVM released a draft guidance on June 28, 2010, entitled, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" *(http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf*). This draft guidance is intended to inform the public of FDA's current thinking on the use of medically important antimicrobial drugs in food-producing animals. It is intended to help minimize antimicrobial resistance by outlining several broad principles for assuring that medically important antimicrobial drugs are used judiciously in animal agriculture.

The draft guidance reviews the major public health reports on this topic – including reports by the Institute of Medicine, the Government Accountability Office, and the World Health Organization. FDA believes the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health.

In the draft guidance, FDA recommends phasing in measures that would (1) limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and (2) include veterinary oversight or consultation. These steps would help reduce overall use of medically important antimicrobial drugs, thereby reducing the selection pressure that generates antimicrobial resistance. Prior to issuing the draft guidance, FDA consulted with USDA to seek their input on the recommendations. FDA and USDA are committed to working collaboratively to address this important public health issue.

FDA is seeking public comment on the draft guidance through August 30, 2010. FDA is committed to working with USDA, animal drug sponsors, the veterinary and public health communities, the animal agriculture community, and all other interested stakeholders in developing a strategy to address antimicrobial resistance concerns in a manner that is protective of both human and animal health. For example, FDA intends to work closely with USDA, producers, and veterinarians on strategies for increasing veterinary involvement in the use of antimicrobial drugs and for assuring that specific animal health needs are met as the measures outlined in the guidance are implemented.

Center for Drug Evaluation and Research (CDER)

FDA's efforts to address antimicrobial resistance are not limited to uses of antibiotics in food-producing animals. It is important that (1) our existing antibacterial drugs for humans be used prudently to preserve their effectiveness and (2) that new antibacterial drugs for humans be developed as we expect that resistance will develop to existing therapies over time. In her recent testimony, Dr. Woodcock described several initiatives under way to address challenges in human medicine at CDER, which include gathering scientific data to inform the development of recommendations on designing informative, ethical, and feasible clinical trials; issuing draft guidance documents concerning clinical trial designs for studying antibacterial drugs; and working towards publishing additional draft guidance documents in the coming months to address the development of antimicrobial drugs intended for use in treating skin infections and hospital-acquired/ventilator-associated bacterial pneumonia. In addition, FDA recently announced a public workshop to be held August 2-3, 2010, regarding issues in the design and conduct of clinical trials for antibacterial drug development. The public workshop is intended to provide information for and gain perspectives from health care providers, researchers, academia,

industry, and regulators on various aspects of design and conduct of clinical trials for antibacterial drugs.

CONCLUSION

Addressing antimicrobial resistance is a challenging task which requires the expertise and efforts of many entities. 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.