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Report to the Honorable Tom Harkin, Ranking Minority Member, Committee on Agriculture, Nutrition, and Forestry, U.S. Senate

April 1999

FOOD SAFETY

The Agricultural Use of Antibiotics and Its Implications for Human Health

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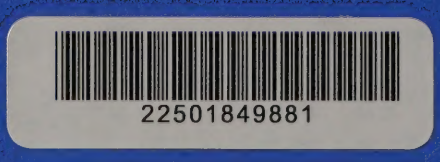

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Resources, Community, and
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April 28, 1999

The Honorable Tom Harkin
Ranking Minority Member, Committee on
Agriculture, Nutrition, and Forestry
United States Senate

Infectious diseases are the third leading cause of death in the United States, behind heart disease and cancer, and antibiotics are often necessary in their treatment. Antibiotic resistance, which occurs when antibiotics that had been used effectively to treat infections are no longer able to kill bacteria growth, is a serious human health problem. The factors that contribute to antibiotic resistance include the nature of disease-producing bacteria (pathogens), environmental pressures, and the use of antibiotics in human medicine as well as in agriculture.

As you have requested, this report explores antibiotic-resistance issues that may stem from the use of antibiotics in agriculture. Specifically, this report examines (1) how antibiotics are used in agriculture and the implications of that use for human health, (2) the federal roles and responsibilities for overseeing the use of antibiotics in agriculture, and (3) the issues surrounding the debate over whether to further regulate or restrict the use of antibiotics in agriculture.

To conduct this work, we reviewed scientific and medical studies, reports, and other literature and spoke with experts in government, academia, and private industry. We performed our review from May 1998 through April 1999 in accordance with generally accepted government auditing standards. Further details of our scope and methodology are discussed in appendix I.

Results in Brief

Antibiotics are used in agriculture to treat and prevent diseases in animals and in food plants and as a feed additive to improve the growth rate in animals. Research has linked the use of antibiotics in agriculture to the emergence of antibiotic-resistant strains of disease-causing bacteria. These bacteria, which are known to cause illness or disease in humans, include *Salmonella*, *Campylobacter*, and *Escherichia coli*, commonly known as *E. coli*. Although the ill effects of these foodborne pathogens are generally mild to moderate, each year several thousand persons have severe illness resulting in hundreds of deaths. However, there are no current comprehensive estimates of the extent to which antibiotic-resistant strains

have resulted in illnesses and deaths. Researchers believe these organisms acquire resistance to antibiotics while in an animal; the resistant strain is then passed to humans through food or through direct contact with animals or animal waste. In addition to this direct transfer of antibiotic-resistant organisms, some research indicates that the use of antibiotics in food animals may reduce the effectiveness of related antibiotics when used to treat humans. While research has linked the use of antibiotics in agriculture to the emergence of antibiotic-resistant foodborne pathogens, agricultural use is only one of several factors that contributes to antibiotic resistance in humans for pathogens that are not foodborne.

Several federal agencies have responsibilities regarding the use of antibiotics in agriculture. Approving antibiotics and setting allowable levels for antibiotic residues in food products is determined by the Department of Health and Human Services' Food and Drug Administration for animals and the Environmental Protection Agency for food plants. Testing for antibiotic levels in foods is performed by the Food Safety and Inspection Service for meat and poultry and by the Food and Drug Administration for eggs, milk, and food plants. Monitoring the development of resistance to antibiotics in humans, including resistance stemming from agricultural sources, is conducted under a program run jointly by the U.S. Department of Agriculture, the Food and Drug Administration, and the Department of Health and Human Services' Centers for Disease Control and Prevention.

The debate over whether to further regulate or restrict the use of antibiotics in animals and plants centers around the risk their use may pose to human health relative to their benefits to agriculture. This concern has prompted several European countries to ban the use in animal feed of four antibiotics that are considered very important in treating humans. Representatives of beef, pork, and poultry producers and pharmaceutical manufacturers assert that antibiotics play an important role in providing an abundant and affordable food supply. In their view, agricultural use is only one potential contributor to antibiotic resistance in humans and the research does not warrant restricting antibiotic use in agriculture. This debate exists within the federal government as well. The U.S. Department of Agriculture believes that more research is needed before decisions are made regarding the further regulation or restriction of antibiotic use in food animals. The Department of Health and Human Services, on the other hand, believes that based on the scientific evidence, steps are needed now—not at some time in the future—to decrease such use. However, the

Food and Drug Administration's recently proposed framework for evaluating the safety of antibiotics for use in food-producing animals does not include specific time frames for reevaluating currently approved antibiotics. The proposed framework targets new antibiotics and new uses of currently approved antibiotics. The framework will apply to the current uses of antibiotics only to the extent resources allow. We are recommending that the departments of Agriculture and Health and Human Services work together to develop and implement a plan with specific goals, time frames, and resources needed for determining the safe use of antibiotics in agriculture.

Background

Many infectious diseases—including pneumonia, tuberculosis, and common childhood ear infections—are caused by bacteria that have developed resistance to one or more previously effective antibiotics. Resistance may occur when the introduction of an antibiotic imposes "selective pressure" on an organism that has mutated by random genetic change. The antibiotic will not be able to kill the resistant strain of the organism. If susceptible bacteria are killed, remaining resistant bacteria may then become the dominant strain. For example, for nearly 40 years after penicillin was introduced, it was used successfully to treat pneumonia; today, penicillin-resistant strains of pneumonia are dominant in many countries. Also, disease-causing bacteria—or pathogens—may develop resistance spontaneously. For further information about the development of antibiotic resistance and the public health burden associated with resistant bacteria, see Antimicrobial Resistance: Data to Assess Public Health Threat From Resistant Bacteria Are Limited (GAO/HEHS/NSIAD/RCED-99-132, Apr. 28, 1999).[1]

Experts Believe the Use of Antibiotics in Agriculture Is Linked to the Emergence of Antibiotic Resistance

Antibiotics are used in both food-producing animals and on food plants to treat specific diseases afflicting specific animals and plants and to prevent the spread of diseases that are known to occur in particular herds, flocks, and crops under certain conditions. Antibiotics are also used in food animals to enhance their growth rate and feed efficiency—that is, increasing the amount of feed that is absorbed by the animal. Antibiotics used on animals may be obtained over-the-counter in feed stores and are included in commercially available animal feed. Antibiotics may also be dispensed under a veterinarian's prescription. For larger animals (such as cattle), antibiotics may be administered by injection or mixed with water; for smaller animals (such as poultry), they are generally mixed with feed

[1]An antimicrobial is a substance used to treat a bacterial, fungal, or viral infection.

or water. As a pesticide for disease treatment and prevention, antibiotics are generally sprayed onto plants. However, data are not available on the quantities of specific antibiotics used in agriculture and the purposes for which they are used. Appendix II presents information on the major classes of antibiotics, provides examples of specific antibiotics within each class, and indicates the antibiotics within that class have been approved for use on animals, plants, and/or humans.

Research Has Linked Three Diseases With Antibiotic-Resistant Strains Affecting Humans to the Use of Antibiotics in Animals

Experts, including those in the Department of Health and Human Service's (HHS) Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC), believe that resistant strains of three specific organisms that cause illness or disease in humans—*Salmonella*, *Campylobacter*, and *E. coli*—are linked to the use of antibiotics in animals. *Salmonella* and *Campylobacter* infections generally cause intestinal distress and do not require medical treatment.

However, each year several thousand persons have severe illnesses resulting in hundreds of deaths. Young children, the elderly, and patients whose immune systems are compromised are especially at risk. Severe cases of *Salmonella* have been associated with infections in the blood and the lining of the brain and other deep body tissue. According to CDC, each year an estimated 8,000 to 18,000 hospitalizations, 2,400 bloodstream infections, and 500 deaths are associated with *Salmonella* infections. One in 1,000 *Campylobacter* infections result in Guillain-Barre Syndrome, a disease that can cause paralysis. Most *E. coli* strains are relatively harmless in humans, but one strain causes a potentially serious illness in children and individuals with weakened immune systems. However, there are no current comprehensive estimates of the extent to which antibiotic-resistant strains of *Salmonella*, *Campylobacter* and *E. coli* have resulted in severe illnesses or deaths in humans. According to scientists at CDC, resistant strains of these organisms acquire resistance to antibiotics while in the animal. The resistant strain of the disease is then transferred to humans through food or through contact with animals or animal waste. A more detailed discussion of these organisms and their development of antibiotic resistance is presented in appendix II.

In addition to the direct foodborne transfer of antibiotic resistance from these three specific organisms, some research suggests that the use of antibiotics in food animals may reduce the effectiveness of related antibiotics used to treat humans. This concern is often raised about antibiotics administered in low doses over a continuous period, such as

those used in agriculture to promote animal growth. The research most often cited with this issue was conducted in Denmark during the early 1990s and concerns the closely related antibiotics avoparcin and vancomycin. Scientists there reported linking the use of avoparcin in animals to the emergence of vancomycin-resistant enterococci—generally known as VRE—in humans. VRE is an organism generally contracted in a hospital setting that causes serious, and in some cases untreatable, infections in humans.

In the United States, avoparcin has never been approved for use in agriculture or human medicine, and vancomycin has never been approved for use in agriculture. However, according to FDA officials, FDA discovered an instance in which avoparcin was used illegally in the United States in the production of veal and possibly other meat products. FDA pursued regulatory enforcement, and, according to officials, the individual responsible was convicted of a crime.

Vancomycin is an extremely important drug in the treatment of antibiotic-resistant bacterial infections in humans, many of which are serious and life-threatening and cannot be treated by any other currently approved antibiotic. According to CDC, the excessive use of vancomycin in human medicine is a primary cause for the rapid rise of VRE in the United States. Studies estimate that doctors inappropriately prescribe vancomycin in treating illnesses in humans 30 to 80 percent of the time.

While research is available on the emergence of antibiotic-resistant strains of foodborne pathogens, such as *Salmonella*, *Campylobacter*, and *E. coli*, for nonfoodborne human pathogens (such as VRE), agricultural use is only one factor that contributes to the problem of antibiotic resistance in humans. Only a few studies, primarily in Europe, have examined agriculture's contribution—relative to the contributions of other factors, such as the inappropriate prescribing of antibiotics in human medicine—to the development of resistance in nonfoodborne human pathogens. Appendix I identifies several studies, reports, and scientific articles by, among others, the National Research Council, World Health Organization, Institutes of Medicine, Office of Technology Assessment, and British House of Lords, that discuss and assess the research on these issues.

Several Agencies Have Responsibilities Regarding the Use of Antibiotics in Agriculture

Several federal agencies have roles involving the use of antibiotics in agriculture and a multiagency program—the National Antimicrobial Resistance Monitoring System-Enteric Bacteria—tracks the development of antibiotic-resistant strains of *Salmonella* and *Campylobacter* (see table 1).

Table 1: Federal Agencies' Roles Related to the Use of Antibiotics in Agriculture

Federal agencies	Approval for agriculture use	Testing for residual levels	Monitoring resistance development	Related monitoring programs
U.S. Department of Agriculture				
Agricultural Research Service			X	
Animal and Plant Health Inspection Service			X	X
Food Safety and Inspection Service		X	X	
Department of Health and Human Services				
Centers for Disease Control and Prevention			X	X
Food and Drug Administration	X		X	
Environmental Protection Agency				
Office of Pesticide Programs	X			

Two agencies are responsible for approving the use of antibiotics by the agriculture industry. FDA approves all antibiotics used for food-producing animals; the Environmental Protection Agency (EPA) approves antibiotics used as pesticides on produce and plants. FDA has approved many antibiotics for use on food-producing animals; EPA has approved two antibiotics for use on plants. FDA and EPA each establish maximum allowable residue levels (tolerances) for the antibiotics they approve and have regulatory authority to withdraw approvals, although withdrawing approval can be a lengthy and difficult process.

The U.S. Department of Agriculture's (USDA) Food Safety and Inspection Service (FSIS) operates a program to ensure that antibiotic residues in food products are within established limits. FSIS' National Residue Program tests meat and poultry products for antibiotic residues. These tests are

performed on the carcasses of slaughtered animals and on samples collected at ports of entry throughout the United States.[2]

The National Antimicrobial Resistance Monitoring System's-Enteric Bacteria program is the only federal program specifically focused on testing for antimicrobial resistance related to agriculture. The program was created in 1996 as a joint effort by FDA, CDC, and USDA. Initially, *Salmonella* was selected as the sentinel organism for tracking antibiotic resistance. Samples for this program are collected from humans in clinical settings and from animals in clinical and nonclinical settings. The samples are tested for susceptibility to 17 antibiotics. These antibiotics were selected because they are either commonly used in animal and/or human medicine or because they are very important to human medicine. CDC tests the samples collected from humans, and USDA tests the samples collected from animals. In 1997, the program was expanded to include testing of *Campylobacter* samples. The head of veterinary testing for this program told us that its scope has been relatively limited, however, because the resources devoted to it have been limited.

Two other federal programs collect information related to disease-causing organisms and antibiotic use, but neither is focused on antibiotic resistance. USDA's Animal and Plant Health Inspection Service operates the National Animal Health Monitoring System. Through this program, the agency conducts studies on animal health that include information about antibiotic use—the reasons producers use antibiotics, the way antibiotics are administered to the animals, and the size of producers' operations. The studies do not collect information about the quantities of antibiotics used. However, the program has contributed samples for the National Antimicrobial Resistance Monitoring System-Enteric Bacteria program. CDC operates the Foodborne Disease Active Surveillance Network—also known as FoodNet. This is a surveillance system designed to allow more accurate and precise estimates and interpretation of the prevalence of foodborne diseases over time.

[2]FSIS is planning to eventually include the testing of egg products in the National Residue Program.

Debate Is Ongoing Over the Potential Risk to Human Health From the Agricultural Use of Antibiotics

The debate over whether to further regulate or restrict the use of antibiotics in agriculture centers around the risk their use may pose to human health relative to their benefits to agriculture. Much of this debate concerns the uncertainty about whether and to what extent antibiotic resistance in humans may be acquired from the continued application of low doses of certain antibiotics in animal feeds. We first questioned the health implications of using antibiotics in animal feeds in 1977.[3] We noted that the safety and effectiveness of the practice had not been established and that the possibility existed that antibiotic-resistant bacteria may develop and be transferred from animals to humans. Among other things, we recommended that FDA determine the safety of antibiotics used in animal feeds on the basis of available data and withdraw approval of any not shown to be safe.

According to the Director of FDA's Center for Veterinary Medicine, in 1978, FDA proposed withdrawing approval of penicillin and tetracycline for other than disease treatment in animals. In response to concerns over the absence of definitive data to confirm that those antibiotics presented a hazard to human health, FDA contracted with the National Academy of Sciences to review the available data. According to a June 1980 report by a House appropriations subcommittee, the Academy's review found that "the postulated hazards to human health...were neither proven nor disproven." The Academy recommended that additional research be conducted to fill data gaps. The subcommittee report asked FDA to delay implementing its proposal pending the final results of the additional research and evidentiary hearings.

The World Health Organization, the United Nations' group responsible for monitoring global health, sponsored two recent conferences to examine the research on antibiotic resistance and agriculture. The first conference, in October 1997, addressed the medical impacts of the use of antimicrobials in food-producing animals. At the conclusion of this conference, scientists advocated (1) a more thorough assessment of the risks, (2) increased monitoring to detect the emergence of resistance, and (3) terminating the use of antibiotics for growth promotion in animals if they are also used in human medicine or are known to potentially become cross-resistant to antibiotics used in human medicine. Scientists attending the second conference in June 1998 recommended more research on the emergence of resistance to, and prudent practices for using, the class of antibiotics known as quinolones in animals.

[3]Need to Establish Safety and Effectiveness of Antibiotics Used in Animal Feeds (GAO/HRD-77-81, June 27, 1977).

Other Countries Believe Potential Human Health Risks Warrant Limiting Antibiotic Use in Agriculture

On the basis of their assessment of the potential risks, several countries have acted to reduce the agricultural use of antibiotics. The United Kingdom banned the use of penicillin and tetracycline for growth promotion in the early 1970s; other European countries followed suit shortly thereafter. Sweden banned the use of all antibiotics for growth promotion in 1986, and Denmark banned the use of one antibiotic in animal feed in 1998.[4] Canada's health department has called for a voluntary reduction in the amount of antibiotics used in agriculture. In December 1998, health ministers for the European Union voted to ban four antibiotics that were widely used to promote animal growth. They announced that they were taking this action as a precaution to minimize the risk of the development of resistant bacteria and to preserve the efficacy of certain antibiotics used in human medicine.[5] The ban is scheduled to become effective for the 15 members of the European Union on July 1, 1999.

Associations Representing Agriculture and Pharmaceutical Industries and Veterinarians Believe Restricting Antibiotics Is Not Warranted

In the United States, associations representing beef, pork, and poultry producers and pharmaceutical manufacturers have stated that restricting the use of antibiotics in agriculture is not warranted and is not supported by science. In their view, the use of antibiotics in agriculture is only one potential contributor to antibiotic resistance in humans and the extent of agriculture's contribution has not been determined. They also believe that the research does not warrant restricting the use of antibiotics in agriculture. These associations believe that antibiotics are vital to agricultural industries and contend that most producers are already using antibiotics prudently.

The Animal Health Institute, a trade association representing manufacturers of animal health products, including pharmaceuticals, has announced a plan that calls for (1) assessing the benefits and risks to humans from treating animals with antibiotics, (2) developing guidelines for prudently using antibiotics in farm animals, and (3) supporting improved surveillance and monitoring of the use of antibiotics.

Associations representing beef, pork, and dairy producers are also advising their members on antibiotic use. The National Cattlemen's Beef Association has advised its members to "strive to limit the need for

[4]Denmark's ban on virginiamycin went into effect in January 1998.

[5]The European Union, which is comprised of Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom, has proposed a ban on bacitracin zinc, spiramycin, virginiamycin, and tylosin phosphate.

[antibiotic] use through sound husbandry and preventative practices." Both the National Milk Producers Federation and the National Pork Producers Council have developed 10-point Quality Assurance programs that advise members how to properly use antibiotics during production.

The National Broiler Council told us that poultry producers use antibiotics prudently. Officials from Tyson, the nation's largest poultry producer, told us that the company stopped using antibiotics to promote animal growth more than 2 years ago and has been experimenting with alternative poultry production practices.

The American Veterinary Medical Association has been working with its members to develop a set of principles aimed at safeguarding public health and educating veterinarians on the potential risks posed by antibiotic use in agriculture. The proposed principles include (1) emphasizing appropriate animal husbandry and hygiene, routine health examinations, and vaccinations in preference to antibiotics; (2) considering therapeutic alternatives prior to using antibiotics; (3) avoiding, in initial therapy, those antibiotics that are considered important in treating infections in humans, and (4) avoiding the inappropriate use of antibiotics, such as for viral infections without bacterial complications.

Federal Efforts to Identify and Address Potential Risks

USDA, CDC, and FDA agree that antibiotics are critical in treating diseases in animals as well as humans. As we noted earlier, under the National Antimicrobial Resistance Monitoring System-Enteric Bacteria program, these agencies have been active in monitoring the emergence of antibiotic-resistant Salmonella since 1996 and resistant *Campylobacter* since 1997. They shared their concerns with us about the potential impact on human health from using antibiotics in agriculture. CDC and FDA agree that the agricultural use of antibiotics is a significant source of antibiotic resistance among foodborne pathogens. They also agree that the extent to which the agricultural use of antibiotics contributes to resistance in other—nonfoodborne—pathogens that cause diseases in humans is not precisely known, although evidence is increasing that these uses can be an important contributing factor.

USDA's activities have been limited to the testing and monitoring that the Food Safety and Inspection Service, the Animal and Plant Health Inspection Service, and the Agricultural Research Service do under the National Antimicrobial Resistance Monitoring System-Enteric Bacteria program. With regard to the debate over whether to further regulate or

restrict the use of antibiotics in agriculture, USDA believes that, before any decisions are made, more research is needed to determine how animals acquire resistant strains of *Salmonella*, *Campylobacter*, and *E. coli*. USDA also believes that research is needed to determine the extent to which environmental sources contribute to the development of resistance in these pathogens. In addition, according to USDA officials, the potential health risks to humans from using antibiotics to promote animal growth need to be weighed against the economic benefits to the consumers of this use.

CDC's experts have advocated several measures to reduce the use of antibiotics in agriculture. CDC researchers believe that some antibiotics should not be used in animal feed to promote growth. These researchers told us that, in treating diseases, veterinarians need to ensure that they are prescribing the appropriate doses of antibiotics. To prevent the spread of disease, alternatives to antibiotics—such as improved hygiene and sanitation, feed safety, and "direct-fed microbials"—good or harmless bacteria that can be used to outcompete harmful or bad bacteria—should be used when appropriate. With regard to promoting growth in animals, CDC supports restricting the use of antibiotics because CDC believes such use results in antibiotic resistance that is transmitted to humans through the food supply and may limit treatment options in ill persons. CDC has specifically suggested that FDA reconsider its approval of penicillin and tetracycline for promoting growth in animals, as well as its approval of fluoroquinolones for disease treatment and prevention in poultry. According to CDC, fluoroquinolones are vital antibiotics for the treatment of serious *Salmonella* and *Campylobacter* infections in humans.

According to FDA officials, the development of fluoroquinolone-resistant strains of *Salmonella* and *Campylobacter* highlights the need to better address the potential development of bacterial resistance as part of the safety determination prior to approving new antibiotics for use in food-producing animals. FDA has publicly stated that the current regulatory structure is inadequate to properly evaluate the human health impact of antibiotic resistance from the use of antibiotics in food-producing animals. To address these concerns, in November 1998 FDA's Center for Veterinary Medicine published Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food- Producing Animals. This framework is intended to provide a mechanism for evaluating and ensuring the human safety of antibiotics and other antimicrobials used in food animals, including those used for growth promotion.

The proposed framework includes components for assessing antibiotics on the basis of (1) the importance of the antibiotic to human medicine, (2) preapproval data showing a safe level of resistance transfer, (3) the establishment of thresholds for monitoring safe resistance levels, (4) the effect of proposed uses on human pathogen load, and (5) post approval studies and monitoring. The Animal Health Institute objects to the post-approval monitoring requirements of FDA's proposed framework, saying that it would be cost-prohibitive and that it is not justified from a public health standpoint.

HHS noted that the framework sets out a conceptual risk-based process, the goal of which is to ensure that the antibiotics that are significant in human treatment are not lost because of the use of antimicrobials in animals while also providing for the safe use of antimicrobials in animals. The proposed framework includes a footnote indicating that the agency anticipates that the framework will be used, as resources allow, to review existing approved uses of antibiotics on food-producing animals. Although FDA officials told us that they intend to use the framework for evaluating the safety of all antibiotics currently approved, the framework does not specify a specific strategy and time frame for this reevaluation. In January 1999, FDA convened a public meeting to discuss and obtain comments on the proposed framework. FDA is in the process of revising the framework in response to the meeting and the written comments it has received.

Finally, although FDA officials told us in July 1998 that they shared CDC's concerns about fluoroquinolone resistance, FDA has not initiated an action to withdraw its earlier approval for the use of fluoroquinolones on poultry. In addition, FDA approved fluoroquinolones for use on beef cattle in August 1998.

Conclusions

Although research has linked the use of antibiotics in agriculture to antibiotic-resistant strains of specific foodborne pathogens that affect humans, agricultural use is only one factor in the emergence of antibiotic resistance in nonfoodborne pathogens. Debate exists over whether the role of agricultural use in the overall burden of antibiotic-resistant infections of humans warrants further regulation or restriction. CDC believes the potential human health risks call for action to restrict antibiotics for growth promotion in animals. We first raised concerns in 1977 about the potential human health risks of this practice. Today, more than two decades later, federal agencies have not reached agreement on

the safe use of antibiotics in agriculture. In developing a federal response, both human health concerns and the impact on the agriculture industry are factors to consider.

Recommendation to the Secretaries of Agriculture and Health and Human Services

In light of the emergence of antibiotic resistance in humans, questions about the extent that the agricultural use of antibiotics contributes to the human health burden, and the debate over whether further regulation or restriction of use in agriculture is needed, we recommend that the Secretaries of Agriculture and of Health and Human Services develop and implement a plan that contains specific goals, time frames, and resources needed to evaluate the risks and benefits of the existing and future use of antibiotics in agriculture, including identifying and filling critical data gaps and research needs.

Agency Comments

We provided copies of a draft of this report to USDA, HHS, and EPA for their review and comment. To obtain USDA's comments, we met with officials in the Food Safety and Inspection Service; the Animal and Plant Health Inspection Service; and the Agricultural Research Service, including the Associate Deputy Administrator for Animal Production, Product Value and Safety. HHS provided written comments, which appear with our response in appendix IV. EPA had no formal comments on the draft report. The agencies also provided technical comments that we incorporated throughout the report as appropriate.

USDA generally found the draft report to be an accurate presentation of the facts and agreed with the recommendation but believed the draft overstated the extent to which antibiotic use in agriculture may be linked to the emergence of antibiotic resistance in humans. USDA acknowledged that the use of antimicrobials can lead to the development of resistance but does not believe that there is consensus among experts that research has linked the use of antibiotics in agriculture to the emergence of resistant strains of *Salmonella*, *Campylobacter*, and *E. coli* in humans. USDA also commented that more research is needed before decisions are made to further regulate or restrict the use of antibiotics in agriculture. We have incorporated USDA's positions into the report.

HHS, on the other hand, believed the draft report did not fully recognize what HHS believes is the current state of knowledge—the increasing body of evidence pointing to the connection between the agricultural use of antibiotics and resistant foodborne illnesses, and the potential adverse

human health consequences of antibiotic use in agriculture. Noting that preventive action is needed now, the Department stated, "steps need to be taken to decrease the use in agriculture of antibiotics that contribute to the development of resistant strains of human pathogens." It also pointed out that the public health community is concerned not only with the growth promotion uses of antibiotics in agriculture but also with uses to treat and prevent disease, which "can be significant contributors to the pool of resistant microorganisms that enter the food chain" and often involve "critical drugs of last resort in treating a variety of human infections." While the Department believes no further research is needed to prove the link for foodborne pathogens, it does believes more research would be beneficial in assessing agricultural practices that can reduce antimicrobial use, identifying the types of use that are high or low risk, and better understanding the potential risks of resistance transfer from animal organisms other than typical foodborne pathogens.

With regard to our recommendation, HHS pointed out that under the Food and Drug Administration's proposed framework, applicants would have to conduct tests to determine the potential for inducing resistance for new animal drugs. It also stated that the framework would allow the Food and Drug Administration to withdraw already marketed antibiotics. While we agree that the framework is an important step, especially for developing data on antibiotic use, it does not include specific goals and time frames. Moreover, the proposal states that currently approved antibiotics and their uses will be assessed only to the extent resources allow. Without a specific plan, goals, time frames, and the identification of needed resources for such assessments, human health concerns that were raised more than two decades ago may remain unanswered. Finally, the disparity between USDA's and the HHS' views further highlights the need for the departments to work together to ensure that both human health concerns and the impact on the agriculture industry are considered. We have incorporated HHS' comments into the report as appropriate.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 14 days from the date of this letter. At that time, we will send copies of this report to the Honorable Richard Lugar, Chairman, Senate Committee on Agriculture, Nutrition, and Forestry; the Honorable Larry Combest, Chairman, and the Honorable Charles Stenholm, Ranking Minority Member, House Committee on Agriculture; the Honorable James Jefford, Chairman, and the Honorable Edward M. Kennedy, Ranking Minority Member, Senate

Committee on Health, Education, Labor, and Pensions; and the Honorable Tom Bliley, Chairman, and the Honorable John Dingell, Ranking Minority Member, House Committee on Commerce. We will also send copies to the Honorable Dan Glickman, Secretary of Agriculture; the Honorable Donna Shalala, Secretary of Health and Human Services; the Honorable Carol Browner, Administrator, Environmental Protection Agency; the Honorable Jane Henney, M.D., Commissioner, Food and Drug Administration; the Honorable Jeffrey P. Koplan, M.D., Director, Centers for Disease Control and Prevention; the Honorable Jacob J. Lew, Director, Office of Management and Budget; and other interested parties. We will also make copies available to other on request.

If you any questions about this report, please contact me at (202) 512-5138. Major contributors to the report are listed appendix V.

Lawrence J. Dyckman
Director, Food and Agriculture Issues

Contents

Abbreviations

APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
CDC	Centers for Disease Control and Prevention
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FSIS	Food Safety and Inspection Service
HHS	Department of Health and Human Services
VRE	vancomycin-resistant enterococci
USDA	Department of Agriculture

Objectives, Scope, and Methodology

This report examines (1) how antibiotics are used in agriculture and the implications of that use for human health; (2) federal roles and responsibilities for overseeing the use of antibiotics in agriculture; and (3) issues surrounding the debate over whether to further regulate or restrict the use of antibiotics in agriculture.

To determine how antibiotics are used in agriculture, we spoke with officials from the Center for Veterinary Medicine in the Food and Drug Administration (FDA); the Office of Pesticide Programs in the Environmental Protection Agency (EPA); and the Agricultural Research Service (ARS), Animal and Plant Health Inspection Service (APHIS) and Food Safety and Inspection Service (FSIS) in the U.S. Department of Agriculture (USDA). We also met with officials representing specific agricultural industries, including the National Pork Producers Council, the National Milk Producers Federation, the National Broiler Council, and the National Cattlemen's Beef Association. In addition, we spoke with officials from the American Feed Industry Association, the American Veterinary Medical Association, and the Animal Health Institute. From these meetings, we also identified the classes of antibiotics with examples of specific antibiotics approved for agriculture and the agricultural use for which they are approved. For comparison, we used the Physicians' Desk Reference to identify classes of antibiotics and examples of antibiotics used on humans.

To determine the implications for human health of the agricultural use of antibiotics, we reviewed the relevant research findings of studies, reports, and other scientific and medical literature, including, among others, "The Use of Drugs in Food Animals: Benefits and Risk;" National Research Council, July 9, 1998; "The Medical Impact of the Use of Antimicrobials in Food Animals," World Health Organization, October 1997; Workshop Report, "Orphans and Incentives: Developing Technologies to Address Emerging Infections," Institute of Medicine, 1997; Workshop Report, "Antimicrobial Resistance: Issues and Options," Institute of Medicine,1998; Impacts of Antibiotic-Resistant Bacteria," U.S. Congress, Office of Technology Assessment (OTA-H-629; Washington, D.C., U..S. Government Printing Office, September 1995); "Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine," November 1969 (Swann Report); the British House of Lords, Select Committee on Science and Technology Seventh Report; "Emergence of Multidrug-Resistant *Salmonella Enterica* Serotype Typhimurium DT-104 Infections in the United States," The New England Journal of Medicine (May 1998); "Technology Crisis and the Future of Agribusiness: Antibiotic

Resistance in Humans and Animals," Harvard Business School, July 1997; "Can We Use Less Antibiotics?" Swedish Ministry of Agriculture, Food, and Fisheries, 1997; "Protecting the Crown Jewels of Medicine, A strategic plan to preserve the effectiveness of antibiotics." Center for Science in the Public Interest, 1998. We met with officials and scientists from the Centers for Disease Control and Prevention (CDC), FDA and USDA and other experts, both in and out of government, to obtain their expert opinions of the studies and research that has been done on the subject.

To determine federal roles and responsibilities for overseeing the use of antibiotics in agriculture, we spoke with officials and collected data from FDA, EPA, CDC, and USDA's Agricultural Research Service, Animal and Plant Health Inspection Service, and Food Safety and Inspection Service. We also reviewed applicable laws and regulations for these agencies.

To determine the issues surrounding the debate over whether to further regulate or restrict the use of antibiotics in agriculture, we reviewed and analyzed reports and documents published by, among others, the Institute of Medicine, the National Research Council, the Office of Technology Assessment, CDC, FDA, USDA, EPA, agricultural industry associations, the New England Journal of Medicine, and the World Health Organization. We discussed the issues with officials from the National Institutes of Health, CDC, FDA, USDA, EPA, and the World Health Organization, and from associations representing agricultural associations, veterinarians, and pharmaceutical manufacturers.

We performed our review from May 1998 through April 1999 in accordance with generally accepted government auditing standards.

Approved Uses of Selected Classes of Antibiotics in the United States

Table II.1 lists major classes of antibiotics, provides examples of specific antibiotics within each class, and indicates whether any antibiotics within the class have been approved for use on animals, plants, and/or humans. Based on information in the Physicians' Desk Reference, this classification of antibiotics is grouped according to specific characteristics, such as similarities in chemical composition or in the way they kill or inhibit bacterial organisms. (The Physicians' Desk Reference provides the latest available information on more than 2,500 specific pharmaceutical products. Each entry provides an exact copy of the product's FDA-approved labeling.) While the table shows that many classes of antibiotics approved for use in agriculture are also approved for use in human medicine, it is important to note that the antibiotics cited as examples may or may not be the antibiotic approved for a particular use. For example, only two antibiotics have been approved for use on food plants: streptomycin, which is an antibiotic in the class of aminoglycosides, and oxytetracycline, an antibiotic in the class of tetracyclines.

Table II.1: Major Classes of Antibiotics, Examples in Each Class, and Approval for Use on Animals, Plants, and/or Humans

		Agriculture				
		Animals				
Antibiotic classes (selected examples)	**Species**	**Disease treatment**	**Disease prevention**	**Growth promotion**	**Plants**	**Humans**
Aminoglycosides (gentamicin, neomycin, streptomycin)	beef cattle, goats, poultry,[a] sheep, swine, certain plants	•	•		•	•
Beta-Lactams — penicillins (amoxocillin, ampicillin)	beef cattle, dairy cows, fowl,[b] poultry, sheep, swine	•	•	•		•
—Cephalosporins 1st generation (cefadroxil)						•
—Cephalosporins 2nd generation (cefuroxime)						•
—Cephalosporins 3rd generation (ceftiofur)	beef cattle, dairy cows, poultry, sheep, swine	•	•			•
Chloramphenicol						•
Florfenicol	beef cattle	•				

(continued)

Antibiotic classes (selected examples)	Species	Agriculture: Animals: Disease treatment	Agriculture: Animals: Disease prevention	Agriculture: Animals: Growth promotion	Agriculture: Plants	Humans
Cycloserines (cycloserine)						•
Glycopeptides (vancomycin)						•
Ionophores (monensin, salinomycin, semduramicin, lasalocid)	beef cattle, fowl, goats, poultry, rabbits, sheep		•	•		
Lincosamides (lincomycin)	poultry, swine	•	•			•
Macrolides (erythromycin, tilmicosin, tylosin)	beef cattle, poultry, swine	•	•	•		•
Monobactams (aztreonam)						•
Polypeptides (bacitracin)	fowl, poultry, swine	•	•	•		•
Quinolones Fluoroquinolones (sarafloxacin, enrofloxacin)	beef cattle, poultry	•	•			•
Streptogramins (virginiamycin)	beef cattle, poultry, swine	•	•	•		
Sulfonamides (sulfadimethoxine, sulfamethazine, sulfisoxazole)	beef cattle, dairy cows, fowl, poultry, swine, catfish, trout, salmon	•		•		•
Tetracyclines (chlortetracycline, oxytetracycline, tetracycline)	Beef cattle, dairy cows, fowl, honey bees, poultry, sheep, swine, catfish, trout, salmon, lobster, certain plants	•	•	•	•	•
Other antibiotics						
Bambermycin	beef cattle, poultry, swine		•	•		
Carbadox	swine		•	•		•
Novobiocin	fowl, poultry	•	•			•
Spectinomycin	poultry, swine		•			•

(Table notes on next page)

[a]Poultry includes at least one of the following birds: broiler chickens, laying hens, and turkeys.

[b]Fowl includes at least one of the following birds: ducks, pheasants, and quail.

Source: GAO

Antibiotic-Resistant Strains Have Emerged in Three Food-Related Organisms That Cause Diseases in Humans

Federal experts believe that research has linked the use of antibiotics in agriculture to the emergence of antibiotic-resistant strains of three disease-causing organisms. These organisms, which are known to cause illness or disease in humans, are *Salmonella*, *Campylobacter*, and *Escherichia coli*, commonly known as E. coli.

Salmonella

Salmonella is an organism commonly found in poultry, eggs, beef, and other foods of animal origin. According to public health officials, an estimated 800,000 to 4 million cases of *Salmonella* infections occur each year in the United States. *Salmonella* typically causes intestinal distress and does not require medical treatment. However, severe cases of *Salmonella* have been associated with reactive arthritis, as well as with infections in the blood, in the meningeal linings of the brain, and in other deep body tissues. Persons experiencing severe symptoms often seek medical treatment. According to CDC, each year an estimated 8,000 to 18,000 hospitalizations, 2,400 bloodstream infections, and 500 deaths are associated with *Salmonella* infections. Also, according to CDC, 40 percent of people with a *Salmonella* infection who seek medical attention are treated with antibiotics.

One particularly serious strain of *Salmonella*—*Salmonella* DT-104—is known to be resistant to several antibiotics. CDC estimates that between 68,000 and 340,000 cases of Salmonella DT-104 occur annually in the United States. About 95 percent of *Salmonella* DT-104 strains are resistant to five antimicrobials—ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. Human illness from Salmonella DT-104 was first recognized in the United Kingdom in the mid-1980s. In 1993, veterinarians in England began to treat poultry with fluoroquinolones, an important class of antibiotics for treating diseases in humans. By 1996, United Kingdom scientists reported that 14 percent of the Salmonella DT-104 strains had a decreased susceptibility to fluoroquinolones. Scientists are very concerned about the development of fluoroquinolone-resistant Salmonella, because fluoroquinolones are the drugs of choice to treat *Salmonella* infections in adults. Although fluoroquinolone-resistant *Salmonella* infections are currently rare in the United States, there has been a trend of decreasing susceptibility to fluoroquinolones since they were first approved for agricultural use in 1995.

Campylobacter

Campylobacter is also an organism commonly found in poultry and other food of animal origin, including pork and beef. According to public health officials, 2 million to 4 million people suffer Campylobacter infections annually. *Campylobacter* infections generally cause intestinal distress and do not require medical treatment. However, one in every 1,000 reported cases of *Campylobacter* results in Guillain-Barre Syndrome, a disease associated with paralysis. The first case of domestically acquired fluoroquinolone-resistant *Campylobacter* in humans in the United States were identified in 1996, shortly after FDA approved fluoroquinolones for use in poultry. World Health Organization scientists concluded that prior to the use of fluoroquinolones in animals, there had been no reports of fluoroquinolone-resistant *Campylobacter* infections in humans who had no previous exposure to this class of antibiotics. CDC scientists believe this provides evidence that antibiotic-resistant strains of *Campylobacter* are transmitted directly from animals to humans.

E. Coli

Although many strains of *E. coli* are carried normally in the intestines of humans and animals, some strains cause foodborne illnesses. One strain—*E. coli* O157:H7—causes potentially serious illness, particularly for children and individuals with weakened immune systems. Each year in the United States, an estimated 50 to 100 people die from *E. coli* 0157:H7 infections. Although antibiotics are not the recommended treatment for *E. coli* O157:H7 infections, antibiotics are often given because of the symptoms displayed in the patient and because some doctors believe antibiotics will help. Antibiotic-resistant strains of *E. coli* O157:H7 have been identified in animals, food, and humans, and the emergence of antibiotic resistance in *E. coli* O157:H7 is of concern to scientists because laboratory studies have demonstrated that organisms may exchange genes, including the gene that allows an organism to resist an antibiotic.

Comments From the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of Inspector General

Washington, D.C. 20201

APR - 7 1999

Lawrence J. Dyckman
Director, Food and Agriculture Issues
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Dyckman:

Enclosed are the Department's comments on your draft report entitled, "Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department also provided extensive technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

Michael Mangano

for June Gibbs Brown
Inspector General

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for General Accounting Office reports. The OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

Department of Health and Human Services Comments on the General Accounting Office Draft Report Entitled, FOOD SAFETY: The Agricultural Use of Antibiotics and Its Implications for Human Health GAO/RCED-99-74

The Department of Health and Human Services has reviewed the draft report and has the following comments.

See comment 1.

Overall, we find that the draft report oversimplifies the public health issues surrounding the agricultural use of antibiotics. It does not fully recognize the current state of knowledge, the increasing body of information available that points to a connection between agricultural uses of antimicrobials and food-borne illnesses, or the Department's position on the potential adverse human health consequences of antibiotic use in agriculture. Furthermore, we believe the problem of drug resistance is more complex than implied by the draft report.

See comment 2.

Drug resistant human infections may be acquired in the community, in the health care system, through the food supply, or internationally. Generally, the pathogens in each of these settings are different. Drug resistant community-acquired respiratory infections have developed primarily because of heavy use of antibiotics to treat respiratory infections, including colds and the influenza for which antibiotics are unnecessary. Drug resistant infections in hospitals and nursing homes have developed primarily because of heavy use of antibiotics in these institutions. Drug resistant food-borne infections such as *Salmonella* may be linked to the use of antimicrobials in food-producing animals.

See comment 3.

There is a pressing need to promote more prudent antibiotic use in each setting. It is not possible, however, to quantify the contribution of drug use in one setting to the entire multifaceted problem of drug resistance in humans. Therefore, we do not believe it is accurate or appropriate to consider that a major scientific objective should be to examine agriculture's contribution relative to other factors, such as the use of antibiotics in human medicine or to say that little is known about the extent to which agricultural use is a factor. The contribution of drug use in animals versus drug use in humans to development of the total pool of bacterial resistance genes in the ecosphere is, indeed, unknown, but the fact that use of antimicrobials in agriculture contributes to resistance in food-borne pathogens has been established.

See comment 4.

The Department's position on the issue of antimicrobial use in food-producing animals is also more complex than stated in the draft report. The Food and Drug Administration's (FDA) recently published *Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-producing Animals* (Framework or Framework Document) provides a mechanism for evaluating and ensuring the human safety of antimicrobial drugs used in food animals, including growth promotant uses. The Framework Document sets out a conceptual risk-based process for evaluating the microbial safety of antimicrobial drugs intended for use in food-producing animals. The goal of this process is to protect the public health by ensuring that significant human antimicrobial therapies are not lost because of the use of antimicrobials in food-producing animals while also providing for the safe use of antimicrobial drugs in animals. While FDA and the Centers for Disease Control and Prevention (CDC) agree that growth promotants, because they are

administered for long time periods at sub-inhibitory levels deserve careful scrutiny, a major advantage of the Framework is that it addresses all uses of antibiotics in food-producing animals. All uses would not be addressed by a simple ban on growth promotants. The CDC strongly supports the proposed FDA Framework as an important step forward and is committed to working with FDA and other partners to promote its effective implementation. The Framework should be addressed fully in GAO's report if the public is to be appropriately informed regarding these issues, and if Congress is expected to utilize the report in making public policy regarding antimicrobial resistance.

See comment 5.

See comment 6.

The draft report does not include data from the National Antimicrobial Resistance Monitoring System (NARMS): Enteric Bacteria, which suggest a trend of increasing antimicrobial resistance, including increasing multi-drug resistance, among *Salmonella* and *Campylobacter*. Also, the draft report does not mention that the lack of detailed animal drug use information (e.g., by species, region, and type of usage) is a barrier to advancing scientific discussions on the adverse human health consequences of antibiotic use in agriculture. These data should be available from the animal health industry, and would be obtained through implementation of the proposed FDA Framework.

See comment 7.

We believe the draft report (as have segments of industry) does not distinguish the link between the agricultural use of antimicrobials and resistance emergence in food-borne pathogens such as *Salmonella* and *Campylobacter*, for which there is a link, from other antimicrobial uses for which the link is less clear (i.e., nonfood-borne pathogens.) The report thereby lends support to the assertions by animal producers and pharmaceutical manufacturers that little is known about the role agricultural use of antimicrobials plays in resistance development. We strongly disagree with their position, and believe the report would be more informative and accurate if it presented a balanced perspective with respect to the body of knowledge regarding resistance of food-borne diseases. As written, the report could interfere with FDA's ability to go forward with its proposed program for reducing the extent to which resistance to antimicrobials is induced through their agricultural use.

See comment 8.

The report does not articulate the difficult and unresolved issue of the transfer of resistance elements from non-pathogenic organisms to human pathogens. Such non-pathogens can also become resistant to antimicrobials and may result in the transfer of resistance to both food-borne and nonfood-borne pathogens in humans.

See comment 9.

The report does not correctly state the extent to which *Salmonella* and *Campylobacter* pose a threat to humans. *Salmonella* and *Campylobacter* infections generally cause self-limited intestinal infections; however, the illnesses can cause severe symptoms. Each year an estimated 8,000-18,000 hospitalizations, 2,400 bloodstream infections, and 500 deaths are associated with *Salmonella* infections, as are infections of the lining of the brain and other deep body tissues. This is of particular concern for young children, elderly people, and immune-compromised people. In addition, *Campylobacter* infection appears to be major cause of the paralyzing disease, Guillain-Barre Syndrome.

See comment 10.

The report does not acknowledge that the concerns of the public health community are not limited

to growth promotion uses of antibiotics in agriculture, but also extend to therapeutic and prophylactic uses. Both uses can be significant contributors to the pool of resistant microorganisms that enter the food chain. These nongrowth-promoting uses cannot be ignored because they often involve the use of newer antimicrobials which have become critical drugs of last resort in treating a variety of human infections.

GAO Recommendation

In light of the emergence of antibiotic resistance in humans and the recognition that science has not determined the extent that the agricultural use of antibiotics contributes to this resistance, we recommend that the Secretaries of Agriculture and Health and Human Services develop a plan with specific goals and time frames for evaluating the safety of antibiotics as they are used in agriculture, including identifying any data and research needs.

Department Comment

The Department agrees that steps need to be taken to decrease the use in agriculture of antibiotics that contribute to the development of resistant strains of human pathogens. To that purpose, FDA has initiated an endeavor to require sponsors of New Animal Drug Applications to conduct tests appropriate to determining an antibiotic's potential for inducing resistance. Criteria are being established to help determine which food-animal drug uses can be safe. We do not agree, however, that for food-borne pathogens "...science has not determined the extent that the agricultural use of antibiotics contributes to ... resistance...." This claim made by the animal drug industry and human-food-animal producers is not substantiated. Both CDC and FDA scientists disagree with this position, based on recent and increasing epidemiologic and genetic evidence linking food animal use of antimicrobials to the development of antibiotic resistance in food-borne pathogens. As mentioned above, this statement should only be used to describe the role of agricultural use of antimicrobials in the generation of resistant nonfood-borne pathogens.

See comment 11.

We believe that preventive action is needed now, not at some time in the future. FDA efforts to create a new process for approval of safe antimicrobials (or, where merited, withdrawal of already marketed antimicrobials) for either therapeutic or subtherapeutic uses in food-producing animals are well underway and should not be delayed. In addition, more support is needed for the surveillance and monitoring of resistance development, including augmentation of NARMS: Enteric Bacteria. Such preventive action would be prudent to help reduce the future risk of outbreaks of treatment resistant food-borne illnesses.

While we do not agree that further research is needed to prove the link between food-animal antimicrobial use and drug resistance in food-borne infections of humans, we do agree that more research and data would be beneficial in certain related areas. These include developing and assessing agricultural practices which can reduce antimicrobial use, identifying types of use which are high or low risk, and better understanding the potential risks of resistance transfer from animal organisms other than typical food-borne pathogens. In fact, multiple Federal agencies are currently engaged in a process for developing a public health action plan to combat antimicrobial resistance. This process will include multiple opportunities to obtain expert consultation and

public comment. The FDA's proposed Framework and the data it will generate will provide important new knowledge that will contribute significantly to the overall effort.

GAO's Comments

1. We recognize the complexity of antimicrobial resistance and have reviewed the considerable body of research on the human health implications of the agricultural use of antibiotics. However, this report is not intended to be a complete technical assessment of the public health issues surrounding the agricultural use of antibiotics. Rather, it provides information on agricultural use and the implications of that use for human health, federal roles and responsibilities regarding the use of antibiotics in agriculture, and the issues surrounding the debate over whether to further regulate or restrict agricultural use. With regard to this debate, we present the many divergent, sometimes conflicting, viewpoints. For a more technical discussion of this complex public health issue, with citations to several specific research papers, see Antimicrobial Resistance: Data to Assess Public Health Threat From Resistant Bacteria Are Limited (GAO/HEHS/NSIAD/RCED-99-132, Apr. 28, 1999).

2. The report acknowledges that the factors that contribute to antibiotic resistance include the nature of pathogens, environmental pressures, and the use of antibiotics in human medicine and in agriculture. The report also discusses three antibiotic-resistant foodborne infections linked to the use of antibiotics in food-producing animals.

3. It was not our intent to suggest that a major scientific study should be undertaken to quantify agriculture's contribution to the resistance problem relative to other factors. However, the report does recognize that there is not consensus on agriculture's role. Indeed, the U.S. Department of Agriculture (USDA) does not believe there is consensus among experts that research has linked the use of antibiotics in agriculture to the emergence of resistant strains of *Salmonella*, *Campylobacter*, and *E. coli* in humans. We revised the report to clarify the Department of Health and Human Services' (HHS) positions that research has established that the use of antimicrobials in agriculture contributes to resistant foodborne pathogens and that there is a pressing need to promote the more prudent use of antibiotics in each setting.

4. HHS notes that growth promotants deserve careful scrutiny but that a simple ban on growth promotants would not address all uses of antibiotics in agriculture. HHS states that the Food and Drug Administration's (FDA) proposal: Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals will address all uses of antibiotics in agriculture. While the framework is an important step forward, it does not include specific goals and time frames for such

assessments to help ensure that needed evaluations occur in a timely manner. Moreover, the framework will be applied to currently approved antibiotics—including currently used growth promotants—only to the extent resources allow. We revised the report to clarify HHS' position on the issue of antibiotic use in food-producing animals and to more fully describe FDA's proposal.

5. The report text discusses the National Antimicrobial Resistance Monitoring System-Enteric Bacteria program, and appendix II discusses the emergence of multidrug-resistant strains of foodborne diseases.

6. HHS notes that the draft report did not mention that the lack of detailed animal drug use information is a barrier to advancing scientific discussion on the adverse human health consequences of antibiotic use in agriculture. HHS states that the implementation of FDA's framework would obtain these data. We have revised the report to acknowledge that data are not available on the quantities of specific antibiotics used in agriculture and the purposes for which they are used. Our recommendation directs HHS and USDA to identify data gaps as part of a plan for evaluating the risks and benefits of existing and future uses of antibiotics in agriculture. As stated previously, however, we do not agree that the implementation of FDA's framework would obtain these data in a timely fashion for new antibiotic uses or, necessarily, at any time for existing uses.

7. As our report states, only a few studies, primarily conducted in Europe, have examined agriculture's contribution to the development of resistance in nonfoodborne human pathogens. We believe our report presents a balanced perspective with respect to the positions of industry, researchers, and federal agencies. However, in recognition of the different perspectives on the issue, we modified the recommendation to focus on the debate over the need to further regulate or restrict the agricultural use of antibiotics.

8. While our report does not discuss in detail the transfer of resistance from nonpathogenic organisms to human pathogens, which, as HHS points out, is a difficult and unresolved issue, it does discuss the development of resistance from other than direct pathogen transfer and the fact that laboratory studies have demonstrated that organisms can exchange genes, including the gene that allows resistance.

9. We revised the report to include the data on the extent to which *Salmonella* and *Campylobacter* pose a threat to humans.

10. HHS also pointed out that the public health community is concerned not only with growth promotion uses of antibiotics in agriculture but also with disease treatment and prevention uses, which "can be significant contributors to the pool of resistant microorganisms that enter the food chain" and often involve "critical drugs of last resort in treating a variety of human infections." It was not our intent to suggest otherwise. Our report discusses several antibiotics that are importance to human medicine that have been approved for use on animals, including fluoroquinolones, which FDA has recently approved for disease treatment on poultry and cattle. We included this comment in the Agency Comments section of the report.

11. Finally, with regard to our recommendation, HHS pointed out that under FDA's proposed framework, applicants would have to conduct tests to determine new animal drugs' potential for inducing resistance. HHS also stated that the framework would allow FDA to withdraw already marketed antibiotics. As we noted earlier, the FDA framework is an important step, especially for developing data on antibiotic use; however, the proposal states that currently approved antibiotics and their uses will be assessed only to the extent resources allow. Moreover, without a specific plan, goals, time frames, and the identification of needed resources for such assessments, human health concerns that were raised more than two decades ago may remain unanswered.

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