USDA/HHS Response to the House and Senate Reports: Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2000

Antibiotic Resistance in Livestock

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Executive Summary

In its April 1999 report, "The Agricultural Use of Antibiotics and Its Implications for Human Health" (GAO/RCED – 99 – 74 Food Safety), GAO made the following recommendation: "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."

In their reports accompanying FY2000 appropriations for Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, the Committees on Appropriations in both Houses asked the Secretaries of Agriculture and of Health and Human Services to implement GAO's recommendation and develop a joint strategy for addressing antimicrobial resistance. This document explains the strategy and includes a timetable and budget for tackling the problem of agricultural antimicrobial use and the emergence of antimicrobial resistance. The House and Senate Committees on Appropriations also asked for a strategy to conduct a risk assessment of the human health risk linked to on-farm antimicrobial use. The House Committee further directed the report to compare the risk of resistance in foodborne pathogens from the on-farm use of antimicrobials with that of the other uses of antimicrobials. The House and Senate Committees also directed that the report detail how the results of the risk assessment would be incorporated into regulations governing the use and approval of on-farm antimicrobials.

More than a dozen Federal agencies have an interest in the problem of antimicrobial resistance, and several of these agencies have responsibilities regarding the use of antimicrobials in agriculture. Coordinated interagency efforts toward an effective public health response to the problem began several years ago.

In 1996, the Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM); Centers for Disease Control and Prevention (CDC); and United States Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS), Agricultural Research Service (ARS) and Animal and Plant Health Inspection Service (APHIS) launched the National Antimicrobial Resistance Monitoring System (NARMS). It is a surveillance system for antimicrobial resistance in foodborne pathogens. Coordinated efforts continued under the President's Food Safety Initiative (FSI), announced in 1997. The FSI laid out a multi-year strategy coordinating agency efforts in the prevention of foodborne illness, with program areas of surveillance, research, education, risk assessment, inspection, and coordination. The FSI clearly articulated agencies' roles to prevent the emergence of antimicrobial resistance in foodborne pathogens. FSI funding has supported expansion of

NARMS, research programs, education programs on judicious antimicrobial use, and the first FDA risk assessment on antimicrobial resistance in a foodborne pathogen.

Recognizing the diversity of agencies responsible for food safety, Congressional funding of the FSI has served a key role in establishing a coordinated approach to food safety and antimicrobial resistance. In keeping with a commitment to implementing a long-term strategy for harmonized Federal action, the President created the President's Council on Food Safety in 1998, co-chaired by the Secretaries of Agriculture and Health and Human Services, and the Director of the White House Office of Science and Technology Policy.

The Council on Food Safety has recognized the importance of preventing antimicrobial resistance, and in 1999 helped to form an interagency task force to look at the issue in its broadest terms, studying not only food safety, but all aspects of resistance as a public health problem. On June 22, 2000, (*Federal Register* Vol. 65, No. 121, 38832) the task force released its *Draft Public Health Action Plan to Combat Antimicrobial Resistance*, a strategic plan to achieve dozens of distinct goals within the next one to five years. Many of these goals involve assessing agricultural antimicrobial use and examining the problem of resistance as a food safety issue.

CVM, with responsibility for protecting public health and approving all animal drugs, has taken the lead in assessment of health risks posed by the use of antimicrobial drugs in food-producing animals. Such risk assessments can be conducted for only specific pathogen/drug/outcome combinations, using data provided from FSI-supported research at FDA, CDC, ARS, APHIS, and grantees from USDA's Cooperative State Research, Education and Extension Service (CSREES), the interagency NARMS surveillance system, and private-sector peer-reviewed research. FDA is finalizing a *Campylobacter* assessment on the human health risk from fluoroquinolone use in chickens, and directing a feasibility analysis on conducting a second risk assessment using *Enterococcus.*

The House Committee on Appropriations has asked for a plan for a risk assessment comparing risk from agricultural to that of other antimicrobial uses. Such an analysis is not possible at this time. Microbial risk assessment is a young science, limited primarily to specific drug and organism assessments. The requested task is infeasible not only due to its breadth, but also due to the lack of appropriate technical methods, the magnitude of data gaps, and the burden of ascribing each specific health event to a specific cause. Nonetheless, incremental efforts in qualitative and quantitative risk assessment are feasible and worthwhile, and are planned by USDA (e.g. Draft Acton Plan, Action Item #52 for growth promoting antimicrobials), and by FDA, (e.g. specific organism-drug combination human health risk assessments).

In 1998, FDA issued a discussion paper, *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* (known as the *Framework Document*). The discussion paper states concepts for a risk-based regulatory system for assessing the risk from the development of resistant bacteria through the use of antimicrobials in food-producing animals.

Strategy to Address the Problem of Agricultural Antimicrobial Use and the Emergence of Resistance

The strategy consists of the following major elements: regulation of animal drugs, risk assessment, surveillance, research, and education.

Agency Roles and Responsibilities

Several Federal agencies have responsibilities regarding the use of antimicrobials in agriculture. Regulatory authorities approve drugs, monitor to assure use as approved, and enforce laws. The FDA regulates the approval of antimicrobials for use in food-producing animals. The Environmental Protection Agency (EPA) approves uses of antimicrobials on crops intended for food. Each Agency sets tolerances for residues in food. FSIS tests for illegal residues of antimicrobials in meat and poultry. FDA carries out enforcement action against violative residues.

Surveillance for resistance development in foodborne pathogens involves several agencies in a cooperative effort. ARS and APHIS participate with FSIS, FDA, the CDC, and 17 State and local health departments to conduct surveillance of antimicrobial resistance in pathogens from animals, meat and poultry products, and people with foodborne illness. NARMS began in 1996, and has been expanded annually with the support of FSI funds.

A multi-disciplinary, multi-agency research effort is also underway, again largely supported by FSI funds. Studies are conducted in mechanisms of resistance, rapid test methods, alternative agricultural production practices, and other areas. ARS, APHIS, the National Institutes of Health (NIH), and FDA work with stakeholders to prepare cooperative research plans at least annually. In addition, CSREES and FDA provide competitive grants for similar research activities.

Educational activities focus on the concept of judicious antimicrobial use, a set of "best practices" to minimize resistance problems. The development of judicious-use guidelines for producers, veterinarians, and others is a joint public and private effort involving FDA-CVM, FSIS's Animal Production Food Safety staff, and producer and professional groups.

"Draft Public Health Action Plan to Combat Antimicrobial Resistance"

On June 22, 2000, the Interagency Task Force on Antimicrobial Resistance published in the *Federal Register* a draft for comment on Part I of its Action Plan. The Task Force is co-chaired by CDC, FDA, and NIH, and also includes the Agency for Healthcare Research and Quality, USDA, the Department of Defense, the Department of Veterans Affairs, EPA, the Health Care Financing Administration, and the Health Resources and Services Administration. The comment period ended on August 4, 2000.

The *Draft Action Plan* reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance. The consensus was reached based on input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. The Plan includes 87 action items addressing four focus areas: Surveillance, Prevention and Control, Research, and Product Development. For each action item, "coordinator" and "collaborator" agencies/departments and one- to five-year timelines are specified. While some actions are already underway, complete implementation of this plan will require close collaboration with all of these partners, a major goal of the process.

The *Draft Action Plan* addresses the issue of antimicrobial resistance (AR) in all sectors, including human and agricultural uses. Part I focuses on domestic issues. Since AR transcends national borders and requires a global approach to its prevention and control, Part II of the Plan, to be developed subsequently, will identify actions that more specifically address international issues.

Proposed goals for addressing the problem of resistance from agricultural uses are stated for each focus area, including the following top-priority action items for Federal agencies:

Surveillance:

- With collaborators, design and implement a national AR surveillance plan that defines national, regional, State, and local surveillance activities, the roles of clinical, reference, public health, and veterinary laboratories, and is consistent with the local and national surveillance methodology and infrastructure that currently exist or are being developed.

- Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, in agriculture, and in consumer products.

Prevention and Control:

- Develop and implement a public education campaign to promote judicious antimicrobial use as a national health priority.

- In collaboration with professional societies and other stakeholders, develop, disseminate, and evaluate clinical guidelines that address judicious antimicrobial use.

- In consultation with stakeholders, refine and implement the proposed FDA framework for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for reevaluating currently approved veterinary antimicrobial drugs.

- Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote judicious drug use and reduce infection rates in order to assess how interventions found to be effective in research studies can be effectively, routinely, and economically applied on a large scale.

Research:

- Provide to the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostic methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens.

- Identify, develop, test, and evaluate the impact of new rapid diagnostic methods (e.g., tests for resistance genes including nonculture specimens, point-of-care diagnostics for patients with respiratory infections and syndromes, and diagnostics for drug resistance in microbial pathogens).

Product Development:

- Create an Interagency AR Product Development Working group to identify and publicize priority public health needs for new AR products (e.g., innovative drugs, targeted spectrum antimicrobials, point-of-care-diagnostics, vaccines, anti-infective medical devices, and biologics).

- In consultation with stakeholders, economic consultants, and the AR Product Development Working group, identify ways (e.g., financial and/or other incentives or investments) to promote the development and/or prudent use of priority AR products for which market incentives are inadequate.

Regulation of Animal Drugs

Under the Federal Food, Drug, and Cosmetic Act, FDA is charged with assuring the safety and effectiveness of new animal drugs. The term 'safety' encompasses the safety of new animal drugs to treated animals and to humans consuming products from treated animals. The FDA's responsibilities include approving safe and effective new animal drugs, as well as assuring that such drugs do not compromise the public health.

FDA's *Framework Document* states concepts for a risk based regulatory system for assessing the risk from the development of resistant bacteria through the use of antimicrobials in food-producing animals.

The *Framework Document* is written with a clear understanding of these two responsibilities of the FDA. It describes a regulatory approach for approving antimicrobial animal drugs that carefully balances the approval of safe and effective drugs for use in animals and protection of the public health. The *Framework Document* notes that the Agency's primary public health goal must be to protect the public health by preserving the long-term effectiveness of antimicrobial drugs for treating diseases in humans. The strategy is to implement some of the concepts outlined in the *Framework Document* and continue to refine other concepts in the *Framework Document*, as well as develop additional appropriate concepts for implementation of a regulatory approach for antimicrobials used in food-producing animals. The Agency intends that the implementation of appropriate concepts will be based on scientific knowledge gathered from five critical areas: risk assessment, surveillance, research, pre-approval studies to address microbial safety, and prudent use strategies.

Risk Assessment

The *Framework Document* states concepts for a risk based regulatory system for assessing the risk from the development of resistant bacteria through the use of antimicrobials in food-producing animals.

To better estimate the risks from the use of antimicrobials in food animals, the FDA-CVM conducted a quantitative risk assessment that modeled the human health impact of fluoroquinolone resistant *Campylobacter* infections associated with the consumption of chicken. The FDA-CVM has contracted for a second risk assessment to assess the indirect transfer of resistance from animals to humans. It will model the impact of virginiamycin resistance in *Enterococcus faecium* in animals on the ability to treat *E. faecium* in humans with the human antimicrobial, quinupristin/dalfopristin (a new human drug recently approved under the brand name Synercid®).

The FDA expects to finalize the *Campylobacter* risk assessment in the summer of 2000. The *Enterococcus* risk assessment feasibility study is to be completed by the second quarter of 2001. A quantitative risk assessment on virginiamycin-resistant *Enterococcus* could begin in 2001 and conclude a year or so later, but if available data are insufficient it could take several years to complete.

The draft of the *Campylobacter* risk assessment has demonstrated that resistance development in food-producing animals does impact human health. Given the availability of robust scientific data, this risk assessment also has demonstrated that it is possible to quantitatively assess the human health impact of a specific antimicrobial use in a particular species. The linkage in the risk assessment between fluoroquinolone resistance in chickens and a human health impact strengthens the basis for future regulations on this issue in food-producing animals. Any new regulations will be the subject of notice and comment rulemaking.

Surveillance

A key component of an overall Federal strategy on antimicrobial resistance is a national surveillance program that monitors resistance among foodborne pathogens in both animals and humans. FDA proposed NARMS in 1995, in response to growing concern about the emergence of untreatable antimicrobial resistance. In 1996, HHS and USDA established NARMS to prospectively monitor changes in antimicrobial susceptibilities of foodborne pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter. NARMS was greatly enhanced and expanded under the FSI. The system is composed of two arms, human and animal, that follow identical collection, isolation, and susceptibility testing procedures. Non-typhoid *Salmonella* was selected as the initial sentinel organism.

The goals and objectives of the NARMS are to:

(1) Provide descriptive data on the extent and the temporal trends of antimicrobial susceptibility in *Salmonella* and other enteric organisms from the human and animal populations,

(2) Provide timely information to veterinarians and physicians,

(3) Prolong the life span of approved drugs by promoting the prudent use of antimicrobials,

(4) Identify areas for more detailed investigation, and

(5) Conduct research on antimicrobial resistance.

Animal isolate testing of *Salmonella* and *Campylobacter* is conducted at the ARS Russell Research Center, with financial support from FDA through an interagency agreement. Animal clinical samples from veterinary diagnostic labs are submitted through ARS. Samples from healthy animals are submitted through APHIS in conjunction with surveys of production practices. FSIS submits samples from meat and poultry carcasses at slaughter. In addition, the Minnesota, Georgia, Maryland, and Oregon State Health Departments submit *Campylobacter* isolates from poultry retail samples. In 2000, a pilot surveillance project for *Enterococcus* in FSIS slaughter samples was begun. Ground beef samples at retail are collected by States and isolates are sent to CDC for testing.

Human isolate testing of non-typhoid *Salmonella*, *Campylobacter* and *Escherichia coli* O157: H7 is conducted at CDC's National Center for Infectious Diseases Foodborne Disease Laboratory. Seventeen State and local health departments (California, Colorado, Connecticut, Florida, Georgia, Kansas, Los Angeles County, Massachusetts, Maryland, Minnesota, New Jersey, New York City and State, Oregon, Tennessee, Washington, and West Virginia) submit human clinical isolates of *Salmonella* and *E. coli* O157-H7 to the laboratory. Eight health departments submit human clinical *Campylobacter* isolates.

NARMS data provide baseline information on the prevalence of resistance in studied pathogens. Early findings indicate a low prevalence of resistance in beef *Salmonella*, certain *Salmonella* strains with resistance to multiple drugs, and the emergence of resistance in *Campylobacter* to fluoroquinolones.

Although it is called a Resistance Monitoring System, NARMS actually tests for susceptibility along a gradient. Rather than determining when an isolate has become fully resistant, the analysis used allows for detection of small decreases in susceptibility, before resistance occurs. As such, NARMS may predict trends in time sufficient to allow for mitigation steps aimed at slowing or stopping the progression of the resistance.

Data from the NARMS has spawned a number of research efforts. Epidemiological studies of human cases of salmonellosis and campylobacteriosis with decreased susceptibility to quinolones were begun in 1998. Ongoing projects in California and Michigan compare organic and conventional dairy farms to evaluate differences in antimicrobial resistance. A pilot study involving Minnesota, Georgia, Maryland, and

Oregon to monitor the resistance of human and poultry *Enterococcus* isolates to 27 antimicrobials was begun in 1998. Data from chicken slaughter samples was used in the risk assessment on the human health impact of fluoroquinolone resistant *Campylobacter* associated with the consumption of chicken.

Research

On July 3, 1998, President Clinton directed DHHS and USDA to establish a plan to create a Joint Institute for Food Safety Research ("the Institute"). The Institute is to (1) coordinate planning and priority setting for food safety research among the two Departments, other government agencies, and the private sector, and (2) foster effective translation of research results into practice along the farm-to-table continuum. Enhanced and more efficient national investment in food safety research will do much to lower incidence of foodborne illness in the United States.

DHHS and USDA will have joint leadership of the Institute and will use existing resources to support it. This acknowledgment of the critical need to expand and coordinate food safety research also emphasizes the companion need to expand and strengthen public-private partnerships and to augment collaboration among State, local, and other Federal agencies, thereby effectively providing the scientific information required to help achieve public health goals.

FDA has initiated intramural, extramural, and collaborative research efforts to investigate factors associated with the development, dissemination, and persistence of bacterial antimicrobial resistance in both the animal production environment and food supply. Collaborative molecular genetic studies have begun at FDA's National Center for Toxicological Research in Arkansas to identify regions of fluoroquinolone resistance in foodborne pathogens. Microbiologists from FDA are conducting or participating in projects to gather data on such issues as resistance transfer between pathogens, presence of resistant organisms in animal feeds, resistance in aquaculture and other food animal production systems, environmental levels of resistant organisms, and molecular mechanisms of antimicrobial resistance.

ARS recognizes that the emergence of resistance to antimicrobials has compromised control of bacterial pathogens in both animals and humans. The development of similar types of antimicrobial resistance in animals and humans identifies antimicrobial use in animals as one possible cause of treatment ineffectiveness in humans. Although basic information will be applicable to any species, more applied investigations need to take place in poultry, swine, and cattle since the respective bacterial floras and gut environments are different for each species. ARS is seeking solutions to this highly visible public health problem, redirecting resources and requesting increases to evaluate means to delay and control the emergence of resistance in pathogens associated with food production and food products. Planned projects include investigating the ecology of resistant organisms in a variety of animal production systems, defining additional virulence factors that accompany resistance in pathogens, and identifying alternatives to antimicrobial use, such as vaccines, competitive exclusion cultures, and best management practices.

Within the portfolio of research supported by CSREES in FY 1999, several projects focused on antimicrobial resistance in livestock. Two projects addressed the issue of the ecology of antimicrobial resistance in production units, two addressed the mechanisms of development of resistance, and one focused on tracing the resistant organisms through the food chain. Other projects specifically addressed the issue of resistance to fluoroquinolones. Targeted organisms included *Salmonella, E. coli,* and *Campylobacter*. The Request for Proposals from CSREES for FY 2000 under the food safety programs again includes a clear statement identifying antimicrobial resistance as one of the targeted areas. Specific topics mentioned are mechanisms leading to antimicrobial resistance, models for quantitative and qualitative risk assessment and hazard evaluation, and transfer or movement of resistance in the food chain.

Education

The Animal Medicinal Drug Use Clarification Act of 1994 provides veterinarians the authority to use certain approved animal drugs "extra-label." This Act allows veterinarians to exercise greater clinical judgment in choosing an effective therapeutic drug. An essential element of this judgment is the avoidance or proper use of drugs that could result in violative drug residues when used in food-producing animals. Prudent use of antimicrobials requires attention to problems both with residues and the development of antimicrobial resistance.

Veterinarians have relied on a public-private database for residue avoidance, although program funding has been inconsistent. The Food Animal Residue Avoidance Database (FARAD) originated with the 1982 Residue Avoidance Program sponsored by FSIS and involved cooperation with several academic institutions. FARAD contains drug information that can help veterinarians in the prudent use of drugs, including antimicrobials.

FDA prohibits the extra-label use of certain important human antimicrobials when they are used in food-producing animals. Fluoroquinolones, for example, may be used only according to the specific label directions for which they were approved.

For all other antimicrobials, agencies support veterinarian and producer educational programs to promote prudent use of antimicrobials for the prevention of resistance. For instance, FDA contracted with the American Veterinary Medical Association (AVMA) and the National Pork Producers Council (NPPC) to develop educational material on prudent use of antimicrobials. The AVMA has developed written materials, the script for videotape, and speeches that explain the concept of prudent use to veterinarians. The NPPC has developed written material and the script for videotape that explains the prudent use program for livestock producers, especially swine producers. The projects will be finished in 2000.

Also during 1999, FDA started an exhibit program designed to bring the food safety message to livestock producers and veterinarians at their trade shows. The focus of the exhibits is on preventing the risk to public health from bacteria that have grown resistant

to antimicrobials following the use of the drugs in food-producing animals. Literature presented at the booth explains the Center's programs and how they involve livestock producers and veterinarians. At the booth, FDA officials respond to questions from trade show participants. To date, the exhibit program has been well received by a variety of audiences, including livestock producers and veterinarians. The exhibit program gives these individuals a chance to ask questions in person and get timely responses.

The AVMA formed a Steering Committee on Judicious Therapeutic Antimicrobial Use by Veterinarians in 1999. The Steering Committee will advise the AVMA Executive Board on the means to develop guidelines for judicious therapeutic antimicrobial use by veterinarians and continuing education programs to raise the awareness of the profession to the issue of antimicrobial resistance.

Budget

In FY 2000, the FDA Animal Drugs and Feeds Program budget includes $9.0 million for the President's Food Safety Initiative (FSI). This was an increase of $3.6 million from the FY 99 level. Antimicrobial Resistance fits into all aspects of the Animal Drugs and Feeds Program FSI. In FY 2000, USDA's budget includes $6.7 million under the FSI for bioscience research aimed at increasing the understanding of antimicrobial resistance. This was an increase of $3.2 million over the FY 99 level.

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