Antibiotic Use in Food Animals: Controlling the Human Health Impact

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Resistance to antimicrobial drugs has compromised control of many bacterial pathogens. For foodborne pathogens, the most likely source of resistance is use of antimicrobials in food-producing animals. To control the human health impact from use of antimicrobials in animals, the U.S. Food and Drug Administration (FDA) recently announced plans to assess the microbial safety of all antimicrobials intended for use in food-producing animals. This paper describes the history of antimicrobial use and regulation in animals, the public health concern, the current animal drug approval process in the United States, the international perspective, and FDA’s proposed procedures to evaluate the human health impact of the antimicrobial effects associated with animal drugs intended for use in food-producing animals. The primary public health goal of the improved regulatory paradigm is to ensure that significant human antimicrobial therapies are not lost due to use of antimicrobials in food animals.

Antimicrobial drugs, which affect bacteria by inhibiting their growth or by killing them outright, are used to treat bacterial diseases in humans, and prevent countless deaths worldwide. In animals, these drugs are used to control, prevent, and treat infection, and to enhance animal growth and feed efficiency. Therapeutic use of antimicrobial drugs is essential for maintaining animal health.

Almost 90% of the antimicrobial drugs used in livestock and poultry is used at subtherapeutic levels, at concentrations usually less than 200 g/ton feed, for disease prevention or growth promotion (1). The use of antimicrobial agents in animal production has facilitated confinement housing and allowed higher densities of animals to be maintained. Factors related to farm management, such as feeding practices, sanitation, space utilization, and housing and environmental controls, help to minimize the use of antimicrobial agents. However, even if well managed, the increased density of livestock or poultry in intensive rearing operations requires an aggressive approach to disease control, which can lead to heavy prophylactic and therapeutic antimicrobial use. If such operations are not well managed, heavy antimicrobial use becomes a management crutch. The subtherapeutic use of penicillin, tetracycline, and other feed-additive antimicrobials provides considerable pressure for selection of resistant microorganisms (2).

The global emergence of resistance to antimicrobial drugs has compromised control of many bacterial pathogens. Expert scientific groups such as the Institute of Medicine, the American Society for Microbiology, and the World Health Organization (WHO) have expressed apprehension about the national and global increase in resistance and the complex issues surrounding this increase both in the community and in institutional settings (3, 4). The Centers for Disease Control and Prevention (CDC) has designated antimicrobial resistance as an important factor in emerging infectious diseases (5).

Public Health Concern

Selective pressure resulting from widespread antimicrobial use is the underlying force in the development of resistance. The association between increased antimicrobial use and resistance has been documented for nosocomial infections (6) as well as for community-acquired infections (7). For foodborne pathogens, especially for those such as Salmonella that are rarely transferred from person to person in industrialized countries, the most likely source of antibiotic resistance is use of antimicrobials in food-producing animals.

Foodborne bacterial diseases are a small, but important, part of the increasing problem of antimicrobial resistance (3). Development of resistant zoonotic enteric pathogens results from the direct use of antimicrobial drugs in humans and acquisition of resistant organisms or resistance factors from animals and environmental bacteria. Antimicrobial agents can promote the emergence of resistant bacteria among both target pathogens and normal bacterial flora. The normal bacterial flora in many species of animals include foodborne pathogens such as Salmonella, Escherichia coli, and Campylobacter. All...

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3 bacteria can cause severe foodborne illness in humans. When carcass contamination is measured at the processing plant, it is estimated that 20% of the broiler chickens in the United States are contaminated with *Salmonella* and 80% are contaminated with *Campylobacter*.

Resistant foodborne pathogens are present on animals as a result of drug use in animals. For example, in the United States, 13.5% of the *Campylobacter* isolated from chicken carcasses are fluoroquinolone-resistant (1998 data from the U.S. National Antimicrobial Resistance Monitoring System at http://www.fda.gov/cvm). If these resistant pathogens, which develop in response to antimicrobial drug use in food animals, contaminate food products at slaughter, they can be transmitted to humans through consumption of the contaminated food. If the resistant bacteria cause an illness in a consumer who needs treatment, medical therapy may be compromised if the pathogenic bacteria are resistant to the drug used for treatment. Resistance traits may also be passed to human pathogenic bacteria by mechanisms that allow exchange of the bacteria’s genetic material. Animal enteric bacteria nonpathogenic to humans may then pass resistance traits to pathogenic bacteria. Several bacteria species are known to carry multidrug resistance genes, which may confer resistance to a number of antimicrobials (8). Moreover, structurally different classes of antimicrobial drugs may select for resistance to unrelated drug classes that have a common site of action (9).

Foodborne diseases have a major public health impact in the United States. Recent estimates describe 5000 deaths and 76 million foodborne illnesses annually (10). A 1994 report estimated an annual economic burden due to foodborne illness at $22 billion (11). *Campylobacter* is the most common known cause of foodborne illness in the United States (12). Compared to patients with typical noninvasive salmonellosis, patients with *C. jejuni* or *C. coli* gastroenteritis often experience more severe illness and are ill longer. Among 460 sporadic cases of *campylobacteriosis* recently reported in 19 representative U.S. counties, the mean duration of illness was 10 days, with 7 lost workdays, and one-half hospitalization day. Five patients (1%) died (13). Treatment of campylobacteriosis with fluoroquinolones within the first 2 days of illness decreases the duration of illness from 10 to 5 days. Development of resistance in foodborne pathogens may complicate the medical and public health concern as important treatment options are compromised or lost (3, 14).

Although antimicrobials are not routinely indicated for uncomplicated *Salmonella* infections, patients at greater risk for systemic disease are commonly prescribed antibiotics. In surveys conducted by CDC, 40% of persons with *Salmonella* infections who sought medical attention were treated with antimicrobial agents (14, 15). Moreover, antimicrobials are essential for the treatment of patients with extraintestinal *Salmonella* infections. These invasive infections account for approximately 6% of the culture-confirmed cases reported to CDC annually (16, 17).

After several large outbreaks of human salmonellosis in 1963 were traced to commercial egg products, CDC established a *Salmonella* surveillance system. *Salmonella* isolates submitted to state health department laboratories for serotyping are reported to CDC along with patient information, including age, sex, county of residence, and source of the clinical specimens (14). CDC also conducts prospective studies of salmonellosis in humans at 5-year intervals beginning in 1979. For the prospective studies, random samples of stratified urban and rural counties in the United States are asked to submit all *Salmonella* isolates to CDC and complete detailed questionnaires on the patients (14). The U.S. National Antimicrobial Resistance Monitoring System for Enteric Bacteria, begun in collaboration with the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) in 1996, collects *Salmonella* isolates continuously from 17 state and local health departments; these isolates are submitted to CDC for susceptibility testing (18). Together, these studies provide data on the frequency, significance, and origin of antimicrobial resistance in human *Salmonella*. In addition to the *Salmonella* surveillance and antimicrobial resistance monitoring, outbreak investigations by state, local, and federal agencies provide information on routes and vehicles of transmission, the reservoirs of causative organisms, and risk factor information.

Nontyphoidal salmonellosis in humans in the United States is acquired primarily through contaminated foods of animal origin. This has been demonstrated through several different types of foodborne disease follow-up investigations, including laboratory surveillance, molecular subtyping, outbreak investigations, and studies on infectious dose and carriage rates (19–21). Holmberg et al. were the first to document an outbreak of salmonellosis caused by multidrug-resistant *Salmonella* that infected people who ate hamburger originating from South Dakota beef cattle fed subtherapeutic chlorotetracycline for growth promotion (19).

In 1986, Cohen and Tauxe published a review of infections caused by drug-resistant *Salmonella* in the United States (14). Using data from the 1979 and 1984 CDC prospective studies on *Salmonella*, the authors showed that there was no correlation between antimicrobials used to treat salmonellosis in humans and antimicrobial resistance patterns among *Salmonella* from either human or animal sources. However, a great deal of similarity was found between resistance patterns in *Salmonella* isolates from animals and humans and antimicrobials used in farm animals (14). CDC epidemiologists have recently updated and confirmed these findings with data from the more recent prospective studies on *Salmonella*: antimicrobial use in humans contributes little, and perhaps nothing, to the emergence and development of antimicrobial resistant *Salmonella* in the United States (22). Because human use of antimicrobials is not a significant contributor to development of resistance in *Salmonella*, it is likely that the majority of antimicrobial-resistant *Salmonella* in humans and food animals is the result of antimicrobial use in food animals.

Recent emergence of a resistant foodborne pathogen that has a food animal reservoir is illustrated by *Salmonella enterica* serotype *typhimurium* Definitive Type 104 (DT104). DT104 is a multidrug-resistant pathogen that is currently epidemic in human and food animal populations in the United
Kingdom and has been isolated from several countries in Europe (22–25). DT104 carries chromosomally integrated resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. Because these drugs are only used therapeutically in the United Kingdom, this example shows that resistant bacteria of public health importance can arise following therapeutic treatment of animals with antibiotics. A report from the United Kingdom suggests that infections caused by DT104 may be associated with greater morbidity and mortality than infections by less resistant serotypes of Salmonella (26). An association has been noted between loss of susceptibility to fluoroquinolones among DT104 isolates and the approval and use of a fluoroquinolone for veterinary therapeutic use in the United Kingdom (13, 27, 28). This organism has also been identified in livestock and poultry in the United States (29–31). Human disease caused by DT104 in the United States has been associated with unpasteurized dairy products and direct contact with livestock (31).

Reports from the scientific and public health communities, both domestically and internationally, have identified a relationship between the approval of fluoroquinolones for therapeutic use in food-producing animals and the development of fluoroquinolone resistance in Campylobacter in animals and humans. The approval of these drugs in food-producing animals in the Netherlands (32, 33), the United Kingdom (34), and Spain (35, 36) temporally preceded increases in resistance in Campylobacter isolates from treated animals and ill humans. Despite several restrictions placed on the use of the 2 approved poultry fluoroquinolone products in the United States, fluoroquinolone-resistant Campylobacter were recently isolated from 20% of domestic retail chicken products sampled (37). Molecular subtyping revealed an association between resistant Campylobacter jejuni strains from chicken products and C. jejuni strains from domestically acquired human cases of campylobacteriosis (37).

There is growing scientific evidence that the use of the glycopeptide avoparcin as a growth promoter created a reservoir of vancomycin-resistant Enterococcus faecium in food animals in Europe that was subsequently transferred to humans. There is no effective antimicrobial therapy available for many vancomycin-resistant enterococci (VRE; 38). These infections are associated with increased mortality (39). In Europe, colonization with VRE, a precursor of infection, occurs in the community, possibly from foodborne sources (40). In the United States, colonization has been demonstrated only in the hospital setting (41), although there is a possibility that undetected community VRE transmission may be occurring at low levels (42). No glycopeptide antimicrobials, including avoparcin, are approved as animal drugs in the United States.

Epidemiology studies in several countries in Europe have shown an association between the recovery of VRE from food animals, primarily poultry, and the use of avoparcin at subtherapeutic doses for growth promotion (40, 43–46). Comparison of conventional poultry flocks that used avoparcin with organic poultry flocks that used no growth promoters found no VRE in organic birds and VRE in the majority of the conventionally raised flocks (43). Because conventional and organic production differs in several respects other than growth promoter usage, the investigators next compared conventional swine and poultry flocks that did use and did not use avoparcin. The investigators reported a strong, statistically significant association between the presence of VRE in the animals and the use of avoparcin as a growth promoter (45). As a result of these studies, the use of avoparcin at subtherapeutic levels was banned by Denmark in 1995, followed by Germany in 1996, and subsequently by the entire European Union (47–49).

Historical Perspective

Soon after livestock producers began using antimicrobials in food-producing animals, scientists began studying the possible effects of long-term use of antibiotics. In 1969, the Swann Committee was formed in the United Kingdom to review these concerns and was the first to link an outbreak of salmonellosis in humans to therapeutic use of antibiotics in sick calves. The Committee recommended that antibiotics used in animals be divided into feed and therapeutic classes; the feed antibiotic class should not include drugs used therapeutically in humans or animals, and therapeutic antibiotics should be available only by prescription.

A 1970 FDA Task Force examined the issue and found that use of antibiotics in animal feeds is associated with the development of resistant bacteria. The Task Force concluded that animals receiving antimicrobial treatment may serve as a reservoir of antibiotic resistant pathogens that can produce human disease.

In 1977, FDA proposed to withdraw the subtherapeutic uses of penicillin and tetracyclines from animal feeds when used alone or in combination with other drugs. These 2 drugs were chosen because of their importance in human medical therapy. The proposal was criticized because at the time there was not adequate epidemiological evidence, or only just-emerging evidence, to show that drug-resistant bacteria of animal origin are commonly transmitted to humans and cause serious illness. Critics argued that, while antibiotics used in animals select for resistant bacteria, the transfer of these bacteria from animals to humans is rare.

As a result of the FDA proposal, in 1978 Congress required FDA to spend $1.5 million of its appropriations for a study of the antibiotics in animal feeds issue, to be conducted by the National Academy of Sciences National Research Council (NRC). The NRC study, The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds, was published in 1980 (50). It concluded that existing data could neither prove nor disprove the postulated hazards to human health from subtherapeutic antimicrobial use in animal feeds.

In 1984, the Natural Resources Defense Council, Inc. (NRDC) petitioned the Department of Health and Human Services (HHS) to immediately suspend approval of the subtherapeutic use of penicillin and tetracyclines in animals by invoking the imminent hazard provision of the Food, Drug, and Cosmetic Act, 21 U.S.C. Sec. 360b(E)(1), which authorizes the Secretary of HHS to suspend marketing of an animal
drug if an imminent hazard exists to the health of man or to the animals for which the drug is intended. NRDC based its petition primarily on a study by Holmberg et al. (19), that linked drug-resistant salmonellosis in humans to consumption of hamburger. FDA denied the petition based on limited evidence for a human health hazard.

In 1988, the Institute of Medicine of the National Academy of Sciences (Washington, DC), again reviewed all the information about the antibiotic resistance issue available at the time. An expert committee was convened to determine the human health risks associated with the practice of feeding subtherapeutic levels of penicillin and tetracyclines to animals for growth promotion, feed efficiency, and disease prevention. In the report, Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed, the committee developed a risk-analysis model, using data only on Salmonella infections that resulted in human death (1). The Committee found a considerable amount of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard. The Committee did not find data demonstrating that use of subtherapeutic penicillin or tetracycline directly caused humans to die from salmonellosis. The Committee noted that it was not possible to separate the public health effects of therapeutic and subtherapeutic uses and strongly recommended further study of the issue.

The American Society for Microbiology, which includes members who specialize in medical and animal microbiology, issued a report in 1995 that cited grave concerns about both human and animal antibiotic use and the rise in antimicrobial resistance (3). The report advocated a significant increase in resistance monitoring in the United States, more education about the use and risks of antimicrobials, and more basic research designed to develop new antimicrobials and vaccines and disease prevention measures. The report criticized overuse of antibacterials in human medicine, but also pointed out the large use in food production. The report made it clear that the antibiotic resistance problem is global, and was a precursor to involvement by the United Nations’ World Health Organization (WHO).

In October 1997, WHO convened a meeting of experts in Berlin, Germany, to review the question of whether the use of antimicrobials in animals leads to antimicrobial resistance in humans. The experts sought to define potential medical problems that could arise from antimicrobial use in livestock and to recommend actions WHO should take. The group of experts recommended against using antimicrobials for growth promotion that are also used in human medicine or that can induce cross-resistance to antimicrobials used for human medical therapy (51, 52). The group also recommended that research be conducted on non-antimicrobial growth-promoters and urged that the risk to human health from use of antimicrobials in food animals be accurately assessed. The group called for enhanced monitoring of resistance among isolates of enteric bacteria from food animals and from food of animal origin. In addition, the group recommended managing risk at the producer level through the prudent use of antimicrobials.

In June 1998, WHO held another meeting in Geneva, Switzerland, to specifically address the use of quinolones in food-producing animals. The participants agreed that the use of antimicrobials will cause resistance to develop and that there is a potential human health hazard from resistant Salmonella, E. coli, and Campylobacter organisms transferred to humans through the food supply (53). However, the experts also agreed that antimicrobial drugs, including quinolones in certain instances, are needed to treat sick animals, and urged more research on the possible human health effects from the use of these drugs in animals (53).

In May 1998, the Center for Science in the Public Interest (CSPI; Washington, DC), in a coalition with 15 other health and consumer groups, produced a comprehensive report on the antibiotic resistance problem (54). The focus of the report was on human antimicrobial use; however, CSPI made several recommendations regarding the use of antimicrobials in veterinary medicine. The report recommended that FDA ban all subtherapeutic uses of antimicrobial agents that are used in human medicine or might select for cross-resistance to antimicrobials used in human medicine. The organization also expressed concerns about new human antimicrobials that may be at risk due to use of the same class of drugs in agriculture, at either subtherapeutic or therapeutic levels. Development of resistance to certain classes of drugs that are considered vital in human medical therapy, such as the fluoroquinolones, would cause particular concern. For this reason, CSPI recommended that FDA repeal approval of fluoroquinolones in poultry and only allow additional approvals of fluoroquinolones if the drug sponsor can show that those uses would not reduce their effectiveness for human medical therapy.

The European Union recently took action to minimize the agricultural use of antimicrobial drugs. In December, 1998, health ministers for the European Union voted to ban 4 antibiotics that are widely used at subtherapeutic levels to promote animal growth. The ban on using bacitracin zinc, spiramycin, tylosin, and virginiamycin in animal feed became effective for the 15 member states of the European Union on July 1, 1999.

Current New Animal Drug Approval Process in the United States

Before any animal drug may be legally marketed in the United States, the drug sponsor must have a New Animal Drug Application (NADA) approved by FDA’s Center for Veterinary Medicine. To obtain NADA approval, the drug’s sponsor must demonstrate that the drug is effective and safe for the animal, safe for the environment, and can be manufactured to uniform standards of purity, strength, and identity. If the animal drug product is intended for use in food-producing animals, the drug’s sponsor must also demonstrate that edible products produced from treated animals are safe for consumers (55).

For antimicrobial products, the agency reviews microbiological information in several parts of the application. To support that an antimicrobial product is effective or to support
product labeling, the drug’s sponsor may supply the agency with minimum inhibitory concentration (MIC) information for target pathogens and data on the blood and tissue levels of the drug. Definitive proof of the efficacy of an antimicrobial product is based upon a demonstration of effectiveness in clinical trials (56).

Environmental Safety

In the area of environmental safety, the agency uses an exposure threshold approach to determine if environmental fate and effects studies are needed. Environmental studies are not requested for compounds that have limited environmental introductions. When an environmental assessment is needed, the drug sponsor conducts laboratory toxicity studies with invertebrates, plants, and microorganisms representative of the environmental compartment of concern. The no observed effect level (NOEL), or the MIC in the case of the microbes, is divided by a safety factor to arrive at a Predicted Environmental No Effect Concentration (PNEC). The predicted environmental concentration (PEC) is calculated for the drug and compared to the PNEC. When the PEC/PNEC ratio is less than one, the agency concludes that significant environmental effects will not occur due to the use of the animal drug product (57).

Human Food Safety of Residues

To determine the food safety of residues of an antimicrobial product, the drug sponsor conducts a standard battery of toxicology tests. The battery includes studies that examine the effect of the product on systemic toxicity, genotoxicity/mutagenicity, and reproductive and developmental toxicity. Information on each of these endpoints is required for all products needing an acceptable daily intake (ADI). The toxicology studies are designed to show a dose that causes a toxic effect and a dose that causes no observed effect. The observed effect is not always a classic toxicologic effect. For example, the Center for Veterinary Medicine considers the development of diarrhea following treatment with an antimicrobial as an adverse effect, although clinically this may be considered a side effect of the drug. The FDA views the results of toxicity studies conservatively because consumers should not experience effects from drug residues in the food supply.

Once the NOEL is established for all the toxicity endpoints, the most sensitive effect in the species most predictive of humans is identified. This NOEL is divided by a safety factor to account for uncertainty in extrapolating from animals to humans and for variability, i.e., the difference among individuals, to calculate an ADI for drug residues. The ADI represents the amount of drug residues that can be safely consumed daily for a lifetime.

There are special food safety concerns for the residues of antimicrobial drugs (58). It is well known that therapeutic doses of antimicrobials can cause adverse effects on the human intestinal microflora. The agency has identified the selection of resistant bacteria, the perturbation of the barrier effect, changes in enzymatic activity, and alteration in bacterial counts as potential impacts of antimicrobial drug residues on the human intestinal microflora that are of public health concern. A perturbation in the barrier effect is of concern because the gut microflora provides a barrier against the overgrowth and invasion of pathogenic bacteria. When an antibiotic destroys this barrier, overgrowth of pathogenic bacteria may occur.

Once the ADI is established, the drug’s sponsor conducts drug metabolism and depletion studies to determine how the drug is metabolized and excreted. The tissue in which the drug depletes the slowest is established as the target tissue, and the amount of drug that can be measured with a regulatory method is established as the tolerance. When the drug residue in the target tissue depletes below the tolerance, all edible tissues are safe for consumption. Usually, the Center establishes a withdrawal time to allow the drug residues to deplete below the calculated acceptable daily intake (55).

Microbiological Safety Studies

To ensure that antibiotic treatment of food-producing animals does not alter the pathogen load or the resistance pattern of bacteria in the animal, 2 studies were generally performed for antibiotics used in feed for more than 14 days. These studies were required for long-term feed uses because originally FDA believed that the long-term use of antimicrobials in feed had the greatest potential for selecting for resistant bacteria and for increasing pathogens in the animal. The first study addressed the effect of drug treatment on the excretion of Salmonella in the feces of animals artificially infected with Salmonella serotype typhimurium, i.e., a Salmonella shedding study. The other study, a coliform resistance study, monitored the effect of the drug on the resistance pattern of E. coli present in the endogenous fecal flora.

In the Salmonella shedding study, 7–12 animals were infected with a laboratory strain of Salmonella serotype typhimurium known to accept plasmids. The animals were treated with the drug for 8 weeks and fecal samples were collected weekly. The laboratory strain of Salmonella was isolated from the fecal samples and examined for resistance patterns as well as shedding quantity, duration, and prevalence.

The design for the coliform resistance study was similar to that of the Salmonella shedding study except that the animals were not inoculated with bacteria. Instead, the effect of the drug on the animal’s endogenous E. coli was evaluated. Because it is difficult to detect a change in resistance against a high background, for this study it was necessary to use animals with < 20% resistance in their endogenous E. coli. Changes in coliform susceptibility between the drug-treatment and control groups indicated a drug effect.

International Standards

Most industrialized countries have regulatory bodies, like the FDA, that perform approval assessments for veterinary medicinal products. Although the assessment procedures are
similar, countries differ in the type and number of studies required, the study design, the study interpretation, and the risk management measures applied to ensure proper drug use.

With the globalization of trade in many product sectors, interest in international harmonization issues relating to veterinary products is growing. There has been a focus for several years on harmonization of maximum residue limits (MRLs) or tolerances on a global basis. There is also interest to facilitate the approval of a veterinary product in multiple countries.

The United States, Japan, and the European Union are currently engaged in negotiations to standardize study requirements for veterinary medicinal products under the Veterinary International Cooperation on Harmonization. This effort focuses on standardizing the number and types of studies required for demonstrating efficacy and safety and the design of these studies. Harmonizing study interpretation and risk management decisions associated with product approval is generally considered to be beyond the scope of this effort. It is hoped that standardizing pre-approval requirements will increase the number of approved products available to veterinarians. To date, these efforts do not include efforts to standardize data requirements for demonstrating the effect of antimicrobial treatment on the animal’s intestinal microflora or for demonstrating microbial safety.

In the European Union, antimicrobial products used to improve growth and feed efficiency are regulated as feed additives. The approval process for a feed additive antimicrobial includes a requirement that the product not be used in human medicine and not increase Salmonella shedding in the animal. The European Union banned the use of bacitracin zinc, spiramycin, tylosin, and virginiamycin as growth promoters in animal feeds because these products demonstrate cross-resistance to drugs used in human medicine. For this same reason, avoparcin was banned as a growth promoter in the European Union in April 1997 (47).

In 1962, the Codex Alimentarius Commission (CODEX) was established as a subsidiary of the Food and Agricultural Organization (FAO) and the WHO of the United Nations. CODEX was created to facilitate international trade by developing internationally accepted food standards. The Codex Committee on Residues of Veterinary Drugs in Foods provides expert advice on technical barriers to trade for veterinary products and is responsible for establishing MRLs for veterinary drugs. CODEX MRLs are not mandatory but are established as the standard for trade negotiations. In establishing the MRLs, the Codex Committee on Residues of Veterinary Drugs in Foods receives advice from the FAO/WHO Joint Expert Committee on Food Additives (JECFA). This committee of international experts on toxicology, pharmacology, and metabolism reviews data similar to that reviewed by the FDA for product approval and establishes international ADIs and MRLs for drug residues. Countries that do not have regulatory bodies overseeing animal drug use can adopt the CODEX standard and be assured that their animal products are safe and permitted in international trade. To date, no CODEX Committee has addressed the issue of antibiotic-resistant bacteria on animal products.

The WHO strongly recommends monitoring of antimicrobial resistance in food animals and food of animal origin (52). However, few countries have established resistance surveillance programs for foodborne pathogens, and those surveillance systems that have been initiated are in the early stages of development. WHO is also encouraging international coordination during the early stages of surveillance program development to provide for data compatibility and sharing (52). WHO recommends that resistance surveillance systems be designed to both detect and prevent transmission of resistant bacteria and resistance determinants from animals to humans and contribute to the prudent use of antimicrobials in food animals and humans (52).

The New Regulatory Data Needs

Based upon the increasing evidence that therapeutic as well as growth-promoting uses of antimicrobials in food-producing animals may select for resistant bacteria of public health concern, in November 1998, the FDA announced new regulatory guidance in this area (59). The guidance states that FDA believes it is necessary to evaluate the human health impact of the antimicrobial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals.

Following the publication of this guidance, the agency developed another document entitled, “A 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” (60). This framework document outlines proposed microbiological safety assessments for all food animal uses of antimicrobials, but categorizes requirements based upon public health risks associated with the product use.

The FDA believes it is crucial to determine the importance of an antimicrobial in human medicine before it can determine what effect the development of resistance to that drug from food animal use will have on human health. The agency proposed 3 categories based on importance of the product in human medical therapy. Animal drugs in Category I are the same as or closely related to human antimicrobial drugs that are essential for treating a life-threatening disease or important for treating a foodborne illness. Animal drugs in Category II are the same as or closely related to a human antimicrobial drug of choice for treating human illness but alternative therapies are available. Drugs in Category III are those antimicrobials that are used in food-producing animals but have little or no use in human medicine.

FDA also proposed in the framework document that antimicrobial drugs for use in food-producing animals be categorized by potential exposure to humans. Doses, duration of treatment, and route of exposure are examined to determine whether there is high, medium, or low use of the drug in animals. In addition, there is an assessment of the likelihood that bacteria from the animal will be transferred to humans via food.
Another concept introduced in the framework document is that of regulatory thresholds. The FDA proposes to establish thresholds for the development of resistant bacteria in order to protect public health. There are 2 methods for establishing regulatory thresholds, technology-based and health-based. While technology-based thresholds have an advantage in ease of establishment, these values are not tied to public health outcomes, and therefore are more difficult to enforce legally. Establishing health-based thresholds, however, may be difficult and resource intensive due to the lack of quantitative data on public health outcomes related to use of antimicrobials in food animals. Because public health risk is a product of hazard times exposure, health-based thresholds are generally established by performing a comprehensive evaluation of both the hazard and exposure.

The framework document proposes that 2 thresholds, the resistance threshold and the monitoring threshold, be established to ensure that antimicrobial animal drug products used in food-producing animals are safe for consumers. If the agency decides to base these thresholds on public health risk, the resistance threshold would represent the upper limit for the level of resistant bacteria that can be transferred from animals to consumers and still be considered safe for the consumer. Because the public health risk is different for different antimicrobial products and for different bacteria, the resistance threshold may need to be established for each bacteria of concern. Exceeding the resistance threshold would represent an unacceptable public health risk and the drug’s sponsor would be required to cease marketing the product until the public health threat decreases.

The monitoring threshold would be used as a predictor of the number of resistant bacteria of public health concern that are likely to develop over time due to the approved use of the drug. The monitoring threshold would need to be continually measured to ensure that resistance is developing at a rate consistent with the preapproval projections. Depending on the level of concern for resistance development, this monitoring may occur on a product-specific basis or as part of the U.S. National Antimicrobial Resistance Monitoring Program for Enteric Bacteria.

### Establishing the Resistance Threshold

Before a resistance threshold can be set, the agency must establish a risk standard that expresses a quantitative definition of safety. In the past, these types of definitions have been established through public notice and comment rule making. Once the risk standard is developed, the resistance threshold can be calculated using a standardized risk assessment.

The first step in the assessment of risk is hazard identification. The processes used in this step are closely tied to the definition of harm. The bacterial species of concern and the human therapies that may be compromised as a result of use of the drug in food-producing animals are delineated. In assessing the human therapies that may be compromised as a result of the development of resistant bacteria, human morbidity effects as well as mortality are considered. Morbidity may include the effect of resistance development on the duration of illness, severity of illness, or the cost of illness.

The next step in the risk assessment leading to the establishing of a resistance threshold is to obtain data on the prevalence of bacteria in the food animal species and the extent to which these bacteria are transferred to humans via the food supply. Because the amount of bacteria transferred to humans via the food supply is likely to differ among the different animal species, the resistance threshold may need to be partitioned among the various proposed uses of the product to determine a maximum resistance limit for each animal species. This step is necessary to ensure that the resistance threshold is not exceeded when the product is approved in several different animal species (e.g., chickens, turkeys, swine, and cattle).

### Establishing the Monitoring Thresholds

Drugs in Category I represent those of highest public health hazard. To meet the risk standard, the agency anticipates that there will need to be little or no increase in the number of resistant bacteria of public health concern present on the carcass at slaughter. Preapproval studies for drugs in this category need to determine a baseline level of resistance in the bacteria of public health concern plus demonstrate the rate and extent of resistance development in these bacteria after repeat administration of the drug. If resistant bacteria persist until slaughter, the sponsor will need to identify mitigating actions prior to approval.

Drugs in Category II represent those of modest public health hazard. Pre-approval studies for drugs in this category need to characterize the development of resistant bacteria over several generations and ensure that the level of resistant bacteria does not exceed the resistance threshold established for that species. If the pre-approval studies indicate that the resistance threshold for that species may be exceeded, the sponsor will need to alter the label or identify effective mitigations prior to approval.

### Pathogen Load

As in the past, studies examining the change in pathogen load will be needed for animal drugs categorized as high exposure uses. The design of the studies used to examine *Salmonella* shedding could be modified to assess changes in pathogen quantity and prevalence. For example, animals could be inoculated with a bacterial strain that is resistant to the test antibiotic and which will proliferate when the natural bacterial barrier is destroyed. The animal treatment groups would be dosed with increasing amounts of antibiotic and the number of indicator bacteria present measured. If a margin of safety exists between the intended dose and the dose that causes an overgrowth of the indicator bacteria, the product would be considered safe. If an overgrowth of the indicator bacteria occurs at the intended therapeutic dose, the study could be continued for a recovery period to determine the amount of time required for the natural flora to return to pretreatment levels.
U.S. National Antimicrobial Resistance Monitoring System for Enteric Bacteria

A key component of FDA’s overall strategy on antimicrobial resistance is a national surveillance program that monitors resistance among enteric pathogens in both animals and humans. In 1996, the FDA, the CDC, and the USDA established the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS) to prospectively monitor changes in antimicrobial susceptibilities of zoonotic enteric pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter (18). Non-typhoid Salmonella was initially selected as the sentinel organism and the program expanded each year since its inception. NARMS is currently monitoring susceptibilities of human and animal isolates of Salmonella and E. coli to 17 antimicrobials (Table 1) and Campylobacter isolates to 8 antimicrobials (azithromycin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamicin, nalidixic acid, and tetracycline).

Animal isolate testing is conducted at the USDA Agricultural Research Service, Russell Research Center. Human isolate testing is conducted at the CDC 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, New York state, Oregon, Tennessee, Washington, and West Virginia) submit human clinical isolates of non-typhoid Salmonella and E. coli and began submitting human S. typhi and Shigella isolates in January, 1999. Campylobacter isolates are submitted by 8 health departments, and in addition Minnesota, Georgia, Maryland, and Oregon are submitting Campylobacter isolates from poultry retail samples. A pilot study involving these 4 states to monitor the resistance of human and poultry Enterococcus isolates to 27 antimicrobials began in 1998. Both the CDC and USDA laboratories use a semi-automated system (Sensititre™, TREK™ Diagnostics, Inc., Westlake, OH) for testing Salmonella, E. coli, and Enterococcus isolates, and the E-test (AB Biodisk™, Solna, Sweden) for testing Campylobacter isolates.

The goals and objectives of the monitoring program are to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility of enteric organisms from the human and animal populations; provide timely information to veterinarians, physicians, and public health authorities so that timely action can be taken; prolong the life span of approved drugs by promoting the prudent use of antimicrobials; identify areas for more detailed investigation; and guide research on antibiotic resistance. Annual reports summarizing the data are available on the Internet (http://www.fda.gov/cvm/mappgs/narms.htm and www.cdc.gov/ncidod/dbmd/narms).

The NARMS was substantially expanded during 1998 and 1999. Veterinary diagnostic lab sentinel sites were enrolled and the number of Salmonella isolates collected from slaughter plants was increased. Follow-on epidemiology research and investigations augmented the program. Case-control follow-up investigations of human cases of salmonellosis and campylobacteriosis with losses in susceptibility to quinolones were begun. Two projects on prudent drug use activities were initiated in California and Michigan. On-farm poultry studies, designed to elaborate management, production, and drug use practices that influence the development of resistant zoonotic pathogens, were undertaken in 5 states.

Unfortunately, NARMS does not provide sufficient information to ensure continued safety of specific food animal antimicrobials after approval. The monitoring program is only a sentinel system and has a number of inherent limitations. Although it is possible to identify that a problem exists, the magnitude of the problem cannot be estimated with the monitoring system data alone. NARMS is not capable of identifying how or why the resistance occurred. Data related to the resistance findings, such as demographic information and history of drug use, are not collected in the animal populations. Therefore, the data cannot be linked to particular practices of concern.

### Post-Approval Monitoring Programs

To address the limitations with NARMS, FDA proposed in the framework document that on-farm drug-specific post-approval monitoring programs be undertaken by the drug

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**Table 1. Antimicrobial agents on Sensititre™ plates for 1999 and 2000 for testing animal and human isolates of Salmonella and E. coli**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Concentrations, µg/mL</th>
<th>Breakpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>4–32</td>
<td>64</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>0.5/0.25–32/16</td>
<td>32/16</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2–32</td>
<td>32</td>
</tr>
<tr>
<td>Apramycin</td>
<td>2–32</td>
<td>32</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.25–64</td>
<td>64</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>1–32</td>
<td>32</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>4–32</td>
<td>32</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.015–4</td>
<td>4</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>2–16</td>
<td>Undefined</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.25–16</td>
<td>16</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>16–64</td>
<td>64</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>4–256</td>
<td>32</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>32–256</td>
<td>64</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>128–512</td>
<td>512</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>4–32</td>
<td>16</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>0.12/2.38–4/76</td>
<td>4/76</td>
</tr>
</tbody>
</table>

* Ranges were chosen to detect incremental changes in resistance based on previous 2 years of data; ranges may be outside the breakpoint value.
sponsors for Category I drugs. These programs would be designed to fill data gaps identified in NARMS. On-farm surveys could provide a true prevalence of resistance or decreased susceptibility to specific drugs or drug classes in a food animal production setting under actual use conditions. These surveys could also collect risk factor information such as drug exposure associated with the isolates undergoing susceptibility testing. Because the resistance outcome could be linked to contextual information surrounding the isolate, on-farm data would provide a strong body of scientific evidence that specific factors, drug-related or non-drug-related, are leading to resistance outcomes. A broad national on-farm monitoring program rather than drug-specific post-approval monitoring could meet these objectives. The monitoring programs would need to be species-specific only, because many drug classes could be tested on the same isolates and many pathogens could potentially be isolated from the same sample.

In addition to other scientific data, findings from the on-farm surveys could provide a critical early warning of the emergence of resistance. FDA anticipates that these surveys, together with NARMS, could provide a robust system to monitor for established regulatory thresholds. The on-farm surveys could also be used to investigate intervention strategies to mitigate resistance development and implement promising strategies in a timely fashion. Moreover, on-farm data would provide science-based evidence to evaluate the effectiveness of intervention strategies.

Conclusion

The debate over the human health impact of drug use in food-producing animals has continued for over 30 years. A complete risk assessment of this issue has been hindered by a lack of accurate quantitative data. Recently, FDA published a framework document outlining the types of data that are necessary to provide protection of the public health while enabling the use of safe and effective drugs for veterinary medicine. The agency is seeking public input on how best to refine and implement this regulatory framework and provide the data needed to end the debate.

References

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