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RESTRICTION CODES

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FAX TRANSMISSION

To: Chris Jennings **Date:** 12/7/98

Fax #: 202/456-5557 **Pages:** 2 , including this cover sheet

From: Office of Public Affairs
Food and Drug Administration

Associate Commissioner for
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COMMENTS:

Qs and As on Rezulin
December 7, 1998

Q. *Yesterday, the LAT ran a story stating that the fast track review of rezulin has led to 33 deaths. Is the White House concerned that FDA is approving drugs too fast?*

* Millions of people benefit from the life saving drugs and products approved by the Food and Drug Administration, but all drugs have both benefits and risks. Prescription drugs must be taken carefully and in consultation with a health care provider.

* FDA is committed to ensuring that safe and effective products are available to consumers.

* Specific questions on rezulin should be referred to the FDA.
(FDA will say that we continue to believe that rezulin is safe when used as prescribed for the intended population.)

Q. *Did the FDA remove the chief medical officer from review of the drug?*

* Again, you should call the FDA for specifics on the drug.
(FDA cannot comment on specifics about the case under the Privacy Act.)

A Move to Limit Antibiotic Use In Animal Feed

By DENISE GRADY

Faced with mounting evidence that the routine use of antibiotics in livestock may diminish the drugs' power to cure infections in people, the **Food** and **Drug Administration** has begun a major revision of its guidelines for approving new antibiotics for animals and for monitoring the effects of old ones.

The goal of the revision is to minimize the emergence of bacterial strains that are resistant to antibiotics, which makes them difficult or even impossible to kill. **Drug**-resistant infections, some fatal, have been increasing in people in the United States, and many scientists attribute the problem to the misuse of antibiotics in both humans and animals.

Of particular concern to scientists are recent studies showing bacteria in chickens that are resistant to fluoroquinolones, the most recently approved class of antibiotics and one that scientists had been hoping would remain effective for a long time.

A crucial component of the new guidelines will be the requirement that manufacturers test certain new livestock drugs for a tendency to foster the growth of resistant bacteria that could prove harmful to people. Testing will be required both before a drug is approved and after.

The types of antibiotics that would get special scrutiny are those that are also used by humans or related to drugs used in people. If the drugs are shown to foster bacterial resistance, they could be banned from use as growth promoters in animals.

The proposed guidelines have drawn criticism from both sides of a bitter debate that has been going on for three decades. At issue is the extensive use of antibiotics in livestock: of the 50 million pounds of antibiotics produced every year in the United States, about 40 percent is given to animals, mostly as feed additives to promote growth. Scientists say they do not know how or why the drugs promote growth.

On one side, the **drug** and agriculture industries say the F.D.A. is going too far toward restricting access to antibiotics, which they insist have not been proved to harm people and are essential to produce safe and affordable meat and

poultry. The industries also say the rules will make **drug** development, already difficult and expensive, even more so.

At a January meeting held by the F.D.A. to discuss the changes, Dr. Brendan Fox, president of Elanco Animal Health, a division of the pharmaceutical concern Eli Lilly & Company, said, "We believe the agency is greatly overstating the conclusiveness and the implications of the data and has put forth a seriously flawed proposal."

On the other side, public health and consumer advocates, as well as some scientists, say the F.D.A. is not going far enough, because antibiotics are a precious medical resource that should not be squandered to fatten animals. Tomorrow, a coalition of 37 groups, led by the Center for Science in the Public Interest, a nonprofit group based in Washington, will petition the F.D.A. to separately rule that if a **drug** is used to treat diseases in people, it can no longer be given to animals as a growth promoter.

The agency's working proposal, or framework, which is open for public comment until April 6, will not be translated into new regulations for about two years. But Dr. Stephen F. Sundlof, director of the center for veterinary medicine at the **Food** and **Drug Administration**, said the agency was acting now because the nation is in a vulnerable period, with no new classes of antibiotics expected to come onto the market for several years. That makes it all the more important to preserve the potency of existing drugs, he said.

The reason there are no new types of antibiotics in the pipeline is that in the 1980's there seemed to be more than enough, and companies stopped making new ones, Dr. Sundlof said. They have resumed, but it can take 10 years to bring a **drug** to market.

The last new class of antibiotics approved, fluoroquinolones, came into use in 1986. The drugs are the best treatment for certain infections, like gastrointestinal illness caused by salmonella bacteria. Dr. Sundlof said the agency was especially concerned about averting the development of widespread resistance to these drugs.

"Resistance has always been a problem in human medicine," Dr. Sundlof said. "The way we had avoided any catastrophic events was to continue to develop new products. But it became apparent in the 1990's that there weren't any new classes at the stage of development where they'd be approved and available in the near future, and there was great concern that if resistance developed to this last class of drugs, it could have very bad ramifications for the public."

The petition by the Center for Science in the Public Interest and other groups will ask the United States to follow the lead of Europe, where antibiotics used to treat people cannot be given to animals to promote growth.

In the United States, 6 of the 17 classes of antibiotics given to animals for growth promotion are also used to treat sick people. Though patients need a prescription to get the drugs, farmers can buy many of them, including penicillin and tetracycline, over the counter. Some antibiotics used in humans are also sprayed on crops as pesticides.

Dr. Sundlof said that it was beyond the authority of the F.D.A. to pass a blanket ban.

Dr. Stuart B. Levy, director of the Center for Adaptation Genetics and **Drug** Resistance at Tufts University in Boston, said he did not think it necessary to

ban all antibiotics used for growth. But he also said: "I would very rapidly remove human antibiotics from growth promotion. The U.S. has to join the European Union on that. We look a little silly."

Antibiotic resistance develops from repeated exposure to the drugs. Initially, some bacteria may be naturally resistant, and they will survive treatment and multiply. When antibiotics are given again, more of the bacterial population may become resistant, and as that proportion increases over time, the drugs may become less effective.

Many scientists believe that giving low doses to animals over long periods brings out resistance.

Scientists say that resistant bacteria from animals can make people sick in several ways. A person can become ill from contact with an animal carrying a disease-causing resistant germ, or from handling contaminated meat or eating it when it has not been cooked thoroughly. The infection may be impossible to treat.

In some cases, the resistant bacteria may be harmless, but live on in the gut and cause trouble later by passing their genes for antibiotic resistance to other bacteria, ones that cause disease. Or, if a person's immune system is weakened by illness, what seemed like harmless bacteria can turn dangerous.

At the Centers for Disease Control and Prevention, researchers said they had detected increases in levels of **drug**-resistant bacteria in people with gastrointestinal illness from the microbes salmonella and campylobacter, which are most commonly contracted from meat or eggs.

Last May, a team from the centers reported in the New England Journal of Medicine that the prevalence of a salmonella strain resistant to five different antibiotics increased from 0.6 percent of all specimens from around the country tested by the centers in 1980 to 34 percent in 1996.

Similarly, **drug** resistance in campylobacter bacteria rose from zero in 1991 to 13 percent in 1997 and 14 percent in 1998, said Dr. Fred Angulo, an epidemiologist in the **food**-borne and diarrheal disease branch at the centers. He said epidemiologists had been alarmed by the campylobacter figures, because the resistance was to fluoroquinolones, the very drugs the F.D.A. was trying hardest to preserve.

Dr. Angulo said that he and his colleagues had attributed much of the increase in fluoroquinolone resistance to the **drug** agency's approval of the drugs to treat a respiratory infection in chickens in 1995. It was an approval that the disease control centers opposed, because it would lead to tens of thousands of the birds being treated at one time.

Dr. Angulo said he thought the rising levels of resistance in bacteria taken from sick people had been caused by the heavy use of antibiotics in livestock. "Public health is united in the conclusion," he said. "There is no controversy about where antibiotic resistance in **food**-borne pathogens comes from."

A recent study, scheduled to appear in the New England Journal of Medicine, offers strong evidence that people pick up **drug**-resistant bacteria from chickens. In that study, researchers at the State Health Department in Minnesota found that fluoroquinolone-resistant campylobacter had increased to 10.2 percent of cases in 1998 from 1.3 percent in 1992. The sharpest rise began in 1996, a year after fluoroquinolones were approved for chickens.

Dr. Michael Osterholm, a former state epidemiologist in Minnesota, said in a telephone interview that the health department had also found campylobacter in 88 percent of the chickens they bought in supermarkets in Minneapolis and St. Paul. Twenty percent of the chickens had a resistant strain, and it matched the strain isolated in people.

Healthy people recover from campylobacter, often without even being treated, Dr. Osterholm said. But in patients whose immunity has been lowered the infection can be deadly.

And the proportion of society in that vulnerable category is increasing, because of the aging population, Dr. Osterholm said. "One of the things we're beginning to understand," he said, "is that we'll see a major change in the implications of **food**-borne disease in our population. As we get a little older, it has a much more serious implication."

Given the widespread availability of antibiotics on farms and the entrenched habit of using them, Dr. Angulo said that regulation alone probably would not bring about the changes that were needed. "People would have to accept that there is a problem," he said. "Many don't. It's a societal change, and we have the same problems in human medicine." Many people, he said, demand antibiotics for viral infections and other problems that the drugs cannot help.

"The way we will make major progress, unfortunately," Dr. Angulo said, "is when there is continuing emergence of treatment problems, not just in humans, but when these drugs don't work in sick animals."

Organizations mentioned in this article:
Food and **Drug Administration**

Related Terms:
Livestock; Antibiotics

Q: what have

A:

Q: Are you concerned about reports that ———— .

Q: ~~What are you~~

raised Issue in numerous diff contexts Bridget CDC ~~FDA~~ recently

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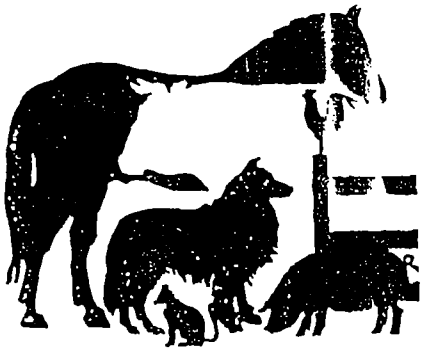
NOTES: The background information on antimicrobial resistance.



Center for Veterinary Medicine
Stephen F. Sundlof, DVM, Ph.D.
Center Director

March 17, 1999

THE ISSUE OF ANTIMICROBIAL USE IN FOOD ANIMALS

The issue of antimicrobial use in food animals has been controversial for more than three decades. The Food and Drug Administration (FDA) first called for several restrictions on antimicrobial use in feed in 1977. That proposal has generated several studies and reports. Definitive answers about the safety of antimicrobial use in animals remain scientifically challenging, but we are continuing to uncover more truths and, more important, have begun updating FDA's process for determining whether antimicrobial products can be used in food animals.

In the United States, FDA is the primary Federal agency responsible for ensuring the safety of the food supply. While the Center for Food Safety and Applied Nutrition regulates the vast majority of human food, FDA's Center for Veterinary Medicine (CVM) ensures that animal drug products are effective and safe for animals and consumers of edible products from treated animals.

CVM, which is part of FDA, is responsible for establishing the safety assessments for the use of antimicrobial drugs in food from animals, and the U.S. Department of Agriculture is primarily responsible for testing the meat supply for microbiological contamination and animal drug residues in the food from animals.

Although the use of antimicrobial products in food-producing animals raises various efficacy and safety concerns, in recent years these concerns have focused on human food safety because foods of animal origin are often identified as the vehicles of foodborne disease in humans. As a result of treatment of the animal with antibiotics, these microbes may also be resistant to antibiotics used to treat humans.

The source for some of the pathogens found on food may be the colon of the slaughtered animal. Feces that contain harmful bacteria can contaminate the meat at slaughter. An estimated 1% of beef carcasses and possibly 20% of poultry carcasses are contaminated with *Salmonella*.

Treatment of food-producing animals with antimicrobials may alter pathogen load and/or the resistance pattern of bacteria associated with the animal. Thus, to ensure the human food safety of edible animal products from animals treated with antibiotics, CVM considers these criteria for non-therapeutic uses:

1. The safety of the chemical residues, including the drug and its metabolites.

2. The microbiological safety, including changes in bacterial pathogen load and resistance pattern that occur as a result of drug use.

The use of antibiotics to treat disease in food-producing animals started in the mid-1940s. The scientific debate over the possible public health risks posed by such use started more than 30 years ago, when researchers first reported that the addition of streptomycin to chicken feed increased the rate of growth of the chickens. The introduction of affordable antibiotics in feed for cattle, pigs, and chickens started in the early 1950s. It launched a new era in livestock management and meat production.

RESEARCH AND ACTIONS

Soon after livestock producers began using antimicrobials in food-producing animals, scientists began studying the possible effects of long-term use of antibiotics. Here's a review of the studies and reports to date.

1960 Netherthrope Committee
It was formed in the U.K. to consider possible human health implications from the use of subtherapeutic antibiotics in livestock and concluded that there was no evidence of a human health hazard associated with the use.

1969 Swann Committee
Also formed in the U.K., the committee reported no hazard to humans or animals from the use of antibiotics in poultry or swine. However, it linked an outbreak of salmonellosis in humans to the therapeutic use of antibiotics in sick calves. The committee recommended:

1. Antibiotics used in animals should be divided into "feed" or "therapeutic" classes.
2. The "feed" antibiotics class should not include drugs used therapeutically in humans or animals.
3. "Therapeutic" antibiotics should be available only by prescription.

1970 FDA Task Force
The task force report, "The Use of Antibiotics in Animal Feeds," concluded:

1. The use of subtherapeutic amounts of antimicrobials favored the selection and development of resistant bacteria.
2. Animals receiving antimicrobial treatment may serve as a reservoir of antibiotic resistant pathogens that can produce human disease.
3. The prevalence of multi-resistant bacteria in animals has increased due to the use of antimicrobials.
4. Resistant bacteria are present in meat and meat products.
5. There has been an increase in the prevalence of antimicrobial resistant bacteria in man.

Based on the report's recommendations, CVM began requiring microbiological safety studies for non-therapeutic uses. The focus of these studies was to preserve efficacy and safety of antibiotics for animal uses and the safety evaluation included an evaluation of human health concerns.

1977 CVM Proposal

In 1977, CVM proposed to withdraw the subtherapeutic uses of penicillin and the tetracyclines from animal feeds when used alone or in combination. These two drugs were chosen because of their importance in human medicine.

The proposals were criticized because at the time because of a lack of epidemiological evidence to show that the drug-resistant bacterial 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. Also, the critics said, no evidence showed that "any transferred organisms actually survive or cause disease in humans. The critics argued instead that the increased antibiotic resistance of bacteria found in humans was a result of the use of antibiotics in human medicine.

1980 NAS Study

As a result of the 1977 proposal, several studies were started. In 1978, FDA began to work with the National Academy of Sciences to study the issue. In 1979, the Congress required FDA to spend $1.5 million of its appropriations for a study of the antibiotics issue, to be conducted by NAS. The NAS study was finished in 1980. It concluded that existing data had neither proved nor disproved the potential hazards to human health from subtherapeutic antimicrobials use in animal feeds.

1984 NRDC Petition

In 1984, the Natural Resources Defense Council, Inc. (NRDC), petitioned the Department Health and Human Services (HHS) to suspend immediately approval of the subtherapeutic use of penicillin and tetracyclines in food animals by invoking the imminent hazard provision of the Food, Drug, and Cosmetic Act, 21 U.S.C. Sec. 360b(E)(1). That provision authorizes the Secretary of HHS to suspend approval of an application for the use of a new 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 case on several studies, two by Holmberg, et al., at the CDC in Atlanta, GA and one published by Thomas O'Brien, et al. in the *New England Journal of Medicine*. However, in November 1985, HHS denied the petition on the basis that an "imminent hazard" had not been demonstrated. This decision was based on an analysis of the NRDC's evidence as well as scientific evidence, information, and opinions coming out of the January 1985 public hearing and other relevant data collected and analyzed by FDA.

1984 King County Study

In 1981, the House Appropriations Committee provided money in FDA's budget for a definitive epidemiological study of the antibiotics in animal feeds issue. The Committee

stated that FDA should hold in abeyance any implementation of the proposed withdrawal pending completion of the studies and reevaluation of FDA's concerns. FDA contracted with the Communicable Disease Control Section of the Seattle-King Country Department of Public Health to review the possibility of the movement of bacteria from chickens to humans. The study focused on poultry workers, slaughterhouse workers and consumers. The report, "Surveillance of the Flow of *Salmonella* and *Campylobacter* in a Community," found the *Campylobacter jejuni* was more common on poultry than was salmonella. Also, it found that *C. jejuni* "does appear to flow from chickens to man via consumption of poultry products." The report stated that the "isolates from human cases and those from retail poultry had similar antibiotic susceptibility patterns, including prevalence of 29.7% and 32.8%, respectively, for tetracycline resistance, which was found to be plasmid-mediated."

1987 FDA Report

In its report, "Antibiotics in Animal Feeds: An Assessment of Scientific Data Concerning Their Safety," FDA concluded that the therapeutic use of antibiotics would not significantly contribute to the frequency of resistant organisms because of the pattern of use of these products. Therapeutic use is typically for a select number of animals and for a short duration, situations that are not likely to lead to antibiotic resistance, the report said.

1988 IOM Review

In 1988, the Institute of Medicine (IOM) 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. The Committee found a considerable amount of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard but did not find data demonstrating that use of subtherapeutic penicillin or tetracycline directly caused a human to die from salmonellosis. The Committee strongly recommended further study of the issue.

1995 AMS Report

The American Society of Microbiology (ASM), 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. The report advocated a significant increase in resistance monitoring in the U.S., 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, which was partly attributed to the consolidation of farms to facilities with large numbers of confined animals. The report made it clear that the antibiotic

resistance problem is global and the ASM report was a precursor to involvement by the United Nation's World Health Organization (WHO).

1997 WHO Meeting

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. 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 food of animal origin. In addition, the group recommended managing risk at the producer level through the prudent use of antimicrobials.

1998 WHO Meeting

In June 1998, the 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. 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.

1998 CSPI Report

In May 1998 the Center for Science in the Public Interest (CSPI) in a coalition with 15 other health and consumer groups produced a comprehensive report on the antibiotic resistance problem. 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.

1998 NRC Report

In July 1998 the National Research Council (NRC) produced a report reviewing antimicrobial resistance issues in broad terms. The NRC recommended establishing of

national databases to support scientific process and policy development for approval and use of antibiotics in food animals. The Council also recommended that FDA use interdisciplinary panels of experts so that "...further development and use of antibiotics in both human and animal medicine have oversight by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy groups, the animal production industry, and the regulatory agencies."

1998 EU Action

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 four 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 becomes effective for the fifteen member states of the European Union on July 1, 1999.

CURRENT ISSUES

For several years, CVM has approved new antimicrobials for use in animals for therapeutic purposes as prescription-only products. This prescription-only policy is based on CVM's desire to assure the proper use of antimicrobials though precise diagnosis and correct treatment of disease to minimize animal suffering and to avoid drug residues in food. Antimicrobial products for use in animals have to meet FDA's standards for safety, efficacy and quality to be approved in the US.

When antimicrobial products are intended for use in food-producing animals, safety considerations include the evaluation of data to ensure that residues in food derived from treated animals, are safe for human consumption. In the past, microbiological safety studies were only required for antimicrobials to be used in feed for more than 14 days. These studies examined resistance patterns and pathogen load.

In the 1990s, several scientists raised concerns about the therapeutic use of fluoroquinolone antibiotics in food-producing animals. The scientists said the use could lead to enteric disease in humans associated with fluoroquinolone-resistant zoonotic pathogens. At least part of this concern was prompted by the fact that the search for new antimicrobial drugs and other novel agents to combat bacterial pathogens had decreased in recent years, leaving fluoroquinolones as the last family of therapeutic agents available to treat some multiply resistant organisms. Adding to that concern were reports of a temporal association between the approval of fluoroquinolone for therapeutic use in poultry and the emergence of a fluoroquinolone-resistant *Campylobacter* spp. from humans.

To further investigate the public health concerns regarding the potential impact of fluoroquinolone use in food-producing animals and to determine whether the 1987 FDA report (which concluded that therapeutic antimicrobials used for short duration were safe) was still valid, FDA held a Joint Advisory Committee meeting in 1994 that included the

CVM Advisory Committee and the Center for Drug Evaluation and Research's Anti-infective Drugs Advisory Committee. The joint committee recommended that fluoroquinolones be approved, but that the use of the drugs should be limited to prescription only, that no extra-label use should be allowed, and that resistance should be monitored after the product was approved.

CVM created a Fluoroquinolone Working Group to address the points raised by the joint committee. The Working Group offered seven recommendations, all of which were accepted by CVM, and subsequently the use of fluoroquinolones was approved for poultry. As part of the recommendations, the sponsors agreed to provide baseline susceptibility information and to conduct continuing monitoring of target animal pathogens through the post approval monitoring program.

More recently, scientists have detected a new multi-resistant pathogen, *Salmonella typhimurium* DT104. The organism carries chromosomally integrated resistance to Ampicillin, Chloramphenicol, Streptomycin, Sulphonamides and Tetracycline. This chromosomally integrated resistance is unique and raises concerns about the establishment of a reservoir of multi-drug resistant organisms that are zoonotic enteric pathogens that may become endemic in food-animal microbial populations. In addition to the chromosomally borne penta-resistance, the organism seems to be losing its susceptibility to quinolone and trimethoprim antibiotics and has been recently shown to carry additional florfenicol and spectinomycin resistance.

A report from the UK suggests that infections caused by DT104 may be associated with greater morbidity and mortality than other infections by *Salmonella*. 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 UK. This organism has also been identified in livestock and poultry in the U.S. Human disease caused by DT104 in the U.S. has been associated with unpasteurized dairy products and direct contact with livestock.

DT104 is currently epidemic in human and animal populations in Great Britain and has been isolated from most countries in Europe. The organism more recently has been found in the U.S. and appears to be increasingly prevalent in both domestic and wild animals. The most notable outbreak of DT104 was on a dairy farm in Vermont.

The DT104 findings DT104 caused FDA to aggressively move ahead with plans to change the regulatory framework for approving antimicrobial products. The discovery of DT104 was a turning point for FDA, and led to the development of a proposed regulatory course for the Agency.

Reports from the scientific and public health communities, both domestically and internationally, have identified concerns about the relationship between the approval of fluoroquinolones for therapeutic use in food-producing animals and the development of fluoroquinolone resistance in *Campylobacter*. The approval of these drugs in food-producing animals in the Netherlands, the United Kingdom, and Spain temporally

preceded increases in resistance in *Campylobacter* isolates from humans. Despite several restrictions placed on the use of the two approved poultry fluoroquinolone products in the U.S., ciprofloxacin-resistant *Campylobacter* were recently isolated from 20% of domestic retail chicken products sampled. Molecular subtyping revealed an association between resistant *C. jejuni* strains from chicken products and *C. jejuni* strains from domestically acquired human cases of campylobacteriosis.

Framework Document

FDA's concept of the best regulatory approach for antimicrobial approvals is explained in what is called the "Framework Document," ("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"), which is available on the CVM Home Page at http://www.fda.gov/cvm/fda/infores/vmac/antim18.htm or http://www.fda.gov/cvm/fda/infores/vmac/antim18.pdf.

The document was released to the public December 9, 1998, and FDA will accept comments on it until April 6, 1999.

The proposed framework takes into consideration two factors that would be used in evaluating human health concerns associated with food-animal use of antimicrobials:
1. The importance of the drug or class of drugs for human medicine, and
2. The potential exposure humans would face to resistant pathogens or resistant elements originating from animals treated with an antimicrobial, and the impact this exposure would have on the availability and effectiveness for human medicine of drugs to which the resistance has developed.

Depending on the importance of the drug (or a related drug) to human health, FDA would place it in one of three major Tiers. Each Tier would have different requirements for approval. The requirements for approval may include both pre-approval screening and post-approval monitoring conducted on farms.

FDA's implementation of the framework will require the development of guidance documents and perhaps new or amended rules. All such guidance or rules would be developed with public input, and FDA will consider any needed change as a high priority.

Under the framework document, antimicrobial drugs would be placed in Class I, the level with the greatest approval requirements, if:
1. They are needed to treat a serious or life-threatening disease for which there is no satisfactory alternative therapy, and
2. They are important for the treatment of foodborne diseases.
Drugs that can select for cross-resistance to Class I human agents would also be listed in Class I, unless the sponsor could demonstrate that animal use did not result in the induction of resistant pathogens or the transfer of resistant elements to human pathogens.

Drugs would be placed in Class II if:

1. They are of high importance or are the drugs of choice to treat a serious or life-threatening disease, but a satisfactory alternative therapy exists.
2. They are members of a class of drugs that have a unique mechanism of action or nature of resistance-induction, that rarely produce resistance in human pathogens, and that hold potential for long-term therapy in human medicine.

FDA would put products into Class III if they do not meet any of the requirements of the other two classes.

NARMS

CVM now believes that the safety assessment of antimicrobials must include evaluation of resistance concerns with the conduct of pre-approval studies and post approval monitoring programs, which are aided by the National Antimicrobial Resistance Monitoring Systems (NARMS).

The program was proposed by CVM as a post-marketing activity to monitor the emergence and spread of resistance in enteric bacteria and to help ensure the continued safety and effectiveness of veterinary antimicrobials. In 1996, the FDA, CDC, and the U.S. Department of Agriculture (USDA) 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. Non-typhoid *Salmonella* was selected as the sentinel organism; the NARMS has been expanded each year since its inception. At the present time, NARMS is monitoring susceptibilities of *Salmonella* and *E. coli* isolates to 17 antimicrobics and *Campylobacter* isolates to 8 antimicrobics (azithromycin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamycin, nalidixic acid, and tetracycline.

Veterinary testing is conducted at USDA's 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 (CA, CO, CT, FL, GA, KS, Los Angeles County, MA, MD, MN, NJ, NEW YORK City, NY, OR, TN, WA, and WV) submit human clinical isolates of non-typhoid Salmonella and E. coli. *Campylobacter* isolates are submitted by eight health departments and in addition MN, GA, MD and OR are submitting *Campylobacter* isolates from poultry retail samples. A pilot study involving MN, GA, MD and OR to monitor the resistance of human and poultry *Enterococcus* isolates to 27 antimicrobials was begun in 1998.

The goals and objectives of the monitoring program are to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in *Salmonella* and other enteric organisms from the human and animal populations; provide timely information to veterinarians and physicians; prolong the life span of approved drugs by promoting the prudent use of antimicrobics; 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/fda/mappgs/narms/html and www.cdc.gov/ncidod/dbmd/narms).

The NARMS was substantially expanded during 1998. Veterinary diagnostic lab sentinel sites were enrolled as well as additional FoodNet sites and the number of *Salmonella* isolates collected from slaughter plants was increased. Beginning January 1, 1999, the State and local health departments began to submit human *S. typhi* and *Shigella* isolates.

Also in 1998, follow-on epidemiology research and investigations augmented the program. On-farm poultry studies were begun in five states, which are designed to elaborate management, production, and drug use practices that influence the development of resistant zoonotic pathogens. Collaborative molecular genetic studies have begun at FDA's National Center for Toxicological Research in Arkansas to identify regions of fluoroquinolone resistance in zoonotic enteric organisms. This information will be applied to enteric and environmental bacteria to provide improved monitoring for resistance emergence and transfer. Case-control follow-up investigations of human cases of salmonellosis and campylobacteriosis with losses in susceptibility to quinolones were begun in 1998. Also in 1998, two projects on prudent drug use activities were initiated in California and Michigan.

PRUDENT USE

CVM believes it is critical that prudent use of antimicrobials be emphasized in order to minimize the development of antimicrobial resistance and to ensure the continued efficacy and availability of antimicrobial products for use in food-producing animals. To promote this concept, CVM and CDC facilitated a meeting on "Prudent Use" held in May last year in Rockville, Maryland.

The objective of the meeting was to develop a plan to promote the prudent use of therapeutic antimicrobials in veterinary medicine. At the meeting, several groups agreed to develop programs about Prudent Use, and the effort was led by the American Veterinary Medical Association (AVMA), which has developed its prudent use program of "Judicious Use."

The Executive Board of AVMA has agreed to principles concerning Judicious Use developed by a special AVMA Steering Committee. CVM and CDC provided experts to advise the Steering Committee. CVM strongly supports the effort to develop judicious use principles for veterinary practitioners, and will financially support efforts to publicize the guidelines.

Key elements of prudent use that CVM believes should be addressed:

1. Development of prudent use principles.
2. Therapeutically based antimicrobial use guidelines
3. Recommendations on appropriate measures to reduce disease transmission.
4. Educational programs for prescribers and users of these drugs.

CVM defines "Prudent Use" of therapeutic antimicrobial agents as the...

> "Use that maximizes therapeutic effect while minimizing the development of

resistance."

At that meeting and in other contacts, CVM will solicit advice from the human medical community in the development of "Prudent Use" principles because their expertise about what has worked and not worked in human medicine will be useful. The development of the Prudent Use principles won't be static. Instead, the process will likely demand continued attention. In fact, CVM will probably engage food animal producers on this issue at some time in the future.

JFS - 1
March 17, 1999

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b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Chris Jennings Schedule
Thursday, March 25, 1999

9:15 - DPS Staff Mtg - **Rm 211**

10:30 - **Briefing President**
"Nursing Homes"

12:15 - **Conf. Call** " Grijalva"
w/Jeanne, H. Raab
(will call here)

1:30 to 3:00 - Mtg w/ Seniors
on OAA w/B. Woolley
Truman Room (Jackson Place)

4:00 - Health Strategy Mtg
Bruce's ofc

5:00 - Medicare Deputies Mtg
Rm 100 -(M. Hash by phone)

6:00 - Conf. Call w/ K. Thurm, Elena
"HC Provisions in Crime Bill (Nursing Hm)"
(Kevin will call here)
(Elena will come to Chris's ofc)

7:00 - P6/(b)(6) [001]
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Revised: 11:25am-3/25