The Issue of Antimicrobial Use in Food Animals

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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 over the subsequent years. 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 regulatory process for evaluating antimicrobial drugs intended for use 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 is responsible for establishing the safety assessments for the use of antimicrobial drugs in food from animals, and the U.S. Department of Agriculture (USDA) 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 treating an animal with antimicrobials, these microbes may also be resistant to antimicrobials used to treat humans.

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 antimicrobials, 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.

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 must meet FDA's standards for safety, efficacy, and quality to be approved in the United States.

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 required only 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 antimicrobials 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 multiple-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 effect of fluoroquinolone use in food-producing animals and to determine whether an earlier FDA report (concluding that therapeutic antimicrobials used for short duration were safe) was still valid, FDA held a Joint Advisory Committee meeting in 1994. The meeting 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.

More recently, scientists have detected a new multiresistant pathogen, *Salmonella typhimurium* DT104. The organism carries chromosomally integrated resistance (penta-resistance) to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. This chromosomally integrated resistance is unique and raises concerns about the establishment of a reservoir of multidrug 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 antimicrobials and has been recently shown to carry additional florfenicol and spectinomycin resistance.

A report from the United Kingdom suggests that infections caused by DT104 may be associated with greater morbidity and mortality than other infections caused 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. Human disease caused by DT104 in the U.S. has been associated with unpasteurized dairy products and direct contact with livestock. DT104 has been found in livestock and poultry 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.

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 UK, 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 domestic retail chicken products. Molecular subtyping revealed an association between resistant *C. jejuni* strains from chicken products and *C. jejuni* strains from domestically acquired human cases of campylobacteriosis.

The discovery of DT104 and increasing evidence of fluoroquinolone resistance in *Campylobacter* led to the development of a proposed regulatory course for the Agency.

Framework Document

FDA's concept of the best regulatory approach for antimicrobial approvals is explained in what has been termed 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"). The document is available on the CVM Home Page, www.fda.gov/cvm. It can be found under the "Antimicrobial Resistance" category listed on the Home Page.

The document was released to the public December 9, 1998, and the comment period was scheduled to last 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 that 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.

Under the proposed framework, 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.

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.

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 System (NARMS).

NARMS 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 USDA created 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 antimicrobials and *Campylobacter* isolates to eight antimicrobial drugs (azithromycin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamycin, nalidixic acid, and tetracycline).

Animal isolate testing is conducted at USDA's Agricultural Research Service Russell Research Center. Human isolate testing is conducted at the Centers for Disease Control and Prevention's 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*. Eight health departments are submitting human clinical *Campylobacter* isolates, 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 antimicrobial drugs; identify areas for more detailed investigation; and guide research on antibiotic resistance. Annual reports summarizing the data are available through the CVM Website.

The NARMS was substantially expanded during 1998. Veterinary diagnostic lab sentinel sites were enrolled as well as additional sites to gather human isolates, and the number of Salmonella isolates collected from slaughter plants was increased.

Also in 1998, follow-on epidemiology research and investigations augmented the program. 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 1998 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, which has developed its prudent use program of "Judicious Use."

Conclusion

CVM's duty is to protect the public health. CVM has the additional duty to approve the safe use of antimicrobials in food animals when the approval is appropriate. CVM also has the responsibility to make sure that all of its work is based on science.

To address these responsibilities, CVM created the Framework Document. It gives FDA a way to protect public health, and consider future approvals of antimicrobials for food animals.

Many of the details about the framework are yet to be worked out. FDA and CVM will use open forums and public comments to gather the best science to settle those issues.

Without a regulatory course like the one provided in the Framework Document, CVM would have a difficult time moving ahead with any new approvals of antimicrobials for food animals.