CSPI Center for Science in the Public Interest

Publisher of *Nutrition Action Healthletter*

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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

To whom it may concern:

Please add the following comments to the docket [98D-1146] titled "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."

Sincerely,

Patricia B. Lieberman, Ph.D.
Staff Scientist

98D-1146

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Tel: (202) 332-9110
Fax: (202) 265-4954
Home Page: www.cspinet.org
E-mail: cspi@cspinet.org

Suite 300
1875 Connecticut Ave., N.W.
Washington, D.C. 20009-5728

Michael F. Jacobson, Ph.D.
Executive Director

IH-D-6

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Statement of Patricia B. Lieberman, Ph.D.
Staff Scientist
Veterinary Medicine Advisory Committee
January 25, 1999

CSPI has been working since 1971 on nutrition and food safety issues. We are the largest consumer organization which focuses primarily on food issues, reaching more than 1,000,000 North Americans with our publication, *Nutrition Action Healthletter*. While we are best known for our nutrition work, recently we have represented consumer interests in efforts to bring about changes in policy concerning the use of antibiotics in doctors' offices, hospitals, and on the farm. We released a report in May 1998, *Protecting the Crown Jewels of Medicine: A strategic plan to preserve the effectiveness of antibiotics,* and we work with a coalition of other health groups and scientific experts in antibiotic resistance. We appreciate the opportunity to speak at this important meeting.

In the past few years, many leading experts have urged reductions in agricultural uses of antibiotics. As you know,

- In the fall of 1997, a World Health Organization (WHO) commission stated that the use of any antimicrobial agent for growth promotion in animals should be terminated if it is used in human therapeutics or if it is known to select for cross-resistance to antimicrobials used in human medicine.

- In February 1998, Wolfgang Witte of the Robert Koch Institute in Germany stated in a commentary in *Science* magazine, "In the future, it seems desirable to refrain from using any antimicrobials for the promotion of animal growth. As exemplified by the use of virginiamycin in animal feed and the subsequent emergence of enterococci resistant to antibiotics, the use of any antimicrobial can lead to unexpected consequences that limit medical choices."

- In May 1998, Stuart Levy of Tufts University wrote in a *New England Journal of Medicine* editorial that recent findings have "made it even clearer that the use of growth promoters affects the drug resistance of environmental reservoirs, with direct consequences for the treatment of disease in humans" and that "such findings led to a ban on avoparcin in the European Union countries and, recently, on virginiamycin in Denmark."

- In December 1998, the European Union voted to ban the use of tylosin, spiramycin, virginiamycin, and bacitracin for growth promotion in livestock to come into line with the WHO recommendation.

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But in the U.S., instead of reducing uses of antibiotics in livestock, we are still expanding into new uses that have the potential to endanger human health. We applaud the FDA for at least attempting to slow this trend by including in the new animal drug approvals process new criteria that will consider antibiotic resistance. We strongly agree with the statement in the Framework Document, that "FDA's primary public health goal must be to protect the public health by preserving the long-term effectiveness of antimicrobial drugs for treating diseases of humans." That is a standard that must not be undermined by agribusiness's economic concerns.

The FDA Framework Document has several strengths. The first is that the proposal would require that detailed drug sales information be submitted as part of drug experience reports. In addition to sales data, it is imperative to know how the antibiotics are being used, in what species, in what dosages, for what purpose, and for how long. Currently, drug usage information is sorely lacking. Instead, the FDA must rely on rough estimates of how much antibiotics are used. Without detailed information it is difficult to correlate antibiotic use with the emergence of resistance. In order for any post-approval monitoring system to be effective, the FDA needs that piece of the puzzle. Furthermore, that usage information should not only be available to FDA but should be made publicly available to consumers and researchers.

In general, CSPI is supportive of a tiered approach to new animal antibiotic approvals, but we disagree on which categories are appropriate for use in food animals. We agree that the categorization should be based on several criteria.

- First, it should be based on how important the antibiotic is in treating human infections.

- Second, it should be based on how likely that its use in animals will cause resistance.

- Third, it should take into account the level of exposure to humans that the use in animals will cause.

Certainly a fluoroquinolone, because of its extreme importance in human medicine should be subjected to a higher level of scrutiny than would an ionophore. And antibiotics that are given for a long duration or to an entire flock should receive more scrutiny than a short-term use injectable product.

It is abundantly clear that the use of antibiotics in livestock leads to resistance among commensal bacteria in animals that can make people sick (for example in enterococci), or can horizontally transfer their resistance factors to human pathogens.

A striking example of horizontal transfer of resistance genes to a human pathogen due to agricultural uses of an antibiotic comes from Germany. In 1983, German farmers introduced a new antibiotic, nourseothricin, for growth promotion in swine. Before nourseothricin was used, nourseothricin resistance had never been observed in bacteria from animals or humans. In 1985, nourseothricin-resistance genes were found in *E. coli* in swine and pork products. By 1990, *E.*

coli containing the resistance gene were found in farm workers, farmers' families, citizens in the community in which nourseothricin was used, and patients suffering from urinary tract infections caused by *E. coli*. No nourseothricin-resistant bacteria were isolated from people or animals in other parts of Germany where the antibiotic was not being used. A few years later, the resistance gene was found in *Shigella,* a bacterium found in primates but not in swine. The appearance of nourseothricin-resistant *Shigella* suggested that resistance emerged due to the transfer of a resistance gene from bacteria exposed to antibiotics on the farm to a human pathogen. Therefore, the potential horizontal transfer of antibiotic resistance from commensal bacteria to pathogenic bacteria must be considered in ranking the antibiotic's importance. Similar consideration should be paid to antibiotics that select for multi-drug resistance.

While we agree with the FDA on the basic principles of how antibiotics should be categorized, we disagree on what would be the appropriate way to handle approvals of antibiotics in certain categories. The biggest problem is that Category I drugs should not be approved at all for use in livestock. Drugs that are essential for treating serious or life-threatening diseases in humans, for which there are no satisfactory alternatives; antibiotics that are important for treating foodborne diseases where there are limited therapeutic options; and drugs that are members of classes of drugs that have a unique mechanism of action or a unique resistance mechanism, should be preserved to protect human health. As previously stated, the FDA's primary responsibility is to protect the public health by preserving the long-term effectiveness of antimicrobial drugs for treating diseases of humans. Approving any Category I drug for livestock endanger public health and should only be considered if there are no other effective means -- either other available antimicrobials or changes in management practice -- to reduce a particular livestock disease.

Category II drugs delineated in the Framework Document should be held to the standards that FDA put forth for Category I drugs. Even though satisfactory alternatives currently exist, we must not allow their use in livestock to compromise their effectiveness in treating human disease.

Drugs deemed Category III in the existing Framework Document should be subdivided into two categories. Antibiotics that are little used in human medicine should be subjected to pre- and post-approval monitoring, detailed drug sales information should be kept, and resistance should trigger withdrawal of approval (as described in the Framework Document for Category II drugs).

Drugs that are not used in human medicine, such as ionophores or polymixins, should be held to the pre- and post-approval studies and monitoring laid out for Category III drugs, unless there is new evidence to suggest that their use in animals endangers human health, for example by causing cross resistance to antibiotics important in human medicine, or selecting for multi-drug resistance.

To adequately protect public health, FDA's framework must prevent agricultural drug use from causing human illness. It is not enough to just set guidelines for revoking a drug approval

once people get sick. For any antibiotic that is the drug of choice or important in treating potentially serious human diseases, decreased *in vitro* susceptibility in animal isolates may be the appropriate threshold instead of waiting to see decreased susceptibility develop in human isolates, or complete clinical resistance.

If after an approval is granted a resistance threshold is reached, the drug should immediately be withdrawn. Our concern is that if the drug is not withdrawn immediately, and a protracted regulatory process is necessary to stop the drug's sale, the public health may be put in danger. For example, if the FDA must apply section 512(e) that allows for industry to request a hearing if FDA wants to revoke an approval, it may be years before an antibiotic that is causing resistance to develop is removed from the market. We also are concerned that the industry will endlessly stall the FDA by arguing that no action should be taken because the threshold is inappropriate or that is was not based on sound science.

After the product is off the market, the drug's sponsor could propose mitigation strategies (such as changes in dosage or duration of treatment, education of veterinarians and farmers about proper use, and restrictions on how the drug is marketed) that might decrease the development of resistance and increase safety. If the proposed mitigation strategy is acceptable to the FDA then approval could be reinstated.

In the current Framework Document there is no proposal on how thresholds will be set. In general we are concerned that they will be too high. For antibiotics used in human medicine, thresholds should be set extremely conservatively to adequately protect the public health. Additionally, any post-approval monitoring system must be sensitive enough to detect even small changes in resistance, and include non-foodborne as well as foodborne pathogens.

A major weakness in the Framework Document is that, as written, it does not address already-approved antimicrobials. Since almost half of all antibiotics used in the U.S. are used in agriculture, and those drugs already are approved by the FDA, the Framework must be applied to drugs already on the market in order to protect the effectiveness of antibiotics for human, as well as veterinary, medicine.

We are particularly concerned about the antibiotics approved for subtherapeutic use in livestock. In FDA's own words, prudent use of antimicrobials is use that "maximizes therapeutic effect while minimizing the development of resistance." CSPI believes that under that definition of prudent use, the subtherapeutic (or nontherapeutic) use of antibiotics would not be allowed. Subtherapeutic use for growth promotion is not prudent because it increases the likelihood of antimicrobial resistance and jeopardizes the continued efficacy and availability of antimicrobials for use in livestock while providing no therapeutic effect. We urge the FDA to take steps similar to what the World Health Organization has proposed and the European Union has implemented to stop wasting these vital drugs on growth promotion. The minor and often unnecessary benefits of improved feed efficiency are not worth the threat that such uses pose to the continued effectiveness of antibiotics and to the public's health.

We also are concerned about certain therapeutic uses of antibiotics already on the market. For instance, in 1995, fluoroquinolones were approved for use in the drinking water of poultry flocks. Already fluoroquinolone resistance is emerging in poultry in the U.S. Michael Osterholm from the Minnesota Department of Health has reported preliminary findings from a study of poultry. He found that as many as 79% of supermarket chickens are contaminated with *Campylobacter* bacteria, and that 20% of those bacteria are resistant to fluoroquinolones. Among turkeys, 60% were contaminated with *Campylobacter*, 84% of which were resistant to fluoroquinolones. *Campylobacter* causes 2 million to 8 million illnesses and 200-800 deaths per year and is linked to Guillain-Barre syndrome.

We also think that the FDA should not have approved Baytril, the injectable fluoroquinolone product for cattle, in 1998. Previously approved antibiotics are just as effective in treating bovine respiratory infections. At a minimum, the FDA should have required *automatic* withdrawal of Baytril if harmful fluoroquinolone-resistant bacteria reached predetermined levels set by the FDA and CDC. Bayer agreed to *voluntarily* withdraw the product from the market if the FDA finds significant increases in fluoroquinolone resistance in post-approval monitoring. But that agreement lacks teeth. And if resistance develops due to Baytril's use it is likely to result in endless stalling and negotiations.

I am encouraged by Dr. Sundlof's recent comments at the FDLI meeting stating that review of already-approved antimicrobials would be possible within the new Framework contingent upon available funds. However, the language of the Framework Document should explicitly state that it will be applied to previously approved antimicrobials. Also, a review of the fluoroquinolone approvals, especially in poultry, should be among CVM's highest priorities.

We applaud the FDA for considering adding criteria on antibiotic resistance to the animal drug approval process. Let me summarize, if the FDA really wanted to protect the public health and preserve the effectiveness of these miracle drugs then it would need to strengthen the Framework by:

- applying the Framework to drugs that are already on the market such as antibiotics used for growth promotion and fluoroquinolones for disease treatment in poultry and cattle,

- more clearly laying out the process that would occur if thresholds are reached to withdraw a drug from the market, and

- not allowing Category I drugs to be approved for livestock other than in the most extreme cases to alleviate animal suffering when no other options exist.

We urge the members of VMAC to take into account these comments in their deliberation of the Framework Document. Thank you very much.