



Michael D. Maves, MD, MBA, Executive Vice President, CEO

September 22, 2006

Ms. Aleta Sindelar
Veterinary Medicine Advisory Committee
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

Dear Ms. Sindelar:

The American Medical Association (AMA) respectfully submits the following comments for consideration by the Food and Drug Administration's Center for Veterinary Medicine's Veterinary Medicine Advisory Committee (VMAC) regarding the proposed approval of the use of a 4th generation cephalosporin in food animals (cattle) in the United States.

The AMA notes that currently no 4th generation cephalosporins are approved for use in food animals in this country. The AMA is concerned by data that have accumulated on the use of a 3rd generation cephalosporin in food animals. The only 3rd generation cephalosporin approved for use in these animals in the United States is ceftiofur, which is widely used in cattle, chickens, and turkeys, in part because there is no withdrawal time. With the unrestricted use of ceftiofur, data from the National Antimicrobial Resistance Monitoring System (NARMS) indicate that ceftriaxone-resistant *Salmonella* and *E. coli* have emerged and spread in the United States. Ceftriaxone is commonly used for the treatment of severe infections, and the spread of resistance to this agent is therefore of clinical concern. Given the current outbreak of *E. coli* O157:H7 in this country, this increase in resistance is particularly troubling.

The scientific association between the use of ceftiofur in food animals and increased clinical resistance to ceftriaxone is compelling. In the United States, almost all ceftiofur and ceftriaxone resistance is due to a novel AmpC *cmv-2* gene. For many years, ceftiofur has not been used in many countries in Europe, such as Denmark and Sweden, and, indeed, the AmpC *cmv-2* mechanism for resistance to ceftriaxone is rare. However, cefquinome, a 4th generation cephalosporin, is approved for use in food animals in Europe and its use in some

food animals has been associated with dissemination of extended-spectrum beta-lactamase resistance, including cefepime-resistance in humans, due to the production of the novel beta-lactamase, CTM-X, by the resistant bacteria.

While the AMA recognizes that the proposal in question is for use of the 4th generation cephalosporin by injection only and only for “treatment,” significant concerns remain. Current technology enables injection of tens of thousands of chickens at one time through injection of the antibiotic into eggs one day prior to hatching, thereby increasing the unnecessary use of the drug. Indeed, this is the current mechanism by which 3rd generation cephalosporins are used in chickens in this country. “Treatment” does not mean the antibiotic is only employed when animals are sick; a veterinarian can choose to use a antibiotic for “treatment” when there is only a threat of infection (that is, as a preventive measure). Thus, while the 4th generation cephalosporin is not intended for use in animal feed at subtherapeutic levels, in the absence of appropriate regulation, it will be administered to a large number of animals, thereby increasing the risk of resistance that will eventually adversely affect public health.

For these reasons, the AMA opposes the use of 4th generation cephalosporins in food animals. Furthermore, if 4th generation cephalosporins are approved for such use, the AMA strongly recommends that public health safeguards be put in place. Minimally, these must include:

1. Enhanced national surveillance to include data on the quantity of 4th generation cephalosporins used in food animals. (Currently, no drug use reporting is available.)
2. Enhanced national surveillance to include monitoring for emergence of the CTM-X mechanisms.
3. Enactment of an extra-label prohibition to ensure that 4th generation cephalosporins are used only according to the label.

Thank you for considering the AMA’s concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "Mike Maves". The signature is written in a cursive, flowing style. To the right of the signature is a vertical red line.

Michael D. Maves, MD, MBA