



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

March 19, 2007

Andrew C. von Eschenbach, MD
Commissioner
Food and Drug Administration
5600 Fishers Lane
Parklawn Building, Room 1471
Rockville, MD 20857

Dear Commissioner von Eschenbach:

On behalf of the physician and medical student members of the American Medical Association (AMA), I am writing to express the AMA's concern about the potential approval by the Food and Drug Administration (FDA) of the use of a 4th generation cephalosporin to treat specific bacterial infections in cattle in the United States. Approval of the use of this drug in animals potentially could increase resistance to 4th generation cephalosporins currently used in humans. The AMA previously submitted comments in September of 2006 on this issue to the FDA's Veterinary Medicine Advisory Committee (VMAC). The VMAC voted to reject InterVet Inc.'s request to market cefquinome for use in cattle in the United States. We strongly urge you to follow VMAC's recommendation.

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. 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 in humans, and the spread of resistance in bacteria to this agent is therefore of clinical and public health concern. Given the recent outbreaks of *E. coli* O157:H7 and *Salmonella* 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.

Andrew C. von Eschenbach, MD

March 19, 2007

Page 2

While the AMA recognizes that the proposal in question is for use of the 4th generation cephalosporin by injection only and only for “treatment,” we continue to have significant concerns. 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.

In reviewing an antimicrobial new animal drug application, CVM must determine that the drug is safe and effective for its intended use in the animal. In addition, an antimicrobial new animal drug intended for use in food-producing animals must be shown to be safe with regard to human health (21 CFR 514.1(b)(8)). FDA considers an antimicrobial new animal drug to be “safe” if it concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals. Based on the data showing the increase in resistance to ceftiofur and ceftriaxone in the United States and the evidence of cefepime resistance in humans associated with the use of cefquinome in food animals in Europe, it is clear that the “reasonable certainty of no harm to human health” standard is not met in this case.

For these reasons, the AMA opposes the use of 4th generation cephalosporins in food animals, and urges the FDA to reject the application for the use of cefquinome in cattle. If 4th generation cephalosporins are approved for such use, however, 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,



Michael D. Maves, MD, MBA

cc: Stephen F. Sundlof, DVM, PhD