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January 8, 2007

Andrew C. von Eschenbach, M.D., Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857-0001

Dear Commissioner von Eschenbach:

I write once again on behalf of Keep Antibiotics Working (KAW) to ask that you follow the advice of the Veterinary Medicine Advisory Committee (VMAC) and not approve the antimicrobial drug cefquinome for use in cattle. The drug, the first of the 4th generation cephalosporins to be considered for animal use in the US, threatens to elicit resistance to both the 3rd and 4th generation cephalosporins. As a physician, we know you appreciate the importance of these drugs to human medicine in an era with so few new antibiotics in the drug pipeline.

Since we last communicated with the FDA, we have learned of two new scientific studies showing that traits that could confer resistance to 4th generation cephalosporins (extended spectrum beta lactamases or ESBLs) are widespread in European animal operations. These studies are important because a 4th generation drug has been in use in animals in Europe for almost ten years. They were not considered in the risk assessment on resistance produced by cefquinome's sponsor, Intervet.

In the first study, published in December of 2006, the United Kingdom Department of Environment Food and Rural Affairs reported that the ESBL-producing *Escherichia coli* of the CTX-M class had been detected on 11 separate farms in the United Kingdom (DEFRA, 2006). The second article, published in *Veterinary Microbiology* (Blanc et al., 2006), reported that ESBL-producing *Escherichia coli* were detected in Spain on all 10 poultry farms examined and on 4 out of 10 swine farms.

KAW is concerned that the Intervet risk assessment did not adequately consider the emerging evidence that livestock can play a significant role as a reservoir for ESBL producing bacteria. The Intervet (2006) assessment states on page 24 that "ESBLs in *Salmonella* spp. and *E. coli* isolates from livestock have not been reported, and are not a focus of this risk assessment."

KAW, The Infectious Diseases Society of America and other organizations raised concerns about the CTX-M class of ESBL-producing bacteria before VMAC, but at that time we were not aware of these new studies.

In the view of the VMAC, the Intervet risk assessment provided insufficient assurance of safety with regard to resistance even without this new evidence. These studies--which are not likely to be the last ones documenting the rising levels of CTX-M traits in the animal

operations in Europe—strengthen the case that use of cefquinome in animals will compromise the effectiveness of drugs vital for human medicine. We hope you will ensure that they are taken into account by CVM.

Thank you in advance for your thoughtful consideration of this pressing public health matter. A hard copy of this letter is being mailed to your office.

Sincerely,

Richard R. Wood
Steering Committee Chair
Keep Antibiotics Working

cc: Stephen F. Sundlof, D.V.M., Ph.D.

References:

Blanc et al., 2006. ESBL- and plasmidic class C beta-lactamase-producing *E. coli* strains isolated from poultry, pig and rabbit farms. *Veterinary Microbiology* 118(3-4):299-304.

DEFRA, 2006. Zoonoses: Extended-Spectrum Beta-Lactamase (ESBL) in *Escherichia coli* associated with animals – Defra Position. Accessed January 4, 2007. Available at:

<http://www.defra.gov.uk/animalh/diseases/zoonoses/esbl.htm>

Intervet, 2006. Cefquinome formulations for parenteral injection for the treatment of bovine respiratory disease. Risk estimation under FDA/CVM Guidance #152 for cefquinome to evaluate potential microbiological effects on bacteria of human health concern (microbial safety). Available at: <http://www.fda.gov/cvm/Documents/VMAC0906Cefquinome.pdf>