

The Comments of Keep Antibiotics Working  
Before FDA's Veterinary Medicine Advisory Committee  
on the Microbial Food Safety of the New Animal Drug Cefquinome

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Keep Antibiotics Working appreciates this opportunity to provide comments on the proposed approval of the fourth generation cephalosporin class of antimicrobials in food animals. I am Steven Roach, Director of the Food Safety Program for Food Animal Concerns Trust, a member organization of Keep Antibiotics Working. Keep Antibiotics Working is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than nine million members working to protect public health through the promotion of the responsible and appropriate use of antibiotics in animal agriculture.

This topic and this meeting are important. For the first time since the FDA implemented a new approach for assessing the risk to antibiotic resistance from animal drugs (contained in its Guidance #152), this approach is being applied to a class of antibiotics not currently approved for use in livestock production. Two years ago, the VMAC met to consider the microbial risk of another antibiotic, tulathromycin, but that drug was in the macrolide class, a class with a long history of use in animals.

Today, you are being asked to consider the approval of a class of drugs that has never been used in food animals in the U.S. Unsurprisingly, given the lack of selection pressure through drug use, resistance to this class of antimicrobials has not been detected in U.S. in farm animals. There is, however, evidence that an animal approval will lead to such resistance. For instance in Europe, where cefquinome has already been approved under the brand name Cobactin, resistance to this and other classes of cephalosporins has been detected among Salmonella and E coli bacteria isolated from food producing animals on farms where cefquinome was used. Resistance in these isolates is conferred by extended-spectrum beta-lactamases of the CTX-M family.

This family of enzymes has not been detected in livestock in the U.S. While extended-spectrum beta-lactamases, have been detected in U.S. patients, as the Intervet risk assessment noted the U.S. currently has the lowest rate of this type of resistance in the world. We should try to maintain this low rate and you, the members of the VMAC committee, play an important role in assuring that this approval does not lead to an increase in resistance in farm animals, the community, and sick patients.

The Intervet risk assessment plays down the potential for cefquinome use to select for resistance in gram negative bacteria such as E. coli and Salmonella. Their argument is partially based on a claim that levels of the drug are too low in the gut to select for resistance in enteric bacteria. Despite this argument, their own data described on page twenty of the report shows that cefquinome use in an actual field trial did lead to a reduction in numbers of Escherichia coli and to reduced susceptibility to cefquinome in E coli in treated animals. The Intervet risk assessment states that cefquinome in this respect is similar to the third generation cephalosporin, ceftiofur. However, there is good evidence that ceftiofur use in cattle has lead to increased ceftiofur resistance in cattle isolates. I provided to committee members a chart showing how resistance to ceftiofur in Salmonella slaughter isolates from cattle has steadily risen from no resistance detected in 1997, when the NARMS program began, to 21% of isolates resistant in 2003, the last year for which we have data. This is exactly what should be avoided with cefquinome.

Why should we be concerned about potential resistance arising from the livestock use of cefquinome? In Guidance #152, FDA considers the 4<sup>th</sup> generation class of antimicrobials to be highly important because they are the sole or limited therapy for an important human disease. Keep Antibiotics Working believes that fourth generation cephalosporins would be more appropriately placed in the “critically important” class. The World Health Organization, based on a technical consultation including experts from the U.S. FDA and Centers for Disease Control, placed 4<sup>th</sup> generation cephalosporins in the higher “critically important class” because in addition to being the sole treatment for a serious human illness, these drugs are also used to treat bacteria likely to be transferred from animals to humans. The WHO experts specifically mention Escherichia coli and Salmonella. Since Guidance #152 was published in 2003, there has been new evidence showing that urinary tract infections can be foodborne. KAW believes that FDA should update Appendix A of Guidance #152 based on the more recent work of the WHO and on the new information about the role of food in transmitting organisms causing urinary tract infections. Fourth generation cephalosporins are used to treat urinary tract infections in adults and children. It is also important to acknowledge that the use of this drug can select for bacteria containing extended-spectrum beta-lactamases which confer resistance to third generation, as well as 4<sup>th</sup> generation cephalosporins. Third generation cephalosporins are considered by FDA to be critically important.

You, the members of the VMAC committee, have been asked to answer three questions related to the approval of this drug. The first question asks:

Do the findings presented in the sponsor’s (qualitative risk) assessment demonstrate that cefquinome is safe with respect to the potential for transfer of antimicrobial resistant organisms to humans?

The answer to this first question must be no. What does safety mean in the context of a new animal drug approval? The standard required by the FDA for safety is the “reasonable certainty of no harm.” KAW believes in this particular case the sponsors have failed to meet the FDA safety standard specifically because they have failed to account for the likely and predictable risks for the use of this drug in livestock to select for extended-spectrum beta-lactamases in gram negative bacteria, particularly those in the CTX-M class. Such selection could in turn lead to treatment failure with both third and fourth generation cephalosporins. Given the failure of the assessment to address this risk, we recommend that the drug not be approved.

KAW believes that denying approval is also consistent with Guidance #152. Under Guidance #152, the first decision to be made is to determine whether the drug has been shown to be safe. Grounds for denial include “the determination that there is insufficient information as to whether the drug is safe.” Without a more thorough consideration of the potential for livestock use of cefquinome to select for expended-spectrum beta-lactamases this risk assessment does not meet that standard. Keep Antibiotics Working also believes that if this drug is approved it will almost certainly be used metaphylactically to treat groups of animals at risk for Bovine Respiratory Disease despite any label claim for individual animal treatment. This type of use would be inappropriate for “critically important” drugs under Guidance #152. Keep Antibiotics Working acknowledges the importance of drugs to treat animal disease, but feels that in this case the risks to human health are too great unless more information is forthcoming about the potential risks of the extended-spectrum beta-lactamases and more information about how this drug is likely to be used.

If cefquinome is approved, KAW recommends that it be approved for prescription only with an extra-label prohibition. There must also be a commitment from FDA to both monitor resistance to 4<sup>th</sup> generation cephalosporins, including *Escherichia coli* from cattle which is not currently done in a consistent manner, and to collect data on how this drug is used so that resistance data can be interpreted.

The extra-label restriction should be comprehensive, covering both other species and other indications in cattle. Given the likely short withdrawal period of this drug in both milk and meat, it could be used in sick dairy cattle the day before slaughter not the sixty days before slaughter, mentioned in the Intervet risk assessment. The current risk assessment only considers the safety of this drug in cattle, but without an extra-label restriction it could be used flockwide in poultry. The third generation cephalosporin ceftiofur is commonly used extra-label in hatcheries and this is a likely cause of ceftiofur resistance detected in *Salmonella* isolates from chickens.

Thank you for your attention.

USDA NARMS Cattle Slaughter Isolates

