KEEP ANTIBIOTICS WORKING

The Campaign to End Antibiotic Overuse

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October 30, 2008

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

Re: Docket No. FDA-2008-N-0326

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Food Animal Concerns Trust

Keep Antibiotics Working (KAW) appreciates this opportunity to submit comments on the Food and Drug Administration's final rule prohibiting the extralabel use of cephalosporin antimicrobial drugs in food producing animals. Keep Antibiotics Working (www.KeepAntibioticsWorking.com) is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than ten million members dedicated to eliminating a major cause of antibiotic resistance: the inappropriate use of antibiotics in farm animals.

KAW commends the Food and Drug Administration (FDA) for taking this important step to protect public health from the threat of antimicrobial resistance. Antimicrobial resistance is a serious public health crisis that threatens to destroy the efficacy of vital life saving drugs. The available evidence as stated in the July 3, 2008 Federal Register Notice (FRN) announcing this action clearly indicates that the extralabel use of cephalosporins in food animals presents a risk to public health. Restricting this type of use is necessary to reduce and contain the spread of cephalosporin resistant microorganisms from food animals to humans.

KAW agrees with the FDA findings in the FRN concerning the importance of cephalosporins for human medicine and of the potential for cephalosporin resistant pathogens to move from animals to humans. The cephalosporin class of antimicrobials is considered to be critically important in human medicine by both the FDA (2003) and the World Health Organization (WHO, 2007), because of its importance in treating diseases likely to have animals as a source. As the FRN noted, the U.S. National Antimicrobial Resistance Monitoring System (NARMS) has detected a trend of increasing resistance to cephalosporins in *Salmonella* isolates from both humans and food animals. This trend indicates a failure to meet the public health goals of no increase in the proportion of *Salmonella* isolates that are resistant to cephalosporin antibiotics in both humans and animals included in the Healthy People 2010 Public Health Goals, announced in 2000 by U.S. Department of Health and Human Services.

In addition to the evidence of the public health risk shown by the NARMS data, there is further evidence that the extralabel use of cephalosporins presents a risk to public health. Cephalosporins are often used extralabel in broiler and turkey hatcheries in the US (FDA, 2002) to reduce mortality associated with *Escherichia coli* and other poultry diseases. Similar extralabel practices in Canada (Public Health Agency of Canada, 2007) have been shown to be linked to resistant *Salmonella* Heidelberg on retail chicken meat and to cephalosporin resistant human infections. A voluntary withdrawal of the extralabel use of cephalosporins in one region of Canada was associated with a drastic drop in resistance in isolates from both humans and retail meat in that region. Resistant *Salmonella* infections are associated with increased frequency of illness (Barza and Travers, 2002) and increased severity of infection including increased risk of blood stream infection and increased risk of hospitalization (Varma et al., 2005).

While the Canadian case provides a clear example of how extralabel use in broiler hatcheries presents a public health risk, the high levels of cephalosporin resistance in cattle isolates as shown by NARMS indicates that restricting the use in broilers alone will not be sufficient. The cephalosporin drug ceftiofur is available in a long-acting formulation, under the trade name Excede, for use in cattle and swine. Long-acting antimicrobial formulations increase the risk of selecting for antimicrobial resistance (Sun et al., 2004). Several recent risk assessments following FDA's Guidance #152 (FDA, 2006; Intervet, 2006) have placed veterinary uses of cephalosporin drugs in cattle in Category 1, uses with a high risk for "human health to be adversely impacted by the selection or emergence of antimicrobial resistant food-borne bacteria associated with the use of the drug in food-producing animals". Restricting extralabel use is consistent with the risk management recommendations for veterinary applications that are found to be in Category 1, high risk, under Guidance #152 (FDA, 2003). In a 2006, meeting of the FDA's Veterinary Medicine Advisory Committee (VMAC, 2006) evaluating a new veterinary cephalosporin for use in cattle a majority of the members felt that the new drug had not been shown to be safe and voting members were particularly concerned that if it were approved that extralabel restrictions be put in place.

There is clear scientific evidence that the extralabel use of cephalosporins in food animals presents a risk to public health and for this reason KAW strongly supports the decision by FDA to restrict this use. In making this decision and other risk management decisions related to antimicrobial resistance, FDA must keep public health protection as its goal. At the same time KAW acknowledges that the FDA should anticipate and take steps to reduce any potential negative impacts that may result from this extralabel restriction. KAW recognizes two potential areas of concern related to the restriction of extralabel use of cephalosporins: 1) the restriction may lead to switching from cephalosporin to gentamicin use in hatcheries and consequently lead to increased gentamicin resistance and 2) veterinary practice may change as veterinarians no longer have cephalosporins available as a treatment option for indications not currently approved. KAW accepts that both of these are legitimate areas of concern, but believes that actions can be taken to keep them from having negative impacts.

Gentamicin and the cephalosporin ceftiofur are both commonly used extralabel in turkey and broiler hatcheries (FDA, 2002). When the cephalosporin extralabel restriction is put in place, this could result in an increase in the use of gentamicin in hatcheries. Both gentamicin and ceftiofur are labeled for use in hatcheries, so the extent of change that will occur with the cephalosporin restriction is uncertain. Gentamicin is considered by the FDA (2003) to be highly important and by the WHO (2007) to be critically important, so an increase in gentamicin resistance in poultry could create a public health risk. Both FDA and WHO consider gentamicin to be important because of concerns about the gentamicin resistant *Enterococcus spp*. In addition, the WHO considers that there is a human health risk from the potential transmission from animals to humans of gentamicin resistant *Enterobacteriaceae* including *Escherichia coli.*

KAW recommends that FDA take steps to reduce the risks associated with increased gentamicin use in poultry hatcheries. FDA in collaboration with USDA should work with hatcheries to identify alternatives to antibiotic use to control chick and poult mortality. In addition, FDA should monitor through NARMS changes in rates of resistance to gentamicin in *Enterococcus spp. and Escherichia coli.* Rates of resistance to gentamicin at the retail meat level in turkey and poultry are already high, so FDA should consider restricting the extralabel use of gentamicin in poultry as well. The 2001 FDA (2002) hatchery study found significant mishandling and misuse of antibiotics in the hatcheries further increasing the risk to public health. KAW believes that there is currently sufficient evidence to restrict gentamicin use along with cephalosporin use in hatcheries and an increase in gentamicin resistance resulting from the extralabel restriction on cephalosporins would make this even more necessary.

KAW acknowledges that many veterinarians have used cephalosporins extralabel for the benefit of animal health and that the restriction of this use will require them to find alternatives. KAW recommends that the FDA work with veterinarians and other stakeholders to determine how cephalosporins are being used extralabel and to identify and promote alternatives to this use. KAW suggests the FDA work with stakeholders to help implement the recommendations in the Consensus Statement of the American College of Veterinary Internal Medicine (ACVIM, 2005) that veterinarians develop farm level prevention programs and that groups of veterinary experts develop clinical practice guidelines for important animal diseases. In this case, these would be for diseases currently treated with extralabel cephalosporins. The focus should be on promoting alternatives to antimicrobials when feasible and on finding alternative antimicrobials to cephalosporins when necessary. Communication to stakeholders could be part of the recently initiated Animal Health Literacy Campaign by FDA's Center for Veterinary Medicine (FDA, 2008). Reducing the extralabel use of cephalosporins should also help protect the efficacy of cephalosporins when treating sick animals for labeled indications.

The extralabel use of cephalosporins in food animal medicine presents a clear risk to human health and the restriction of this use is necessary. The implementation of this final rule should be part of an integrated program to address the rise of cephalosporin resistance and of resistance in general. KAW hopes that this is just the first step in a

strengthened federal response to antimicrobial resistance arising from non-human uses of antimicrobials.

References:

ACVIM, 2005. ACVIM Consensus Statement, Antimicrobial Drug Use in Veterinary Medicine. J Vet Intern Med 19:617–629. Available from: http://www.acvim.org/uploadedFiles/Consensus_Statements/Antimicrobial.pdf. Accessed October 30, 2008.

Barza and Travers, 2002.Excess infections due to antimicrobial resistance: the "Attributable Fraction". Clin Infect Dis. 34 (Suppl 3):S126-30

FDA, 2002. Summary of Data from Hatchery Inspections Conducted September –October 2001, April 15, 2002. FDA Internal document obtained by Freedom of Information Request.

FDA, 2003. Guidance for Industry #152. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern. Available from: http://www.fda.gov/cvm/Guidance/fguide152.pdf. Accessed October 30,2008.

FDA, 2006. Freedom of information summary, supplemental new animal drug application Nada 141-209, EXCEDE Sterile Suspension (ceftiofur crystalline free acid). Available from: http://www.fda.gov/cvm/FOI/141-209s060206.pdf. Accessed October 30, 2008.

FDA, 2008. FDA Veterinarian Newsletter 23(3). Available from: http://www.fda.gov/cvm/FDAVet2008VolXXIIINo3.htm#7980. Accessed October 30, 2008.

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. Accessed October 30, 2008.

Public Health Agency of Canada. 2007. *Salmonella* Heidelberg Ceftiofur - Related Resistance in Human and Retail Chicken Isolates. Available from: http://www.phac-aspc.gc.ca/cipars-picra/heidelberg/heidelberg-eng.php. Accessed October 30, 2008.

Sun et al., 2004. Issues and challenges in developing long-acting veterinary antibiotic formulations. Adv Drug Deliv Rev. 56(10):1481-96.

Varma et al.,2005. Hospitalization and antimicrobial resistance in *Salmonella* outbreaks, United States, 1984–2002. Emerg Infect Dis Available from http://www.cdc.gov/ncidod/EID/vol11no06/04-1231.htm. Accessed October 30, 2008.

VMAC, 2006. Official Meeting of the Veterinary Medicine Advisory Committee New Drug Microbial Safety Review Under Guidance #152,September 25, 2006 [Transcript]. Available from: http://www.fda.gov/cvm/Documents/VMAC0906Trans.doc. Accessed October 30, 2008.

WHO, 2007. Critically Important Antimicrobials for Human Medicine: Categorization for the Development of Risk Management Strategies to contain Antimicrobial Resistance due to Non-Human Antimicrobial Use Report of the Second WHO Expert Meeting Copenhagen, 29–31 May 2007. Available from: http://www.who.int/foodborne_disease/resistance/antimicrobials_human.pdf. Accessed October 30, 2008.