March 5, 2012

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

RE: [Docket No. FDA-2008-N-0326] New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Use; Order of Prohibition

Dear Sir or Madam:

I am writing on behalf of the American Veterinary Medical Association (AVMA), which was established in 1863 and is the largest veterinary medical association in the world. As a not-for-profit association established to advance the science and art of veterinary medicine, the AVMA is the recognized national voice for the veterinary profession. The AVMA’s more than 82,500 members comprise approximately 83% of US veterinarians and are involved in a myriad of areas of veterinary medical practice, including private, corporate, academic, industrial, governmental, military, and public health services.

The AVMA commends the FDA’s thoughtful consideration of stakeholder comments and revision of the original order\(^1\) prohibiting all extralabel use of cephalosporins in food-producing animals with no exceptions. The revised order\(^2\) prohibiting certain extralabel uses of cephalosporin antimicrobial drugs in certain food-producing animals is consistent with AVMA policy in that it is a narrower, targeted order of prohibition to protect public health and balance the needs of veterinary medicine and animal welfare. The AVMA also appreciates the FDA’s position on the specific areas of extralabel use of cephapirin, extralabel use for unapproved indications, and extralabel use in food-producing minor species.

As a science-based organization, the AVMA encourages science-based risk analysis prior to the institution of any regulatory prohibition. The analysis should include determination of the consequences of the prohibition, such as increased residue risks from alternate products and detrimental effects on animal health and welfare resulting from loss of access to the drug. Unless rigorous risk analysis shows a need for a broad ban, any regulatory prohibition of extralabel drug use should be as limited in scope as possible (eg, limiting the prohibition to a certain species, production stage, age, dosage, duration of therapy, or route of administration).

Although the AVMA understands that the FDA has issued the revised order on the basis of evidence that certain extralabel uses will likely cause adverse events in humans and presents a risk to public health, the evidence presented in the order remains somewhat unclear. The order cites the most important public health risk as human exposure to food containing antimicrobial-resistant bacteria resulting from the exposure of food-producing animals to antimicrobials. On the basis of one study,\(^3\) the
order cites CMY-2 and CTX-M β-lactamases as being of particular concern. Yet, the report of that study\textsuperscript{3} states that most β-lactamases to date have been derived from clinical isolates of humans, β-lactam antimicrobial use in humans is likely more important in selection of resistance, and judicious use of β-lactam antimicrobials is a critical factor in containing β-lactamase–producing bacteria.

The FDA further cites National Antimicrobial Resistance Monitoring System (NARMS) data\textsuperscript{4–7} indicating increasing and somewhat alarming trends of ceftiofur resistance in slaughter isolates as well as in humans. Yet, human exposure to food containing antimicrobial-resistant bacteria would most likely be reflected in retail meat isolates. Review of NARMS retail meat isolate data indicates the following significant trends in β-lactamase inhibitor combinations among \textit{Salmonella} in retail meats from 2002 to 2009\textsuperscript{8}:

- Increasing trend of resistance in chicken breast
- Decreasing trend of resistance in ground turkey
- Decreasing trend of resistance in ground beef
- Stable trend of resistance in pork chops (few isolates found; many years with no resistant isolates found)

Among \textit{Escherichia coli} in retail meats, the only significant trend identifiable was an increasing trend in ground turkey.\textsuperscript{8} Given the conflicting trends from NARMS retail meat data, it is difficult to discern human exposure to food containing β-lactamases and the severity of the resulting public health risk.

The order also references Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) data\textsuperscript{9,10} indicating an increase in the incidence of cephalosporin-resistant \textit{Salmonella enterica} serovar Heidelberg infections in humans in Quebec and an accompanying increase in ceftiofur resistance in \textit{Salmonella} Heidelberg isolates in retail chicken. Following a voluntary withdrawal of ceftiofur use, there was a dramatic decrease in ceftiofur resistance in \textit{Salmonella} Heidelberg isolates from humans and retail chicken in Quebec, accompanied by similar trends in ceftiofur resistance in \textit{E coli} isolates from retail chicken.\textsuperscript{8} Many interpret this temporal correlation to be indicative of an effect of the withdrawal of ceftiofur.

Our review of the complete data available from CIPARS suggests the decrease in ceftiofur resistance in \textit{Salmonella} Heidelberg isolates was multifactorial and inconsistent with the temporal correlation of the withdrawal of ceftiofur in 2005:

- Chicken purchases contaminated with ceftiofur-resistant \textit{Salmonella} Heidelberg as well as the incidence of ceftiofur-resistant \textit{Salmonella} Heidelberg infection in humans show decreasing trends beginning in 2003 in Quebec
- Estimated incidence of reported human cases of \textit{Salmonella} Heidelberg infection show decreasing trends across nearly all Canadian provinces beginning in 2003 and 2004
- Since 2006, resistance to ceftiofur in human isolates of \textit{Salmonella} Heidelberg has remained more or less stable\textsuperscript{11}
The AVMA also recognizes the concern of the resistance trait conferred by the \textit{blaCMY} gene and the premise that the use of cephalosporins provides selection pressure that favors expansion of resistant variants of bacteria and is therefore likely to pose a risk to public health. Yet, it should be noted that most isolates possessing the resistance gene that have been recovered were from animals without a history of cephamycin or cephalosporin exposure.\textsuperscript{12}

**Extralabel uses of greatest concern cited by the FDA**

**Dairy cattle**—The AVMA agrees that violative residues of any kind are of major concern and a food safety hazard. Dairy cattle have had more violative residues than other commodity groups, and we continue to work diligently with both the FDA and the Food Safety and Inspection Service to educate producers, minimize violative residues, and ensure the safety of the food supply.

With respect to cephalosporins in particular, it remains unclear whether residue violations are indeed the result of extralabel drug use. Investigations conducted by the FDA have indicated that most violative residues are a “result of poor recordkeeping and other management practices”\textsuperscript{2}; therefore, it is possible that the violative residues are a result of illegal uses (without the involvement or knowledge of veterinarians), and there is no clear evidence to suggest otherwise, thus requiring further enforcement action.

Although ceftiofur use in dairy herds has been shown to significantly increase herd prevalence of ceftriaxone-resistant \textit{E coli}, the same study\textsuperscript{10} suggests that simply reducing the number of cows in a herd that are treated with ceftiofur will be ineffective in minimizing the dissemination of expanded spectrum cephalosporin resistance genes. Rather than decreasing exposure or improving judiciousness, the likely result of this prohibition will simply be to reduce quantities of drug use. Furthermore, several studies\textsuperscript{13,14} concur that, on an individual animal basis, no association could be detected between the prevalence of pathogens with reduced susceptibility to ceftriaxone and the use of ceftiofur.

**Other uses that increase drug exposure**—The AVMA recognizes that some uses that facilitate mass dosing of large numbers of animals, such as through drinking water or in ovo injections, are unapproved routes of administration and because these uses have not been evaluated for safety and approved by the FDA may pose unknown risks to public health. Yet, the AVMA cautions against broad-based prohibitions on prevention uses of antimicrobials. In 1996, FDA published the implementing regulations for AMDUCA,\textsuperscript{15} stating that “as long as the health of the animals is threatened, extralabel uses for preventive purposes is acceptable”; the purpose of this statement was “to make it clear that preventive uses when the health of the animal is threatened are permitted.” The AVMA understands and agrees that veterinarians must have a rational basis, such as in the case of weaned pigs, for determining that the health of the animals is actually threatened. In keeping with this concept, the AVMA believes it may be necessary to prevent infectious diseases, rather than treat them after they occur, to benefit public health as well as animal health and welfare. Prevention of an infectious disease with antimicrobial therapy can potentially impact resistance trends by decreasing the need and use of antimicrobials for herd-level treatment of disease at higher doses, for longer duration, and with higher-potency classes.
The AVMA has consistently advocated for risk management actions commensurate with the level of actual risk. We understand that the FDA is validly concerned with uses “that facilitate mass dosing of large numbers of animals, such as through drinking water” and that the nature of use of a drug through an unapproved route of administration poses unknown risks, but the AVMA disagrees with the premise that an overall reduction in amount of drug used in livestock will likely achieve the intended goal of decreasing resistance trends in human health. As a general concept, the AVMA supports judicious use of antimicrobials in an effort to balance human and animal health. Simply minimizing quantities of drug use without consideration of other factors (eg, exposure) is unlikely to impact antimicrobial resistance transmission and trends.

The AVMA has a strong position underscoring the importance of veterinary access to antimicrobials for preventive use and believes that any regulatory prohibition of extralabel drug use in animals should be science based and as limited in scope as possible consistent with protection of the food supply, public health, and animal welfare. The AVMA encourages a science-based risk analysis before instituting extralabel drug use prohibitions. The AVMA also encourages a plan to monitor the effect of the prohibition on animal and public health after it takes effect, to be sure the prohibition is needed and beneficial.

Thank you for this opportunity to comment. The AVMA wishes to remain engaged in dialogue on the topic of antimicrobial resistance. We welcome further opportunities to provide our insights and feedback. For further clarification or questions, please contact Dr. Christine Hoang at (800) 248-2862 ext 6742 or at choang@avma.org.

Sincerely,

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CEO and Executive Vice President
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