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Infectious Diseases Society of America

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April 5, 2007

Stephen F. Sundlof, DVM, PhD
Director
Center for Veterinary Medicine
U.S. Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

Dear Dr. Sundlof:

I am writing on behalf of the Infectious Diseases Society of America (IDSociety) concerning the Food and Drug Administration's (FDA) pending decision on the proposed use of cefquinome to treat a pneumonia-like disease in cattle. As a medical society that represents 8,400 infectious diseases physicians and scientists, our ultimate goal is to ensure that patients suffering from serious and life-threatening infections have access to effective anti-infective therapies. IDSociety supports the appropriate use of antimicrobials in the treatment of food-producing animals when warranted. However, available evidence strongly suggests that approval of cefquinome would not be in the best interest of the public's health. Nor would the drug's approval for use in cattle provide significant benefits as alternative agents are already available for this purpose. Thus, we strongly urge you to heed FDA's Veterinary Medicine Advisory Committee's (VMAC) recommendation and reject approval of cefquinome for use in cattle.

In IDSociety's September 25, 2006 statement before VMAC, available at <http://www.idsociety.org/vmactestimony>, we argued that a favorable decision to approve cefquinome could be dangerous to human health. In Europe, CTX-M, a type of extended spectrum beta-lactamase that hydrolyzes third and fourth generation cephalosporins, represents an alarming, emerging problem. Bacteria containing CTX-M have been found in both food-producing animals and patients in Europe. Although the epidemiology is insufficiently understood, there is no doubt that use of fourth generation cephalosporins in feed animals has the potential to increase transmission of CTX-M producing bacteria to humans through the food supply. Thus far, in the United States CTX-mediated resistance is rare; however FDA approval of fourth generation cephalosporins in livestock would represent a dangerous gamble.

Specifically, we are concerned that use of cefquinome would promote resistance to third generation cephalosporins which are used to treat serious and life-threatening infections, including pneumonia, sepsis, and meningitis. We also are concerned that cefquinome use would endanger the effectiveness of cefepime,

the only fourth generation cephalosporin in use in the United States in humans. Cefepime is reserved as a drug of last resort for treating patients with cancer who develop serious infections, and it is often active against bacteria that are resistant to third generation cephalosporins. As our human antimicrobial armamentarium dwindles, it is essential that we preserve the remaining agents and, as such, we should not take actions that could diminish the efficacy of cefepime. A strong and compelling need is necessary to justify such a risk to human health, and the sponsor has failed to justify that need.

Given the potential for use of cefquinome in cattle to adversely impact the effectiveness of cefepime as well as other cephalosporins in the treatment of serious and life threatening diseases in humans for which there are few treatment options, we believe FDA should re-evaluate the criteria used to classify antimicrobials as ‘critically important’ or ‘highly important’ for human health and that the agency should continue to periodically review this criterion over time. In particular, we believe cefepime should be reclassified as ‘critically important’ to be consistent with the World Health Organization (WHO) classification.

Should FDA approve cefquinome for therapeutic use in cattle, IDSA recommends that the agency place several restrictions on the drug’s use in order to minimize the potential for selection of resistant organisms in the food supply. Marketing status should be limited to prescription only. Further, a prohibition on extralabel use is essential. The U.S. Food, Drug and Cosmetic Act, including the Animal Drug Clarification Act (AMDUCA) amendments of 1994, provide a basis for the FDA to prohibit extralabel use of cefquinome. To do so, the Secretary of Health and Human Services must find there is a reasonable probability that extralabel use may present a risk to public health. The recommendations of the VMAC are consistent with that conclusion.

We also recommend the application of four additional restrictions should FDA approve cefquinome. FDA must:

- Limit drug administration to individual animals rather than groups or pens of animals.
- Require post-approval surveillance for resistance in the National Antimicrobial Resistance Monitoring System (NARMS) and provide sufficient funding to include cefquinome in the NARMS susceptibility panel.
- Require the manufacturer to report the volume of product sold or distributed in the United States each calendar year. FDA should establish standard criteria for such reporting. At a minimum, volume should be reported separately for use in poultry, cattle, and swine, as well as total volume sold for use in all food-producing animals. These data should be publicly available to support epidemiologic and microbiologic research on the impact of fourth generation cephalosporin use in food-producing animals.
- Provide funding for molecular epidemiology studies to evaluate the impact of cefquinome use in livestock and the associated risk to human pathogens and commensal flora through the food supply.

PAGE THREE — Cefquinome Letter to Dr. Stephen Sundlof

The Society stands ready to assist the agency in reconsidering Guidance #152 and its classification of antimicrobial agents that are important for human health. Should you have any questions, please do not hesitate to contact Julie Hantman, MPH, jhantman@idsociety.org, or 703-299-0200, x0015.

Sincerely,

A handwritten signature in black ink, appearing to read "Martin J. Blaser". The signature is fluid and cursive, with a long horizontal stroke at the end.

Martin J. Blaser, MD
Immediate Past President

cc: Andrew C. von Eschenbach, MD, Commissioner

Attachment: IDSA's September 25, 2006 Statement, <http://www.idsociety.org/vmactestimony>