



**INFECTIOUS DISEASES SOCIETY OF AMERICA
STATEMENT ON USE OF 4TH GENERATION CEPHALOSPORINS IN LIVESTOCK
BEFORE THE
FOOD AND DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE ADVISORY COMMITTEE
SEPTEMBER 25, 2006 MEETING**

Thank you for providing the Infectious Diseases Society of America (IDSA) the opportunity to comment on the proposed use of cefquinome in food-producing animals. IDSA represents 8,000 physicians and scientists devoted to patient care, education, research, prevention, and community health in infectious diseases. IDSA members care for patients of all ages with serious infections, including antibiotic-resistant bacterial infections, meningitis, pneumonia, foodborne infections, HIV/AIDS, and those with cancer or transplants who have life-threatening infections caused by unusual microorganisms. IDSA is the principal organization representing infectious disease physicians in the United States.

Cephalosporins are essential drugs that are widely used to treat serious and life-threatening human infections. The FDA has classified 4th generation cephalosporins as 'highly important' in human medicine because they are the sole therapy or one of few alternatives to treat serious human disease. For example, cefepime is a 4th generation cephalosporin that has a broader spectrum of antibacterial activity compared to 3rd generation cephalosporins, and it is often effective against organisms that are resistant to cefotaxime and ceftazidime. Currently, there are no 4th generation cephalosporins used in food-producing animals within the United States, but cefquinome has been used in food-producing animals in Europe.

Resistance to 3rd and 4th generation cephalosporins is mediated by extended spectrum beta-lactamases, or ESBLs, in gram negative organisms. ESBLs are an important cause of treatment failure in patients receiving cephalosporins. A specific family of ESBL, known as cefotaximases, or CTX-M, has rapidly expanded in the past decade to include Europe, Africa, Asia, and Latin America (1). The CTX-M gene is located on plasmids, allowing rapid and efficient spread of CTX-M mediated resistance (2). Even more concerning is the fact that CTX-M-producing isolates often exhibit coresistance to other drug classes, including fluoroquinolones. For example, ciprofloxacin resistance was strongly associated (odds ratio = 14) with the presence of CTX-M in a recent Canadian study (3). In the United Kingdom, surveillance for CTX-M producing isolates from outpatient and inpatient sources identified an epidemic strain with multiple resistance to fluoroquinolones, trimethoprim, tetracycline, and aminoglycosides (4).

Most ESBL-mediated resistance has been reported from hospitalized patients, but there is growing evidence that ESBL-producing organisms, and CTX-M producers in particular, represent an emerging problem in the community (5). For example, data from Spain indicate that the rates of ESBL-producing isolates increased significantly in both hospitalized patients and outpatients between 1991 and 2003 (6). In this study, CTX-M enzymes accounted for over 60% of the ESBL isolates. Despite the rapid emergence of CTX-M in Europe and other regions, CTX-M producing

organisms appear to be uncommon in the United States. We are not aware of any published reports of community-onset disease caused by CTX-M producing organisms in this country, and there has been only a single report of 9 *E. coli* isolates with CTX-M from patients in five states (1, 7).

ESBL-producing *E. coli* with CTX-M genes have recently been detected in food-producing animals in the United Kingdom, Denmark, and Spain (8-10). CTX-M genes have also been found in *Salmonella enterica* isolates from food-producing animals in Spain (11). There is a legitimate concern that food producing animals may serve as a reservoir for ESBL-producing human pathogens, and that resistance genes may be transferred to humans through the food supply and ultimately cause treatment failure in patients receiving cephalosporin therapy for serious infections.

FDA Guidance 152 outlines the recommended procedures for a qualitative risk assessment to evaluate the microbial food safety of 4th generation cephalosporins in animals. The overall risk estimate is derived from 3 components: release assessment, exposure assessment, and consequence assessment. For the exposure assessment, the probability of human exposure is determined by the prevalence of *Salmonella* and *Campylobacter* contamination in various food commodities and the amount of the food commodity consumed by the general public. Using this framework, cefquinome is best classified as ‘medium risk’ for human exposure to resistant *Salmonella* or *Campylobacter* in beef. Since 4th generation cephalosporins are classified as ‘highly important’ for treating human infections, the overall level of risk is most appropriately ranked as medium (Category 2) based on Table 6 of Guidance 152.

IDSA supports Guidance 152 and the overall FDA risk assessment approach. However, we note that in this case it fails to consider the human risk posed by horizontal gene transfer or clonal spread of ESBL-producing *E. coli*. In Europe, resistant *E. coli* with CTX-M have been detected on farms where 4th generation cephalosporins were administered to livestock (8, 10). The risk to human health has not been defined, but the potential for selection and horizontal transfer of CTX-M from food-producing animals to human pathogenic bacteria must be taken seriously.

We also note that many infectious disease specialists would consider 4th generation cephalosporins to be ‘critically important’ rather than ‘highly important’ for treating human infections. The 4th generation cephalosporins fail to meet the FDA criteria for ‘critically important’ only because they are not routinely recommended for treating enteric pathogens that cause foodborne disease. However, IDSA guidelines recommend 3rd and 4th generation cephalosporins for complicated, high-severity intra-abdominal infections, as well as for other serious infections in people at risk for multidrug resistant infections. Extended spectrum cephalosporins are also important for treating invasive *Salmonella* infections in humans. We therefore believe the FDA should re-evaluate the criteria used to classify the importance of cephalosporins for human health.

If cefquinome is approved for use in U.S. food-producing animals, IDSA strongly recommends that FDA implement the following measures to minimize selection pressure for ESBL-producing organisms and monitor the public health impact of the new drug.

1. Limit the marketing status to prescription only.
2. Prohibit extra-label use of the product.

3. Limit the extent of use to “low,” meaning that the drug will be administered only to individual animals rather than groups or pens of animals.
4. Require post-approval surveillance for resistance in NARMS and provide sufficient funding to include the new drug in the NARMS panel.
5. 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 reporting. As 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 4th generation cephalosporin use in food-producing animals.
6. Provide funding for molecular epidemiology studies to evaluate the impact of cefquinome use in livestock and the associated risk of CTX-M transmission to human pathogens and commensal flora through the food supply.

Thank you once again for the opportunity to comment on this issue. IDSA’s experts will be happy to elaborate on these and other issues.

***IDSA is grateful to Dr. Edward A. Belongia and other members of our Antimicrobial Resistance Workgroup for their assistance in developing this statement.*

REFERENCES

1. Bonnet R. Growing group of extended-spectrum beta-lactamases: the CTX-M enzymes. *Antimicrob Agents Chemother.* 2004 Jan;48(1):1-14.
2. Batchelor M, Hopkins K, Threlfall EJ, Clifton-Hadley FA, Stallwood AD, Davies RH, et al. bla(CTX-M) genes in clinical Salmonella isolates recovered from humans in England and Wales from 1992 to 2003. *Antimicrob Agents Chemother.* 2005 Apr;49(4):1319-22.
3. Pitout JD, Hanson ND, Church DL, Laupland KB. Population-based laboratory surveillance for *Escherichia coli*-producing extended-spectrum beta-lactamases: importance of community isolates with blaCTX-M genes. *Clin Infect Dis.* 2004 Jun 15;38(12):1736-41.
4. Woodford N, Ward ME, Kaufmann ME, Turton J, Fagan EJ, James D, et al. Community and hospital spread of *Escherichia coli*-producing CTX-M extended-spectrum beta-lactamases in the UK. *J Antimicrob Chemother.* 2004 Oct;54(4):735-43.
5. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. *J Antimicrob Chemother.* 2005 Jul;56(1):52-9.
6. Valverde A, Coque TM, Sanchez-Moreno MP, Rollan A, Baquero F, Canton R. Dramatic increase in prevalence of fecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae during nonoutbreak situations in Spain. *J Clin Microbiol.* 2004 Oct;42(10):4769-75.

7. Moland ES, Black JA, Hossain A, Hanson ND, Thomson KS, Pottumarthy S. Discovery of CTX-M-like extended-spectrum beta-lactamases in *Escherichia coli* isolates from five US States. *Antimicrob Agents Chemother.* 2003 Jul;47(7):2382-3.
8. Aarestrup FM, Hasman H, Agero Y, Jensen LB, Harksen S, Svensmark B. First description of blaCTX-M-1-carrying *Escherichia coli* isolates in Danish primary food production. *J Antimicrob Chemother.* 2006 Jun;57(6):1258-9.
9. Brinas L, Moreno MA, Teshager T, Saenz Y, Porrero MC, Dominguez L, et al. Monitoring and characterization of extended-spectrum beta-lactamases in *Escherichia coli* strains from healthy and sick animals in Spain in 2003. *Antimicrob Agents Chemother.* 2005 Mar;49(3):1262-4.
10. Liebana E, Batchelor M, Hopkins KL, Clifton-Hadley FA, Teale CJ, Foster A, et al. Longitudinal farm study of extended-spectrum beta-lactamase-mediated resistance. *J Clin Microbiol.* 2006 May;44(5):1630-4.
11. Riano I, Moreno MA, Teshager T, Saenz Y, Dominguez L, Torres C. Detection and characterization of extended-spectrum {beta}-lactamases in *Salmonella enterica* strains of healthy food animals in Spain. *J Antimicrob Chemother.* 2006 Aug 24.