KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
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December 13, 2007

Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857-0001

Dear Commissioner von Eschenbach:

The undersigned members of Keep Antibiotics Working, a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than nine million members, are increasingly concerned about the failure of the FDA to adequately respond to the crisis of antimicrobial resistance related to veterinary drug use in the United States. In particular, we are concerned that the FDA is not pursuing the likelihood that US livestock operations are a reservoir for Methicillin-resistant *Staphylococcus aureus (MRSA)* and the FDA is not responding to NARMS data indicating the emergence in the United States of *Enterobacteriaceae* resistant to cephalosporins. FDA's inaction on these and other veterinary antibiotic issues virtually ensures the federal government's failure to meet its own public health goals contained in the Healthy People 2010 initiative. Inaction also increases the likelihood that the suffering and costs due to the explosion in antibiotic-resistant infections will continue unabated.

Livestock Reservoirs of MRSA

FDA is failing to address the likelihood that livestock are a reservoir for MRSA. The latest report from the Centers for Disease Control indicates that MRSA leads to over 90,000 cases of invasive illness and over 18,000 deaths annually in the US (Klevens, 2007). Following multiple studies in Europe showing that pig farmers were at elevated risk for MRSA carriage, researchers in Canada looked at Ontario pig farms and found that both farms and farmers commonly carry MRSA (Khanna et al. 2007). The study sampled 285 pigs on 20 farms. It found MRSA at 45% of farms (9/20) and in nearly one in four pigs (71/285). The strains of MRSA bacteria found in Ontario pigs and pig farmers included both ST398, a strain identified in Europe as primarily coming from pigs, and USA100, a strain commonly associated with human MRSA infections and death in North America.

In Europe, MRSA has been shown to be transmitted from pigs to farmers, their families, veterinarians, and hospital staff treating farm-infected patients (Voss, 2005). Other European studies show that the pig strain ST398, the same pig strain that was detected in Canada, is associated with serious human illness including skin,

wound, breast, and heart infections, as well as pneumonia (Witte, 2007; Huijsdens, 2006; Ekkelenkamp, 2006). In the Netherlands, livestock associated MRSA was first detected in 2003 and by the second half of 2006 accounted for 20% of all human MRSA reported to the national reference center (van Loo, 2007).

1. KAW asks that FDA take immediate steps to determine whether US livestock, including swine, beef and dairy cattle, and poultry, carry MRSA and whether the use of antimicrobials on US farms increases the public health risk from MRSA. Research in Europe suggests that swine farms routinely using antibiotics are more likely to carry MRSA (van Duijkeren, 2007).

2. Given the example of MRSA, an organism of animal origin able to cause serious non-food related illness, the FDA should re-examine criteria used to rank the importance of drugs in Guidance #152, its recommended approach for assessing the safety of antimicrobial animal drugs. Currently, those criteria consider critically important only those drugs used to treat gastroenteritis. Drugs important in the treatment of other diseases, including MRSA and urinary tract infections (UTIs), should also be eligible under Guidance #152 for classification as critically important drugs.

Enteric bacteria resistant to 3rd and 4th Generation Cephalosporins

Multi-drug resistant versions of enteric bacteria such as *Salmonella*, often already resistant to at least five drugs, are now increasingly resistant to the third generation cephalosporins, some of the most valuable drugs in the human arsenal.

The Healthy People 2010 Public Health Goals, released in 2000 by U.S. Department of Health and Human Services, include a target that by 2010 there will be no increase in the proportion of of *Salmonella* isolates resistant to cephalosporin antibiotics in humans and animals. At the 1997 baseline, collected human isolates of *Salmonella* had no resistance to cephalosporin. In the 2005 CDC report (the latest available), the prevalence of cephalosporin-resistant human isolates of *Salmonella* had risen to 3.4%. The increase in animal isolates of *Salmonella* resistant to cephalosporins is even more dramatic than the rise in humans. The percentage of resistant isolates from cattle, broiler chickens, and swine at slaughter is reported by the USDA to have increased from 0.0, 0.5, 0.0 in 1997 to 21.6, 12.2, and 3.7, respectively, in 2005. In the US, this increase in resistance is primarily related to animal isolates having acquired a resistance trait known as AMP-C. This acquisition is attributable to the use in livestock here of the 3rd generation cephalosporin, ceftiofur.

In Europe, there is increasing concern about bacteria acquiring another class of resistance traits, CTX-M, which can confer resistance to both 3rd and 4th generation cephalosporins by producing chemicals called extended spectrum beta-lactamases (ESBL). While 3rd generation cephalosporin resistance itself is already a serious concern, the appearance in livestock of ESBL-producing bacteria would be an even greater threat to public health. ESBL-producing *Enterobacteriaceae* are leading to serious and difficult to treat illness across Europe and other parts of the world (Paterson and Bonomo, 2005). In Europe, bacteria carrying the CTX-M trait often are found in livestock and it appears to be related to veterinary use of 4th generation cephalosporins. News

reports in September described poultry imported into the United Kingdom contaminated with *Escherichia coli* containing the CTX-M trait.

KAW asks that FDA take the following steps to curtail the rise of resistance to *both* third and fourth generation cephalosporins in foodborne pathogens like *Salmonell*a and *Escherichia coli* in the US:

1. The FDA should explicitly reject the Intervet application for approval of the 4th generation cephalosporin cefquinome for use in cattle. The association in Europe between 4th generation cephalosporin use and the emergence of the exceptionally virulent CTX-M traits should be a sufficient warning of the potential dangers of such use.

2. The Agency, in conjunction with the USDA, should make sure that food and feed imports into the US are not a source of bacteria carrying the deadly CTX-M class of resistance traits. FSIS recently agreed to allow imports of fresh poultry from Chile. FDA must work with the USDA to ensure that poultry from Chile is not contaminated with ESBL-producing bacteria. CTX-M producing bacteria are common in South America (Radice et al., 2002).

3. The FDA should quickly work with stakeholders to develop and then implement a comprehensive plan to control and eliminate cephalosporin resistant bacteria in food. Cephalosporins are one of two treatments of choice for many serious zoonotic infections.

It is highly unlikely given the currently high levels of resistance to cephalosporins as indicated by NARMS that the government can meet the public health goals it set for resistant *Salmonella* by 2010, but at least the government should start to move in the right direction. Public health surveillance programs such as NARMS are only useful when the government responds to data signaling danger with measures to counter the public health threat.

Cephalosporin resistance in *Salmonella* has risen each year since surveillance under NARMS began. Now is the time to act to address this growing problem.

Addressing the critical public health problem of antimicrobial resistance requires urgent and sustained effort. We are not yet at the point where dangerous bacterial pathogens are resistant to all available antibiotics, but we come closer to that reality every day.

As Commissioner of a public health agency, KAW urges you to move beyond observing the clear signs of danger and act immediately to address both the rise in cephalosporin-resistant *Enterobacteriaceae* and the potential public health threat from livestock-associated MRSA.

Sincerely,

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Steering Committee Chairman
Keep Antibiotics Working

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Food Animals Concerns Trust

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cc:
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References:

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