KEEP ANTIBIOTICS WORKING

The Campaign to End Antibiotic Overuse

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April 2, 2009

Joshua Sharfstein, MD
Deputy Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857-0001

Dear Deputy Commissioner Sharfstein:

On behalf of the undersigned groups and Keep Antibiotics Working (KAW), a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups working to protect the efficacy of antibiotics in both human and veterinary medicine, we ask that you take quick action to respond to the growing crisis of antimicrobial resistance related to veterinary drug use in the United States.

As you are aware, the overuse and misuse of antibiotics in both human and animal medicine is responsible for the crisis of antibiotic resistance: drug treatments that no longer work, more severe and debilitating disease, and escalating medical costs. This crisis demands a comprehensive response from the FDA.

Despite a long recognition of the problem, the FDA has delayed taking actions that are necessary to protect public health. In particular, the FDA has failed to protect the public from the rapid growth of resistance to cephalosporins in food-producing animals and has failed to complete and act on reviews of the resistance implications of existing veterinary drug approvals.

The undersigned groups ask that you immediately take the following three steps:

First, formally reject the application to approve 4th generation cephalosporins for use in food-producing animals.

Second, reissue the ban on the extra-label use of cephalosporins in food-producing animals.

Third, make public the findings of FDA's review of penicillin and other veterinary drugs currently on the market, and take appropriate action on any drugs shown to be unsafe.

In taking these steps, you would help protect the efficacy of antimicrobials vital for treatment of human and animal diseases. Prompt action is urgently needed on the cephalosporin class of drugs, which are critically important for the treatment of serious infections in children, including those caused by *Salmonella* (Shea, 2004). The ongoing outbreak of *Salmonella* Typhimurium in peanut products that has resulted in over 100 hospitalizations, and a likely 9 deaths, illustrates the importance of this class of drugs. One in five of the patients affected by the contaminated peanuts were children under the age of 5 (CDC, 2009). Fortunately, in this case the *Salmonella* strain was susceptible to drugs used for treatment, but next time we may not be so lucky.

Resistance to cephalosporins in human and animal Salmonella isolates is on the rise and numerous studies connect the increase to the use of cephalosporin drugs in food-producing animals. It is urgent that you address the inappropriate use of cephalosporins in food-producing animals.

Reject the application to approve 4th generation cephalosporins

In September 2006, the FDA Veterinary Medicine Advisory Committee (VMAC) met to consider the application for the approval of the first fourth generation cephalosporin, cefquinome, to be used for disease treatment in food-producing animals, specifically bovine respiratory disease in beef cattle. The major medical organizations American Medical Association, Infectious Disease Society of America, and the American Academy of Pediatrics all opposed its approval because of concerns about losing cephalosporins for treatment of serious human illness. The U.S. Center for Disease Control (CDC) also raised concerns about the approval of this drug. At the end of the meeting, a majority of the committee members voted that the sponsor had failed to show cefquinome was safe with respect to antimicrobial resistance. The FDA has yet to formally reject the application.

KAW also opposed the application. Bovine respiratory disease is common in cattle and cefquinome, if approved, would be widely used in feedlots, where it could select for cephalosporin-resistant bacteria with an easy path back to human populations. KAW was particularly concerned about the potential for widespread cefquinome use leading to the spread of a specific class of enzymes, CTX-M extended spectrum beta-lactamases. The CTX-M class of enzymes is capable of destroying 4th generation cephalosporins and other newer cephalosporin drugs. These resistance enzymes have not been detected in food-producing animals in the U.S., but have been detected on farms and in food in other countries where cefquinome is used. KAW was concerned cefquinome's approval would promote the rise of CTX-M class enzymes in the United States.

In the intervening 2 years, new evidence has come to light documenting a new and more immediate resistance concern. In the U.S., resistance to 3rd generation cephalosporins, which are approved for use in food-producing animals in the U.S., has been conferred mainly by two different enzymes, TEM and AmpC beta-lactamases (Frye, 2008). Until recently, it was believed that these enzymes were incapable of breaking down cefquinome and related cephalosporins, but there is new evidence that mutations in

genes conferring these types of resistance are threatening the 4th generation cephalosporins (Ahmed and Shimamoto, 2008; Gniadkowski, 2008; Kim et al, 2006; Mammeri et al., 2007; Mammeri et al, 2008a; Wachino et al., 2006). The new versions of AmpC beta-lactamases also put at risk non-cephalosporin drugs such as carbapenems (Mammeri et al., 2008b).

We are concerned that the approval of cefquinome for use in the U.S. food animal environment where there are already high levels of bacteria with genes producing AmpC and TEM enzymes could create an ideal situation for spreading the new mutants. The same conditions also encourage the rise of the CTX-M resistance genes. Either way, the continued efficacy of cephalosporins is at risk. To preserve the valuable cephalosporin class of drugs, KAW and the undersigned groups ask that you formally reject the approval of cefquinome for use in food-producing animals, especially in light of the new studies on AmpC and TEM enzymes.

Reissue the order prohibiting the extra-label use of cephalosporins

Cephalosporins, like many drugs, are used for purposes other than those indicated on labels. This use is legal unless the FDA specifically prohibits it. The FDA did just that in an order published July 3, 2008 in the *Federal Register*, which determined that the extra-label use of cephalosporins in food-producing animals presents a risk to human health and should be prohibited. The CDC, in a letter to CVM Director Dunham dated November 7, 2008, agreed with the FDA's assessment and supported the decision. As KAW noted in comments on the notice of the ban (attached), the evidence from both the National Antimicrobial Resistance Monitoring System (NARMS) plus additional evidence from Canada (not cited by FDA) provide strong evidence that extralabel use of cephalosporins in poultry hatcheries has led to the increase in serious resistant *Salmonella* infections in humans.

On November 28, 2008 the FDA revoked the order prohibiting the extra-label use of cephalosporins in food-producing animals. The FDA did not provide reasons for withdrawing the order beyond stating that they had received many comments on the order. KAW has reviewed the comments submitted to the FDA on the order (Docket Number FDA-2008-N-0326) and found nothing in them that warrants FDA's withdrawal of the prohibition. The most cogent of the arguments in the comments against the order were objections that FDA has not shown that every individual extra-label use of cephalosporins creates a risk, so therefore FDA should only take action on specific identified risks. In our view, FDA's determination in its initial decision that it would not select among different classes of cephalosporin drugs was wise. It is reasonable to assume that each use of this class of drugs creates an incremental risk without obtaining specific data on the risks of each possible extra-label use. Collecting the data on all possible or even likely uses would cause unreasonable delay and waste resources if it is even doable given FDA's lack of ability to collect data on how approved antimicrobials are used.

We are aware that veterinarians have been using large amounts of cephalosporins drugs for extra-label purposes. As noted above, such use is legal and it is understandable that veterinarians would prefer to have at hand as large an arsenal as possible. But in this case, the drug class at issue, the cephalosporins, is simply too valuable to human and veterinary medicine to continue to allow extra-label uses in the face of data showing that those uses are leading to resistant disease in humans.

In addition, KAW's review of the comments did not identify any extra-label veterinary indications for which there are not currently alternative drugs. Despite FDA providing an extra month for comments, the major producer organizations did not provide a single peer reviewed article supporting the claim that extra-label cephalosporin use is essential for animal health. Where research articles supporting the claim were mentioned in comments, we found evidence of alternative treatments for the identified indications in the cited articles. For example, the American Association of Bovine Practitioners (AABP) comments cite a review of studies on antimicrobial therapies for the treatment of keratoconjunctivitis in cattle (O'Connor, 2006). The review noted cephalosporins were effective, but also identified 6 other antimicrobial treatments for this indication including the antimicrobial oxytetracycline, a drug with far less significance for human medicine than cephalosporins.

There is no valid scientific reason to withdraw the order. It should be reissued immediately.

Publish reviews of existing veterinary drug approvals

In October 2003, the FDA published *Guidance for Industry # 152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* describing a new qualitative method to be used to assess the safety of drugs with respect to antimicrobial resistance. At that time, FDA stated in public meetings the intention was to apply the Guidance #152 to existing as well as new approvals starting with uses of penicillins and tetracyclines in feed. The 2004 FDA Center for Veterinary Medicine (CVM) annual report stated that reviews of the uses of penicillins based on Guidance #152 were completed and that reviews of tetracyclines had been started. Letters were sent in 2004 to sponsors of penicillin stating that FDA had found that certain feed uses of penicillins were inappropriate. The 2005 CVM annual report once again mentioned the review of penicillin and tetracycline stating the penicillin review was completed and tetracycline reviews were ongoing. The 2006 and 2007 annual reports, however, fail to mention reviews of any existing approvals and no action has been taken to limit or cancel approvals for either class of drug.

KAW and the undersigned groups ask that FDA make public its findings on the safety of these approved drugs. If justified by the findings, we ask you to initiate appropriate action on any approved antimicrobial drugs that have been shown to be unsafe.

Addressing drugs already on the market, in particular the penicillins and tetracyclines, also has implications for the spread of cephalosporin resistance. Because cephalosporins

are chemically related to penicillins, bacteria resistant to cephalosporins are often also resistant to penicillin. Recent studies suggest that repeated exposure of bacterial populations to different beta-lactam antibiotics including both penicillins and cephalosporins may lead to bacteria developing resistance to a wider range of beta-lactam drugs than would occur with exposure to either penicillin or cephalosporins alone (Blazquez et al., 2000).

In addition, cephalosporin resistance in food-producing animals in the United States is often carried on mobile genetic elements that include determinants conferring resistance to tetracycline (Lynne et al., 2008). Since the selection of any of one of determinants on the mobile element will select for all of them, it is likely that the ongoing use of both penicillins and tetracycline is contributing to the selection and dissemination of cephalosporin resistance on farms. NARMS data support that concern. In 2005, NARMS found that 68.3% of human and 81.7% of cattle isolates of *Salmonella* resistant to ceftiofur were also resistant to tetracycline as well as a number of other drugs (FDA, 2009). The role of the ongoing uses of already approved drugs in driving resistance to newer, often chemically unrelated, drugs through linked multidrug resistance elements underscores the urgency of reviewing the safety implications of already approved drugs.

Summary

KAW and the undersigned groups ask that you act quickly to address the risks to human and animal health resulting from the inappropriate use of antimicrobial drugs in food-producing animals by: 1) making a final decision against the approval of cefquinome for use in food-producing animals, 2) reissuing the prohibition against extra-label use of cephalosporins in food-producing animals, and 3) making public findings of the reviews of penicillin and taking appropriate action on any uses of penicillin shown to be unsafe.

Thank you for considering our views.

Sincerely,

Richard R Wood
Chair, Keep Antibiotics Working Steering Committee,
and the following organizations:

American Academy of Pediatrics
Consumer Federation of America
Center for Food Safety
Center for Science in the Public Interest
Environmental Defense Fund
Food Animal Concerns Trust
Humane Society of the United States
Institute for Agriculture and Trade Policy

Safe Tables Our Priority
Union of Concerned Scientists

cc: Dr. Bernadette Dunham
Director, FDA Center for Veterinary Medicine

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