



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Rockville MD 20857

January 25, 2008

Richard Wood  
Steering Committee Chairman  
Keep Antibiotics Working  
P.O. Box 14590  
Chicago, IL 60614-0590

Dear Mr. Wood:

We are writing in response to your letter of December 13, 2007. In that letter, you request the U.S. Food and Drug Administration (FDA) to take immediate steps to determine whether Methicillin-resistant *Staphylococcus aureus* (MRSA) are present among U.S. livestock; to re-examine the criteria used to rank the importance of antimicrobial drugs in Guidance for Industry 152 (GFI #152) "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern;" and to take steps to curtail the rise of resistance in the United States to both third and fourth generation cephalosporins in foodborne pathogens like *Salmonella* and *Escherichia coli*.

In your letter, you stated that FDA is failing to address what you identify as the "likelihood" that U.S. livestock serve as reservoirs of MRSA. We want to make you aware that FDA scientists closely follow the emergence of any antimicrobial resistance, including the MRSA clonal lineage ST398 from humans and animals. We are monitoring the developments in Central Europe and Canada very closely.

The National Antimicrobial Resistance Monitoring System (NARMS) does not currently screen for MRSA, but NARMS is currently working with its partners at the University of Maryland to conduct a pilot study looking for MRSA in retail meats in the Washington D.C. metropolitan area. FDA is also meeting with its FoodNet partners in January to explore the possibility of expanding MRSA testing to a larger collection of retail meats obtained through the NARMS retail program. FoodNet, the Foodborne Diseases Active Surveillance Network, is the principal foodborne disease component of Emerging Infections Program (EIP) at the Centers for Disease Control and Prevention (CDC). FoodNet is a collaborative project of the CDC, ten EIP sites, the U.S. Department of Agriculture (USDA), and FDA.

NARMS is one of the key components of the strategy at FDA's Center for Veterinary Medicine (CVM) to assess relationships between antimicrobial use in agriculture and potential human health consequences. NARMS surveillance and research data are valuable for helping to identify the source and the magnitude of antimicrobial resistance in the food supply and is important for the development of public health recommendations for the use of antimicrobial drugs in humans and food animals. NARMS provides ongoing monitoring data on antimicrobial

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susceptibility/resistance patterns in select zoonotic foodborne bacteria, including *Salmonella*, *Campylobacter*, *E. coli* and *Enterococcus*.

As you know, MRSA was first reported in 1961, soon after methicillin was introduced into human medicine to treat penicillin-resistant staphylococci. MRSA has since emerged as an important human pathogen world wide, with some epidemic strains spreading between hospitals, countries and, more recently, among people who have not been hospitalized (this phenomenon is known as community-associated MRSA or CA-MRSA). More recently, as your letter indicates, concern has arisen among veterinary medicine and food safety scientists about MRSA emerging as a possible zoonosis, particularly with those MRSA strains that belong to clonal lineage ST398. As you state, MRSA isolates in domestic animals have been reported among pigs, cattle and poultry.

FDA is aware that farm pigs colonized with MRSA, especially those reportedly linked to human carriage or infections, have been found. Although no penicillinase-resistant penicillin has ever been approved for use in cattle (except dairy cattle for treatment of mastitis), swine, or poultry in the United States, the finding of MRSA in swine suggests that the MRSA isolates are capable of adapting to some food-producing animals, even though there is no direct antimicrobial pressure.

At this point, there is no evidence to suggest that human carriage is due to exposure to MRSA in animal-derived foods. Currently, most MRSA isolates in humans have been associated with skin or soft tissue infections, necrotizing pneumonia, and in-hospital bacteremias. Both human-to-animal and animal-to-human transmission of MRSA are known to be possible, but it has not yet been determined whether animals are an important primary source of MRSA infections for populations other than high-risk exposure groups (e.g. swine farmers and veterinarians) or if most animals are colonized after contact with human carriers.

We agree, however, that a further step worthy of consideration would be to determine if U.S. livestock (beef cattle, dairy cattle, swine, or poultry) carry MRSA. Such an effort should involve other Federal agencies as well as state and local governments, because many diverse interests are involved in the husbandry, management, processing, and movement of food-producing animals.

It is important to state clearly that regulatory decisions on the safety of new animal antimicrobial drugs are not constrained by Guidance for Industry #152. That guidance, which provides a framework for approaching microbial safety assessments in an organized manner, does not cause FDA to limit its consideration with regard to microbial safety. In accordance with the Federal Food, Drug, and Cosmetic Act, the Agency's decision regarding whether to approve a new animal drug application is driven by factors that include: (1) whether the application includes adequate tests to determine whether or not the drug is safe, (2) whether the results of these tests show the drug is unsafe or fails to demonstrate the drug is safe, or 3) whether, based on

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information either in the application or otherwise available to the Agency, there is sufficient information to determine that the drug is safe.

Antimicrobial resistance is a complex phenomenon. Antimicrobial resistant bacterial populations emerge because of the combined impact of antimicrobial drug use in humans, animals, as well as other selection pressures. Not all of these pathways are clearly defined or understood. FDA believes that human consumption of animal-derived foods is the most significant pathway for human exposure to emerging antimicrobial resistant bacteria. Because of this, FDA decided that GFI #152 should focus primarily on new animal antimicrobial drugs intended for use in food-producing animals and foodborne pathogens, although other non foodborne bacteria may be considered on a case-by-case basis, when deemed necessary. This means, for example, that uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies. Please be assured that FDA uses all of the scientific information available in making decisions on drug approvals.

Regarding your concerns with cephalosporins, the FDA has not made a final decision regarding approval of the new antimicrobial drug cefquinome. FDA is currently reviewing the comments made by its Veterinary Medical Advisory Committee which met September 25, 2006, and is considering any and all other information relevant to the safety of this antimicrobial drug.

The Agency recognizes that cephalosporin resistance, particularly due to CTX-M, is of growing concern in Europe and other countries. Several authors have postulated foodborne transmission of resistant bacteria from animals as a possible source of bacteria later isolated from affected women in Community Acquired Urinary Tract Infection (CA-UTI). However, studies of risk factors for CA-UTI have repeatedly identified previous use of cephalosporins and fluoroquinolones by the patient and prior contact with hospitals and nursing homes as strong risks for CTX-M resistant CA-UTI.

Investigations have not linked CA-UTI cases to foods, as is generally seen with diseases due to traditional foodborne pathogens. A recent review (Carattoli A. 2008. Animal reservoirs for extended spectrum  $\beta$ -lactamase-producers. *Clin Microbiol Infect* 14(suppl 1):117-123.) concluded that extended spectrum beta-lactamase (ESBL) producing bacteria were infrequently found in animals and that there was no compelling evidence of foodborne transmission of this resistance to humans.

Scientists are just beginning to look at these pathogens in retail samples of food. At the same time, FDA is continually monitoring scientific developments in this area, and assessing proprietary data from studies to evaluate emerging resistance. CVM places a high priority on public health in the approval of drugs for food-producing animals.

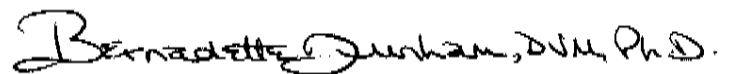
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As can be seen from the above discussion, FDA is proactively addressing potential human health risks associated with the use of antimicrobial drugs in food-producing animals. This approach uses risk assessment methodologies to quantify the human health impact from antimicrobial use in animals, in conjunction with robust monitoring, research, and risk management. In addition, the Agency participates in public meetings with various stakeholders to strengthen and promote science-based approaches for managing the potential human health risks associated with the use of antimicrobial drugs in food-producing animals. These include international meetings to address approaches to combat and prevent resistant pathogens.

Minimizing the emergence of antimicrobial resistant bacteria in animals and the potential spread to humans via the food supply is a complex problem requiring a coordinated, multifaceted approach. More than a dozen Federal agencies have an interest in the antimicrobial resistance problem and several of these agencies have responsibilities regarding the use of antimicrobials in agriculture. The strategy developed by the FDA to address antimicrobial resistance is one component of more broad-reaching strategies being developed by an inter-agency task force at the national level in the Public Health Action Plan to Combat Antimicrobial Resistance.

Thank you again for contacting us with regards to your concerns. If you have any further questions, please do not hesitate to let us know.

Sincerely yours,



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Director, Center for Veterinary Medicine