

KEEP ANTIBIOTICS WORKING

The Campaign to End Antibiotic Overuse

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Dear Drs. Goldberger and Tollefson,

Keep Antibiotics Working: The Campaign to End Antibiotic Overuse (KAW), a coalition of consumer, health, environmental, agricultural, humane and other advocacy groups, appreciates this opportunity to express our views regarding the Center for Drug Evaluation and Research (CDER) meeting held on January 9, 2003, on the Guidance for Industry #152. Although we were not in attendance at this meeting, our experts have reviewed the transcripts and have some concerns that we would like to enumerate. In addition, there are documents that we would like you to consider.

As an initial matter, we note that we support the basic approach taken in the Guidance document regarding ranking antimicrobials according to their importance in human medicine. This factor is obviously of critical relevance in assessing whether antimicrobials are safe and efficacious for use in human medicine.

At the January 9 meeting, representatives of the Animal Health Institute questioned whether in-vivo transfer of resistance genes has been demonstrated. While we agree with the Committee members who observed that it has indeed been demonstrated, we wish to draw your attention to one additional relevant publication that was not discussed in the meeting (a copy of which is attached): N.B. Shoemaker et al., Evidence for Extensive Resistance Gene Transfer among *Bacteroides* spp. and among *Bacteroides* and Other Genera in the Human Colon, Feb. 2001, *Applied and Environmental Microbiology*, 67(2): 561-568. Furthermore, although the Animal Health Institute representative argued, based on Sorensen et al., that in-vivo transfer of resistance genes has not been demonstrated, it must be noted that this paper specifically states that the "study was not designed to measure the rate of transfer of resistance genes, and it is impossible to rule out the occurrence of such a transfer during the study." The study was looking for intestinal carriage of resistant strains of *E. faecium* and found that these organisms did survive the gastric passage of the colon for up to 14 days after ingestion. Finally, Manges, et al., found that in three separate areas of the United States a single clonal group accounted for almost half of the community-

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acquired urinary tract infections in women caused by resistant strains of *E. coli*. The authors noted that additional studies were needed to “determine whether it [*E. coli*] is spread by the ingestion of contaminated foods.” This paper raises the concern that the health risks may go beyond foodborne illnesses caused by bacteria such as *Salmonella* and *Campylobacter*.

Representatives of the animal industry also implicitly argued that any restrictions on agricultural use of antibiotics would severely affect the industry and could affect food safety. The first point is not relevant under the applicable statute, as Dr. David Bell of CDC pointed out; rather, the Food, Drug, and Cosmetic Act requires FDA to ascertain that there is “a reasonable certainty of no harm to human health” from animal drugs. With regard to food safety, available evidence does not support the claim that antibiotic use reduces the amount of pathogens shed by livestock as was discussed in a report prepared for the FDA’s Center for Veterinary Medicine (Exponent, 2000). In addition, evidence from Denmark, which has eliminated nontherapeutic use of medically important antibiotics, indicates that antimicrobial use can be significantly decreased without increasing the risk of foodborne pathogens (Evans, 2002). Data from Denmark also indicate that reducing nontherapeutic use of antibiotics dramatically reduces the prevalence of resistance in foodborne bacteria (Aarestrup, 2001).

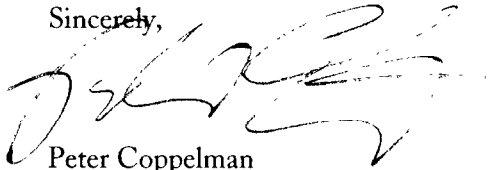
Several studies and reports released recently argue in favor of reducing the use of antimicrobials by the industry, especially those that are used for growth promotion and routine prophylaxis. The Alliance for the Prudent Use of Antibiotics convened an expert panel that conducted a two-year review of over 500 papers on the subject, publishing their results in *Clinical Infectious Diseases* in June 2002. The panel concluded “the elimination of nontherapeutic use of antimicrobials in food animals and in agriculture will lower the burden of antimicrobial resistance in the environment, with consequent benefits to human and animal health” (Alliance for the Prudent Use of Antimicrobials, 2002). Even if the impact on industry were to be viewed as somehow relevant in assessing the importance of drugs to human medicine, available evidence indicates that such impacts would likely be modest. A recent study looked at nearly 25,000 growing pigs in a multisite production system over a 5 year period and found that the growth rate of nursery piglets was improved by a modest 5% when using nontherapeutic growth promoting antimicrobials; however, the use of these compounds in the grower/finisher pigs had little, if any, impact. The authors concluded that the “Use of antimicrobials in the feed of finishing pigs should be limited to therapeutic applications in which a diagnosis of bacterial infection susceptible to the antimicrobial to be used has been confirmed” (Dritz, 2002). Despite the lack of efficacy of feeding antimicrobials in multisite finisher facilities, over 88 percent of finisher facilities use antimicrobial feed additives (NAHMS, 2000a). Given that 83% of finished swine are raised in this type of facility, the swine industry could do much to improve how it uses antibiotics (NAHMS, 2000b).

The Danish experience, although characterized as Draconian in some statements made in the CDER meeting, has given the United States a platform to understand the challenges that the United States may face in the animal industry. Denmark is the largest exporter of pork products in the world and its production has not been compromised by the removal of nontherapeutic antimicrobials from its processes (Verner Wheelock Associates Limited, 2002). The broiler sector in Denmark has, likewise, not suffered from the decision to stop the use of nontherapeutic antimicrobials (Emborg, 2001).

Finally, several large U.S. poultry producers have voluntarily stopped the use of some nontherapeutic antibiotics, as well as the therapeutic use of fluoroquinolones, in their processes. These include poultry suppliers to some U.S. fast food chains, such as McDonald’s, which has been using fluoroquinolone-free chicken for approximately 3 years (Statements on Antibiotic Use by Major Poultry Producers, Statements on Antibiotic Use by Major Restaurant Chains, and Written Direct Testimony of Kenneth M. Koziol (FDA Docket 00N-1571)).

Thank you for your consideration of these points. If you have any questions, please feel free to contact me at the number listed below.

Sincerely,



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Literature cited:

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Sorensen et al., 2001. Transient Intestinal Carriage After Ingestion of Antibiotic-Resistant *Enterococcus faecium* from Chicken and Pork. *New Engl. J. Med.* 345(16): 1161-1166.

Verner Wheelock Associates Limited, 2002. Food Safety and Pig Production in Denmark – Controls on Antibiotics, Veterinary Medicines and Salmonella. September 2002.