

January 10, 2005

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0480

Dear Sir or Madam:

Keep Antibiotics Working (KAW) appreciates this opportunity to submit comments concerning implementation of the Minor Use and Minor Species (MUMS) Animal Health Act of 2004, as requested by FDA's Center for Veterinary Medicine (69 Federal Register 64957). Keep Antibiotics Working (www.KeepAntibioticsWorking.com) is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than nine million members dedicated to eliminating a major cause of antibiotic resistance: the inappropriate use of antibiotics in farm animals. Our comments concern the Food and Drug Administration's (FDA's) consideration of antimicrobial resistance when the agency evaluates antimicrobials for approval or indexing under the MUMS Act.

Antimicrobial use in animals contributes to the development and spread of antimicrobial resistance, and must be considered under the MUMS Animal Health Act

The development and spread of antibiotic resistance is one of U.S. Centers for Disease Control regards as one of the agency's "top concerns,"¹ The massive use of drugs in food animal production contributes to this problem. By one recent estimate, more than 80% of the antibiotics used in the US each year are used in the production of chicken, swine, and beef cattle,² and a large fraction of these antibiotics belong to classes of antibiotics also used in human medicine.³

An array of experts have concluded that agricultural overuse of antibiotics, as well as medical overuse, must be curtailed in order to protect human health. For example:

¹ Centers for Disease Control (CDC). *Background on Antibiotic Resistance*. Atlanta, GA. Available at www.cdc.gov/drugresistance/community, accessed on February 9, 2004.

² M. Mellon et al. (2001). *Hogging It!: Estimates of Antimicrobial Abuse in Livestock*. Washington, DC: Union of Concerned Scientists. Available at http://www.ucsusa.org/food_and_environment/antibiotic_resistance/page.cfm?pageID=264 (accessed September 3, 2004).

³ Mellon et al. (2001).

- A report of the National Academies Institute of Medicine on microbial threats to health found that, "Clearly, a decrease in antimicrobial use in human medicine alone will have little effect on the current situation. Substantial efforts must be made to decrease inappropriate overuse in animals and agriculture as well."⁴
- A report of the Alliance for Prudent Use of Antibiotics, published as special supplement to the journal *Clinical Infectious Diseases* concluded that, "The elimination of non-therapeutic use of antimicrobials in food animals and agriculture will lower the burden of antimicrobial resistance ... with consequent benefits to human and animal health."⁵

Congress clearly recognized that FDA must consider antimicrobial resistance when evaluating the safety of animal drugs under the MUMS law. With regard to both conditional approvals and indexing of animal drugs, the law states:

New animal drugs are subject to application of the same safety standards that would be applied to such drugs under section 512 (d) (including for antimicrobial new animal drugs, with respect to antimicrobial resistance).⁶

FDA should write implementing regulations for the MUMS Animal Health Act that, for antimicrobial new drugs, require consideration of multiple pathways for transmission of antimicrobial resistance.

KAW urges that FDA write implementing regulations for the MUMS Animal Health Act that, for antimicrobial new drugs, require specific consideration of antimicrobial resistance. FDA has already developed a recommended approach for assessing the safety of new animal drugs with regard to antimicrobial resistance. Specifically, FDA in October, 2003, published Guidance #152, which "outlines a comprehensive evidence-based approach to preventing antimicrobial resistance that may result from the use of antimicrobial drugs in animals."⁷

Application of Guidance #152 to antimicrobials evaluated under the MUMS law is an obvious step for FDA. But, Guidance #152 has several serious limitations, one of which is directly pertinent to these comments: The Guidance focuses solely on food as a pathway for transmission of resistance bacteria. FDA defines this pathway as the

⁴ Institute of Medicine, Board on Global Health (2003). *Microbial Threats to Health: Emergence, Detection, and Response*. National Academy of Sciences Press, Washington, DC. Available at: <http://books.nap.edu/books/030908864X/html/R1.html#pagetop>.

⁵ APUA, The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences. *Clinical Infectious Diseases*, Volume 34 Supplement 3. Available at: <http://www.journals.uchicago.edu/CID/journal/contents/v34nS3.html>. Accessed Sept. 4, 2004.

⁶ Minor Use and Minor Species Animal Health Act of 2004, Sections 571 (a) (1) and 572 (a) (1).

⁷ FDA, Guidance for Industry #152, *Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs with regard to their Microbiological Effects on Bacteria of Human Health Concern*, Oct. 23, 2003. Available at: <http://www.fda.gov/cvm/guidance/fguide152.pdf>.

probability of harm to human health as a result of people ingesting resistant bacteria from contaminated meat or flesh products.

For some minor species, particularly fish, the food pathway is almost certainly a less important pathway for transmission of antibiotic resistant bacteria than it is for warm-blooded animals. Unlike warm-blooded animals, the bacteria in the gastro-intestinal (GI) tracts of fish are not closely associated with food-borne disease in people.

Other pathways, however, play an important role for transmission of antibiotic resistant bacteria. A Norwegian study, for example, found very large increases in both resistant bacteria in mussels and wild finfish and antibiotic residues in wild finfish after the antibiotics oxytetracycline and oxolinic acid were administered on the farms.⁸ This study indicates that resistant bacteria and antibiotics can spread through the environment from farmed to wild fish – which may be handled and consumed by people. As another example, Canadian doctors traced invasive infections by *Streptococcus iniae*, which colonize the mucous-covered surface of finfish, to handling of farmed tilapia imported from the United States by consumers preparing meals.⁹ This study implies that, if antibiotics use on fish farms caused these bacteria to become antibiotic resistant, the result could be hard-to-treat infections in people.

The upshot is that for some minor species – and especially fish – the application of Guidance #152 may not be sufficient to establish “safety,” because the most important pathways for transmission of antibiotic resistant bacteria are not considered. Guidance #152 states that:

FDA recognizes that food-borne human exposure to antimicrobial resistant bacteria is complex and often involves the contributions from other sources of exposure (e.g., direct contact between animals and humans, introduction of resistant bacteria and resistance determinants into the environment). However, FDA believes that evaluating antimicrobial new animal drug safety relative to the most significant exposure pathway (i.e., food-borne pathway) is the best way to qualitatively assess the risk of antimicrobial drug use in food-producing animals.¹⁰

Since FDA’s “belief” appears incorrect for at least some minor species, the agency needs to take a more expansive view of transmission pathways for antibiotic resistance with regard to those species.

KAW urges that FDA require that likely pathways for antibiotic resistance be considered when evaluating antimicrobials for conditional approvals or indexing under the MUMS law. Particularly for those species for which the food does not appear a major pathway,

⁸ Ervik A et al., 1994. Impact of administering antibacterial agents on wild fish and blue mussels *Mytilus edulis* in the vicinity of fish farms. *Diseases of Aquatic Organisms* 18:45-51.

⁹ Weinstein M.R., et al. 1997. Invasive infections due to a fish pathogen, *Streptococcus iniae*. *New Engl. J. Med.* 337:589-94.

¹⁰ FDA Guidance #152, p. 15.

FDA should consider explicitly require consideration of additional pathways.¹¹ For example, in lieu of the food-only exposure assessments provisions of Guidance #152, FDA could require consideration of other means of transmission, such as dermal exposure from handling of fish and surface-water pathways.

In short, the under MUMS Animal Health Act, FDA must consider the extremely serious problem of antimicrobial resistance when evaluating the safety of a new animal drug. KAW urges that FDA draft implementing regulations for the MUMS law that require specific consideration of different pathways for transmission of antimicrobial resistance.

Thank you for considering these comments.

Yours truly,

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¹¹ Even when the food pathway IS clearly a major pathway, other pathways may still contribute significantly to the transmission of resistant bacteria. As a result, a conclusion that an antimicrobial is “unsafe” under Guidance #152 is sufficient for FDA decision-making, but a conclusion that an antimicrobial is “safe” is not necessarily sufficient. In the latter instance, the conclusion may ignore important avenues for transmission of resistance.