



AMERICAN VETERINARY MEDICAL ASSOCIATION

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February 7, 2000

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

RE: DOCKET NUMBER 98D-0969

Dear Sir or Madam:

The American Veterinary Medical Association, on behalf of its 64,000 members, provides the following comments on the draft "Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken." The AVMA is the national professional association of veterinarians whose members are charged ethically and legally with the protection of the health of animals within their care, as well as the protection of public health.

We commend the FDA Center for Veterinary Medicine for performing the risk assessment. In our comments to the Veterinary Medicine Advisory Committee in January 1999 and in other forums, we recommended that risk assessments be performed before proceeding too far towards increased regulation of veterinary drugs. We believe that comprehensive risk assessments serve many purposes. The most significant purpose is to enable risk-based management decisions. Additional benefits include serving as a repository of scientific knowledge and the identification of knowledge gaps that can then become research priorities. The fluoroquinolone-*Campylobacter*-chicken risk assessment improves our understanding of the relationship between fluoroquinolone-resistant *Campylobacter* in chicken and human health, and identifies significant scientific limitations that are identified as data gaps.

One of the next steps that is needed is a determination of what constitutes an acceptable public health risk. This determination must involve all of the public, including veterinarians who need the drugs for the benefit of animal welfare, consumers who may be favorably and/or adversely affected by the use of antimicrobials in food animals, producers of food animals whose livelihood depends on efficient health management, and the manufacturers of the drugs. A foundation for these discussions must be recognition that the current standard for approval of animal drugs, a reasonable certainty of no harm, cannot be applied to bacteria or antimicrobial-resistant bacteria. Unlike drug residues, bacteria are dynamic. Bacteria can multiply if exposed

98D-0969

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to favorable growth conditions. Therefore unless food is sterilized, a risk-free standard (i.e., a reasonable certainty of **no** harm) from bacteria is impossible to enforce. Some tolerance of pathogens and antimicrobial-resistant bacteria in raw meat and poultry products needs to be accepted. The risk assessment document discusses this issue extensively in the sections on Risk and Strategies for Controlling the Risk, Defining a Risk Standard for Assessing the Microbial Safety of New Animal Drugs, and Section 5, Using the Model to Manage Risk. As the discussions continue, we recommend that the FDA closely coordinate its efforts regarding establishment of acceptable resistant pathogen levels in meat and poultry with the U.S. Department of Agriculture. The USDA has responsibility for regulating the safety of meat and poultry, including microbiological safety.

The fluoroquinolone-*Campylobacter*-chicken risk assessment has some shortcomings, which are addressed later in this document, but the design and execution appears to be logical and consistent with the current state of scientific knowledge.

Limit the problem statement to *Campylobacter* only

The Food Borne Disease and Microbial Risk Assessment section states, "Food borne diseases caused by bacteria have a major public health impact in the United States. Recent estimates describe 5,000 deaths and 76 million cases of food borne illness annually. A 1994 report estimated an annual economic burden due to food borne illness at 22 billion dollars." All three sentences overstate the problem that is the subject of this risk assessment – food borne *Campylobacter*. The first quoted sentence addresses all bacterial food borne disease, and the second and third sentences provide estimates of all food borne diseases, including non-bacterial food borne disease.

The reference for the second sentence, Mead et al, estimates 99 food borne *Campylobacter* deaths per year and 1,963,141 cases per year. Buzby et al report that the estimated costs of food borne campylobacteriosis range from \$0.6-\$1.0 billion annually in 1993 dollars.¹ Buzby's estimate of cost is based on estimates of food borne cases ranging from 1,375,000 to 1,750,000 and estimated deaths ranging from 110 to 511 annually. The problem statement for this risk assessment for food borne resistant *Campylobacter* should be changed to provide the estimates for *Campylobacter* only, not all food borne diseases.

In the US, is food borne disease an increasing or decreasing problem? Define the US situation, not the worldwide problem.

The Antimicrobial Resistance in Food Borne Disease section states, "Bacterial food borne disease is a growing problem worldwide and has been addressed in many reviews and reports on the topic." In actuality as reported by FoodNet, bacterial food borne disease in the United States may be decreasing. The 1998 FoodNet surveillance results report, "For the five original sites,

¹ Buzby, J., et al. Bacterial Foodborne Disease: Medical Costs and Productivity Losses. Food and Consumer Economics Division, Economic Research Service, U.S. Department of Agriculture. Agricultural Economic Report No. 741, August 1996.

overall incidence rates of illness caused by pathogens under surveillance declined from 1996 to 1998. ... Although *Campylobacter* rates increased slightly from 1996 to 1997 (23.5/100,000 to 25.2/100,000), 1998 rates experienced a substantial decline (21.7/100,000).” The risk assessment needs to be changed to reflect current scientific reports of decreasing incidence of food borne illness in the United States caused by *Campylobacter*.

Inconsistency in defining the need for empiric treatment

The next paragraph states, “Although *Campylobacter* infections are usually self-limiting, antibiotic therapy is used for patients: ... 4) whose symptoms worsen or persist for more than 1 week.” Later in the same paragraph, the statement is made “Fluoroquinolones are frequently used empirically to treat *Campylobacter* illness. Empiric treatment of patients with enteric disease seeking treatment is the norm because when treatment is delayed (e.g., until *C. jejuni* infection is confirmed by a medical laboratory), therapy may not be effective.” The two quotations are contradictory and need to be clarified.

Need to consider the public health benefits of fluoroquinolone use in animals

To limit the complexity of the risk assessment, only the public health risk associated with the use of fluoroquinolones in chickens was assessed. We recognize that the Agency could not evaluate the public health benefit associated with the use of fluoroquinolones because of a lack of data. We recommend funding of a high priority research topic to address the possible beneficial effects to public health of fluoroquinolone use on the prevalence of *Campylobacter* and *Salmonella* in poultry.

The pathogen load in poultry could be increased or decreased by the withdrawal of a drug. The assumption that only good can result from withdrawal of an antimicrobial from use in food animals is unfounded, and is a dangerous precedent to follow. Dr. Glenn Morris’ comment at the workshop is pertinent, “Don’t forget the long-term, down-stream sequelae of the lack of an appropriate first line therapy.” Fluoroquinolones are effective, approved therapy for colibacillosis in chickens. Withdrawal of the approval for the fluoroquinolones would require the extralabel use of antimicrobials to treat the disease with the consequent uncertainties associated with extralabel use of drugs.

Consistency in the expression of risk

The Risk and Strategies for Controlling the Risk section presents four alternatives for expressing the risk of resistant *Campylobacter*. We recommend that the agency continue with the current standard of expression used by the FDA for food additives and for the food safety objectives of U.S. Department of Health and Human Services’ Healthy People 2010. The U.S. consumer is familiar with expressions of risk as a number divided by the U.S. population and expressed for example as X cases per 100,000 population. The U.S. citizens and scientists will benefit from consistency of risk expression because use of a consistent population for risk expression provides a common perspective, and enables a better appreciation of the comparative risks associated with various activities and hazards.

Are bacteria substances? Does Section 512 permit regulation of bacteria?

The section on Defining a Risk Standard for Assessing the Microbial Safety of New Animal Drugs discusses Section 512 of the Federal Food, Drug, and Cosmetic Act. Section 512 requires determination of safety including consideration of the probable consumption of the new animal drug and of any "substance" formed in or on food because of the drug. It is clear that when Section 512 was written, "substance" did not refer to bacteria. It is questionable whether Section 512 can be used to regulate living organisms as opposed to inert chemical substances. The regulations (21 CFR 570.3(i)(2)) state, "The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet." The regulations clearly address chemical substances, not bacteria.

What is the authority for FDA CVM to regulate bacteria in meat and poultry products?

Is the FoodNet catchment representative of the U.S. population?

One of the critical assumptions in Section 1, Estimating the Number of Human Culture-Confirmed Cases of Campylobacteriosis in the U.S. in a Specified Year, is "The incidence rates for culture-confirmed *Campylobacter* infections in the FoodNet catchment are representative of incidence rates for culture-confirmed *Campylobacter* infections in the U.S." The discussion acknowledges the variance of incidence rates among the FoodNet sites but states that the overall rate is likely to reflect isolation rates in the U.S. The justification is that the FoodNet demographic characteristics are similar to the U.S. demographic distributions of sex, age, race and rural/urban.

The incidence of campylobacteriosis ranged from 10.2 per 100,000 in Maryland to 37.7 in California; a significant variance. The next highest sites are Oregon and Minnesota with a rate about 22. Therefore, the high rate of California disproportionately raises the average rate. Is the average truly representative of the U.S. rate? And is the FoodNet demographic distribution really similar to the U.S. population? Table 1.1 compares the demographic distributions of total FoodNet catchment to the U.S. population. FoodNet has smaller proportions of age groups 0-30 years and 60+ years and a larger proportion of ages 30-50 years. FoodNet also has a higher proportion of whites and a smaller proportion of Hispanics. FoodNet also has a smaller proportion of rural population. A review of the FoodNet sites reveals an absence of a site representing the south central U.S. All of the differences can affect the estimate of the U.S. culture-confirmed cases.

Campylobacter susceptibility

At the bottom of page 1.6, it is stated, "... the most susceptible are the very young and elderly..." However, the FoodNet data show the elderly are less susceptible to infection with *Campylobacter*.

Sources of Fluoroquinolone-resistant *Campylobacter*

Section 3 makes a major assumption, "The fluoroquinolone resistance observed in persons ill from campylobacteriosis, (after removal of travelers, those who took a fluoroquinolone prior to

culture and those for whom the time of taking the fluoroquinolone was unknown) is attributed to chicken.” An associated, but unstated assumption, is that all chicken-associated fluoroquinolone-resistance is attributable to the use of fluoroquinolones in chickens. Both assumptions need careful evaluation. What is the potential for chickens to obtain resistant *Campylobacter* through water or exposure to other animals?

The Group Health Cooperative, Western Washington State, study attributed 48% of the etiologic fraction of human campylobacteriosis cases to chicken consumption. Therefore, 52% of the cases were attributed to other risk factors including non-household member with enteritis (12%), household member with enteritis (8%), non-home well or surface water (8%), any animal with diarrhea (6%), and raw milk consumption (5%). The Denver and Fort Collins study attributed 47% of the cases to consumption of undercooked chicken (Matched Odds Ratio 6.3). The matched odds ratios for other risk factors were raw water 10.7, raw milk 6.9, and cats in household 3.2. Are chickens potentially exposed to *Campylobacter* contaminated water? Are some of the *Campylobacter* from human origin? If so, could the human origin *Campylobacter* be resistant as a result of human use of fluoroquinolones? Pathogen transfer from humans to poultry through sewage plant effluents is possible as demonstrated in California with *Salmonella enteritidis* Phage Type 4. Also, the wastewater survey in the Netherlands found an 11% fluoroquinolone resistant *Campylobacter* level in effluent from a sewage purification plant that did not receive meat-processing sewage, indicating that water can be a medium for resistant and susceptible *Campylobacter* of non-poultry origin.

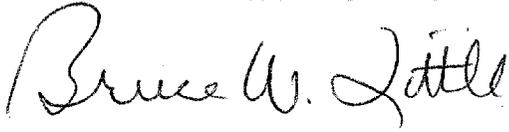
An associated, identified data gap is, “Quantification of the proportion of human disease attributable to various sources and the determination of the level of resistance carriage within the specific exposures would more precisely allow the determination of the relative contributions of the various exposures to fluoroquinolone resistant human disease. A model intended to determine the human health impact of the level of resistance in *Campylobacter* attributable to fluoroquinolone use in food animals will need to distribute the burden of resistant human disease amongst many different food animal species.” In addition to distributing the burden amongst many different food animal species, the potential burden from other sources of infection, such as water and human contact, also needs to be evaluated.

Fluoroquinolones were available for cats and dogs in 1989. Prior to the extralabel use prohibition of fluoroquinolones in 1997, the drugs were used in food animals other than poultry. There is a potential for resistance development from the previous extralabel use. Caution must be followed before attributing all resistance to the approved use of fluoroquinolones in poultry.

Conclusion

We appreciate the opportunity to participate in the development of the strategy to address the potential public health risk associated with the use of antimicrobials in food animals. We pledge to work with the agency to protect public health while also safeguarding the health and welfare of animals. We will continue to contribute to the discussions in the scheduled workshops and by written comments.

Sincerely,

A handwritten signature in cursive script that reads "Bruce W. Little". The signature is written in dark ink and is positioned above the typed name.

Bruce W. Little, DVM
Executive Vice President

BWL/SCJTAU/LPV

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