

Alexander Mathews
President and CEO
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Alexandria, Virginia 22313-1480

Dear Mr. Mathews:

This is in response to your letter of September 16, 1997 regarding the status of the Center for Veterinary Medicine's (CVM) position related to the use of fluoroquinolone drug products for treating disease in animals. As you are aware, CVM can not comment on the existence of specific applications for fluoroquinolone animal drug products, however, in broad terms we have prepared the following responses relative to the four points made in your letter, which are italicized below.

1. Continue to approve new fluoroquinolones for food animals based on the 1994 recommendations of the Joint CVM Advisory Committee, and not based on reports of certain food borne outbreaks whose relationship to antibiotic use in animals is unsubstantiated.

First and foremost in the Center for Veterinary Medicine's list of responsibilities is to ensure that the use of any approved new animal drug product does not adversely impact human health. CVM takes this responsibility very seriously and believes it is incumbent upon the Center to investigate all significant reports of adverse reactions related to approved new animal drugs as well as drugs that may be under review.

In 1995, FDA approved two fluoroquinolone products for use in poultry in the United States. FDA approved these products after having taken the issue of the approvability of fluoroquinolones for use in food animals to a panel of experts in the form of the Joint Advisory Committee (JAC), in 1994. The JAC was comprised of CVM's Advisory Committee as well as the Center for Drug Evaluation and Research's Anti-Infective Drugs Advisory Committee. The JAC agreed that there was a need for fluoroquinolones in food animal medicine and did not object to the approval of fluoroquinolones for such uses. However, based on concerns about antimicrobial resistance, the JAC generally supported several restrictions on the use of this class of drugs in order to maximize benefits and minimize risks related to the development of resistant organisms. Among these suggestions were a prohibition on the extralabel use of fluoroquinolones in animals as well as restricting the use of these products to prescription status and for therapeutic purposes only.

An additional recommendation was made that the Federal government establish a program to monitor for the development of pathogenic resistance that may result from use of approved fluoroquinolone animal products.

In accordance with the JAC recommendations, the two fluoroquinolone poultry products were approved in 1995 under restricted status and for therapeutic purposes only. Based in part upon the JAC recommendations, CVM, in collaboration with the U.S. Department of Agriculture (USDA) and Centers for Disease Control and Prevention (CDC), established a program to monitor antimicrobial resistance, known as the National Antimicrobial Susceptibility Monitoring Program (NASMP) in January 1996. The NASMP was intended, among other things, to signal in advance the development of resistance due to the approved fluoroquinolone animal products. FDA also issued an order to prohibit the extralabel use of fluoroquinolones in animals, which became effective in August 1997.

Recent reports from the scientific and public health communities have raised concerns, both domestically and internationally, about the approval of fluoroquinolones for food animals and the development of fluoroquinolone-resistance in human food borne enteric pathogens. The approval of these drugs in food animals has temporally preceded increases in resistance in The Netherlands (Endtz, 1991), the UK (Threlfall et al. 1997), and Spain (Perez-Trallero et al 1997). The two latter studies were published subsequent to the JAC. It has been suggested that the temporal and repetitive sequence of events in these geographically distinct areas are evidence supportive of an association between food animal fluoroquinolone use and human resistant zoonotic enteric disease.

Moreover, despite the conditions and restrictions placed on the use of the two approved poultry products, recent, as yet unsubstantiated, reports have raised concerns that there may be increasing fluoroquinolone resistance in *Campylobacter* spp. in poultry in the United States. The authors of these reports conclude that the data indicate a temporal link between the increase in fluoroquinolone resistance in poultry and humans to the use of the poultry products. It is uncertain what impact these purported increases in resistance in the United States might have on human health.

As a result of the recent information emerging both abroad and domestically related to use of fluoroquinolones in food-producing animals, FDA believes it is prudent public health policy for the Agency to consider all pertinent information, including the related uncertainties, before moving forward to approve any additional fluoroquinolones for use in food-producing animals. At this time, the Agency is in the process of reviewing both the foreign and domestic information that is available to us. We also are waiting for the complete 1997 data package being prepared by the NASMP, which we hope will bring more clarity to the issue of whether resistance may be developing in this country due to the use of the two approved poultry products. Furthermore, we are attempting to characterize the relationship (similarities and differences) between the use of products approved for poultry and those products that might be appropriate for use in other food-producing animals. This information will be of particular importance to us in developing a

consistent regulatory strategy, should it be determined that the poultry products do present a significant risk to human health. After completing our review, we hope to be in a better position to establish the veracity of the recent report related to the approved poultry products and to make decisions about the approvability of fluoroquinolones for use in other food animals as well as any regulatory controls that may be necessary to assure their safety.

2. Explain the scientific rationale for FDA's thinking on fluoroquinolones used in animals by responding in detail to comments filed to the document pertaining to the extralabel use of these products.

The Food and Drug Administration (FDA) published as a final rule an order of prohibition against the extralabel use in animals of fluoroquinolones (and glycopeptides) in the Federal Register on May 22, 1997 (62 FR 27944). After requesting, receiving, and reviewing several public comments filed in response to the rule, the prohibition became effective on August 20, 1997 (90 days after the date of publication).

In passing the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) (Pub. L. 103-396), Congress granted FDA broad authority to protect public health by allowing the Agency to restrict or prohibit the extralabel use of a drug upon finding that such use presents a risk to the public health. The Agency published AMDUCA implementing regulations in the Federal Register on November 7, 1996 (61 FR 57732). These regulations are codified in the Code of Federal Regulations at 21 CFR part 530. In Sec. 530.3(e) of these regulations, FDA has defined the phrase "presents a risk to the public health" as "likely will cause an adverse event."

FDA believes that the likelihood that resistant human pathogens will be selected is the type of risk contemplated by Congress when it included the broad extralabel prohibition authority in the AMDUCA. We note that fluoroquinolones are used extensively in human medicine to treat many infectious diseases, and they are the only antimicrobial agents that are effective for treatment of certain conditions in humans. Thus, in prohibiting the extralabel use of fluoroquinolones, the Agency acted within the limits of AMDUCA, albeit conservatively, when it balanced the potential risks to human health associated with extralabel use of fluoroquinolones in animals against our primary responsibility to protect public health.

Nonetheless, we believe that the prohibition is based on adequate scientific evidence. The Agency issued the order based on the expert opinion expressed at the 1994 JAC meeting as well as on several comments to the proposed AMDUCA implementing regulations stating that some extralabel uses of fluoroquinolones in food-producing animals are capable of increasing the level of drug resistant zoonotic pathogens (pathogens that are infective to humans) in treated animals at the time of slaughter, thereby increasing the risk of transfer of resistant organisms to humans and the compromise of human therapy. Sections II of the final rule provide detailed scientific analyses of the risks associated with extralabel use of fluoroquinolone drugs, supported by 18

references, most in peer-reviewed journals. It is the Agency's view that the references cited in the prohibition provide a sufficient scientific basis to support a prohibition of all extralabel uses of fluoroquinolones.

AMDUCA requires that opportunity be given for public comment before a prohibition goes into effect. It also provides that the order of prohibition will become effective 90 days after the date of publication, unless FDA revokes the order, modifies it or extends the period of public comment. AMDUCA does not require that CVM provide the detailed response to comments that you have requested in your letter. However, in the interest of making the Agency's current thinking on this important issue as transparent as possible, we have published a comprehensive analyses of the comments FDA received, which is currently available on our homepage. The analyses also may be obtained by contacting the CVM Communication Staff at 301-594-1755.

3. Provide clear guidance to sponsors as to how this may affect their future research and development plans for new antibacterials as well as to producers and veterinarians in need of new therapeutic antibacterials.

CVM recognizes the potential benefits that fluoroquinolones and other new antibacterials may have in the treatment of animal disease. We also are acutely aware of the stresses that the animal health industry has experienced due to our decision to review the complete 1997 NASMP data package as well as other available information before moving forward to approve additional fluoroquinolone animal products.

In response to your question 3, our current focus is specifically targeted toward the issue of approvability of fluoroquinolone drugs for use in food animals. Any policy that may be derived from our consideration of this issue may certainly impact on the future approvals of other antibacterial animal drugs. However, we urge companies not to make assumptions as to what research to pursue or not to pursue without coming in to speak with us first. At that time, we will do the best we can to provide an accurate assessment of their particular situation.

We are unable to advise the industry more generally at this time as to what direction our decisions on antibacterials ultimately may take for fear that any broad statement may be misconstrued. Providing such advice prematurely or to overstate our initial assessment would be unfair to those sponsors who may be considering research in this area and who, based upon an incomplete assessment of the situation, may decide not to complete current projects or not to begin new ones.

Please know that we are moving forward as expeditiously as possible. Therefore, we request your continued patience and cooperation as we continue our review of this important public health matter.

4. Release the draft risk assessment the Center has so far prepared on fluoroquinolones to allow other scientists to assist with filling data gaps which may be preventing completion.

We must deny your request for the draft risk assessment (RA) being developed by CVM related to the issue of fluoroquinolone resistance. The RA is a work in progress, a predecisional document which has not yet been completed. The draft RA contains assumptions, recommendations, and policy discussions within the deliberative processes of the Agency from which factual portions are not reasonably segregable. In fact, they are so inextricably intertwined with the nondisclosable information that to disclose any portion of the document would compromise or impinge upon the entire document.

Moreover, the information you have requested may raise issues concerning the disclosure of trade secret and confidential commercial information. Should you disagree with our position, you may feel free to file a request with FDA's Freedom of Information Staff. The FOI Office is located at 5600 Fishers Lane, Room 12A-16 (HFI-35), Rockville, MD 20857.

Thank you for your continued patience relating to this important public health issue. We hope that you find the information provided here to be useful. We ask that you feel comfortable in contacting us to share any information that you may have, which you believe would be helpful to us as we continue our review as well as to ask any related questions. A similar letter is being sent to the other signees.

Sincerely yours,

/s/

Stephen F. Sundlof, D.V.M., Ph.D.
Director
Center for Veterinary Medicine