

Research and Development
Elanco Animal Health
A Division of Eli Lilly and Company
2001 West Main St., P.O. Box 708
Greenfield, Indiana 46140



November 29, 2000

7167 '00 NOV 30 AM 10:37

Docket No. 00N-1571
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Elanco Animal Health, a Division of Eli Lilly and Company, is a research-based company engaged in bringing innovative, safe, and affordable animal health products to the marketplace. Elanco Animal Health offers the following comments because of the impact on veterinary medicine and even the future of animal health antimicrobials as a consequence of the issuance of the Notice of Opportunity for Hearing on therapeutic fluoroquinolones used in poultry.

The FDA/CVM regulatory process is designed to ensure that stringent public health standards and criteria are used for product approvals. The standards are to be transparent for all stakeholders as they are important to ensure that safe products are brought to the market that enhance the health and welfare of animal product and thus also enhance the safety of animal-derived food. We believe that similar standards must be applied to all FDA/CVM regulatory decisions including those regarding product use limitations.

The issuance of the Notice of Opportunity for Hearing (NOOH) raises questions as to the transparency of the process and the standards and data upon which this decision is based.

Circumstances of Issuance of Notice of Opportunity for Hearing (NOOH)

The NOOH was issued on the basis of the description in the Federal Register that contained the legal and public health justification for the proposed action such that "serious questions" could be raised where the evidence is not conclusive, but merely suggestive of an adverse effect; with the burden of proof of safety passing to the sponsor. We are troubled that this explanatory statement allows a very low standard of justification for FDA/CVM action, and by its very nature gives credence to scientific literature and other data that may be inappropriately applied without the benefit of the same critical evaluation as was required to approve the product. It is apparent from the composition of the "evidence" provided within the NOOH that many of the citations are of questionable quality, relevance and interpretation. Unfortunately, this potentially sets a precedent for issuing future NOOHs that could easily be applied to any antimicrobial product currently on the market, or even in the development stage, with minimal evidence-based data. This

00N-1571

C 2

contradictory approval/removal approach casts serious doubt on the predictability and fairness of the FDA/CVM regulatory process with regard to food animal antimicrobials.

In previous public remarks made by FDA/CVM officials, it was stated that the development, implementation, and application of the "Framework" document would be the appropriate process to determine the public health aspects of foodborne antimicrobial resistance associated with the animal use of those antimicrobials. Included within the Framework was the elaboration of the concept of Thresholds, which can be described as "bright line" standards that are based on antimicrobial resistance monitoring data, and could be used to initiate regulatory action to protect public health. The process for establishment of the threshold that would set an acceptable level of public health risk has yet to be disclosed since the meeting is scheduled for January 23-24, 2001. Thus, in issuing the NOOH, the FDA/CVM has pre-empted and superseded the value of public input on the threshold proposal by declaring that a precautionary approach is necessary without such input because of the "concern that the harm from fluoroquinolone-resistant *Campylobacter* infections will continue to increase." This approach casts serious doubt on the transparency and openness of the FDA/CVM regulatory process with regard to food animal antimicrobials.

Furthermore, within the NOOH, the FDA/CVM negates the value of Judicious Use Guidelines as an effective tool to maintain appropriate use of fluoroquinolones. These guidelines have been painstakingly developed and agreed to by all relevant stakeholders, including several government agencies, the American Veterinary Medical Association, and professional and trade organizations, and are just now being implemented in the field. Adequate time has not yet elapsed to fully capture the improvements in usage and ultimate public health benefit that will be gained from this initiative. This contradictory action that supports Judicious Use Guidelines on one hand, then rejects it as ineffective in specific cases on the other, appears inappropriate.

The NOOH provides neither evidence nor indications that the withdrawal of fluoroquinolones from poultry medicine will decrease the prevalence of campylobacter in chickens, decrease the prevalence of campylobacter with fluoroquinolone resistance, reduce the prevalence of campylobacter infections in humans, or improve the effectiveness of treatment of human campylobacter infections. It is not apparent why the FDA/CVM has chosen to focus on a small subset of fluoroquinolone resistant foodborne pathogens, which appears to have limited *potential* public health impact, when the overall goal of inter-agency efforts within the President's Food Safety Initiative clearly mandates a reduction in all foodborne pathogens and improving food quality specifically through reductions in carcass contamination. The elimination of a specific antimicrobial therapeutic product appears to do little to meet the goals of the Food Safety Initiative to improve public health, and it will have a significant cost associated with it, namely an adverse poultry health and welfare impact.

Scientific Basis of the NOOH

Elanco Animal Health supports a science-based regulatory system for evaluation of the safety, quality, and efficacy of products used in animals. As such, Elanco Animal Health complies with the FDA/CVM requirements for high quality data in NADAs and conducts pivotal registration studies according to GLP and GCP protocols. In situations regarding the potential withdrawal of products that have already met these data quality standards for approval, we believe it is appropriate that the same data quality standards should apply to any studies viewed as pivotal to the decision for removal. Based on the data contained in the NOOH and the accompanying Risk Assessment, and in spite of FDA/CVM's claim that the data used in the risk assessment met the highest quality standards, there is no evidence of compliance with these standards, thus the quality of the data is unknown.

The NOOH states that FDA/CVM concludes from the evidence provided that the use of fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant campylobacter found on poultry carcasses, and therefore a significant cause of fluoroquinolone-resistant campylobacter in humans; and resistant campylobacter infections are a human health hazard. For a foodborne pathogen, this is an obvious conclusion, and the use of a particular resistance phenotype, such as fluoroquinolone resistance, merely serves as a marker for transfer within a particular bacterial species.

The FDA/CVM evidence includes a tremendous amount of information regarding salmonella and fluoroquinolone resistance; however, only campylobacter is at issue in the NOOH. Recent NARMS data shows that there has been no fluoroquinolone resistant salmonella isolated to date; yet this pathogen was originally of most concern at the time of approval. This paradox is mentioned only in passing in the discussion of the assessment of the public health impact of fluoroquinolone use in poultry, yet it shows that the restrictive measures taken initially were effective in achieving the goal of safeguarding public health. So, instead, FDA/CVM has chosen to focus on campylobacter, through the use of a risk assessment that purposefully overlooks and minimizes the important contribution of many of the traditional foodchain data points, such as dose-response and cooking effects that are found in other risk assessments.

Additionally, in order to streamline the risk assessment, the FDA/CVM acknowledges the use of some data of questionable quality, along with the many assumptions made on key issues, and notes the many data gaps in the evaluation. Nevertheless, even in the face of uncertainty and varying estimates; the FDA/CVM takes a temporal association and makes a "cause and effect" conclusion anyway. No attempt has been made with the recent, "final", iteration of the risk assessment to obtain and incorporate input from affected stakeholders, other risk assessors, or to show how the model has been validated.

Within the risk assessment, owing to the low mortality rate and variable parameter of morbidity of campylobacter infections, the specific clinical determination of adverse public health impact was not described for campylobacter with fluoroquinolone resistance.

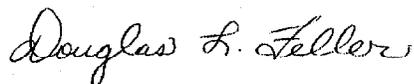
Instead, the treatment failure risk is *presumed* to be similar to that presented in a meeting abstract and personal communication from a Centers for Disease Control scientist, in conjunction with an epidemiological based study in Minnesota (i.e. increased duration of diarrhea). So, the risk assessment only states the *probability* of the number of persons that *could* be affected by campylobacter with fluoroquinolone resistance in a given population, and not an actual number that have actually failed therapy in some way. The fundamental *assumption* is that campylobacter with fluoroquinolone resistance will not respond to fluoroquinolone therapy, but this remains to be documented in a controlled clinical study. Indeed, the risk to the average U.S. citizen is 0.0032% in 1998 and 0.0042% in 1999, according the FDA/CVM's own data. Thus, the issue of fact is whether these lines of reasoning, based in part on questionable data sources, assumptions, and interpretations do indeed meet the requirement for "serious questions". Additionally, there is an issue of fact as to whether the numbers of campylobacter with fluoroquinolone resistance have exceeded some unspecified threshold that has yet to be revealed by the FDA/ CVM.

In conclusion, appropriate stringent public health standards need to be applied in both approving products and limiting their use. Elanco Animal Health supports stringent science-based regulatory standards for the evaluation of the safety, quality, and efficacy of products used in animals. In situations regarding the potential withdrawal of products that have already met rigorous data quality standards for approval, we believe it is appropriate that the same data quality standards should also apply to any studies viewed as pivotal to the decision for removal. It appears that the FDA/CVM uses differing data quality standards leading to the product withdrawal mandate in the NOOH than it does for product approvals.

We also believe that "Judicious Use Guidelines" and validated "Risk Assessments" can provide advancements in the appropriate use of antimicrobials when given an opportunity to be implemented properly. However, the issuance of the NOOH precludes either initiative from achieving the public health benefits that would have been realized over time while also allowing poultry medicine to retain an important antimicrobial. For these reasons, the NOOH represents not only a tremendous disincentive for the discovery and development of new therapeutic products for veterinary medicine, but also an unacceptable business risk for previously approved products formally deemed safe and useful for maintaining animal health and welfare.

Sincerely yours,

ELANCO ANIMAL HEALTH
A Division of Eli Lilly and Company



Douglas L. Feller, D.V.M.
Executive Director, Research and Development