

**AMERICAN VETERINARY MEDICAL ASSOCIATION**

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

**RE: DOCKET NUMBER 98D-1146, Discussion Paper: "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."**

Dear Sir or Madam:

The American Veterinary Medical Association submits the following comments as a supplement to the testimony provided by the AVMA at the Veterinary Medicine Advisory Committee meeting on January 25, 1999. Thank you for the opportunity to expand our comments.

While the AVMA disagrees with the need for a complicated regulatory process as outlined in the Framework document, we pledge to work with the Agency to develop a risk-based, measured response to the potential human health problem caused by the use of antimicrobials in food animals. In fact, the AVMA has already completed the development of general judicious therapeutic antimicrobial use principles and is developing more specific judicious use guidelines and an educational program. We believe these efforts, combined with other food safety efforts, will adequately address any potential risk that might be related to the therapeutic use of antimicrobials. We note that the issue of resistance resulting from the use of antimicrobials in human medicine is being addressed almost exclusively through prudent use principles, education, and monitoring. Additional regulation of human drugs is not contemplated.

We are also encouraging adequate funding to support and expand resistance monitoring programs such as the National Antimicrobial Resistance Monitoring System. Adequate surveillance and monitoring is essential to judicious or prudent use efforts. Uniform monitoring is required for several years to determine resistance trends. One or two year measurements cannot measure trends. A well designed surveillance program can also identify research questions that can then be examined through prospective or retrospective epidemiological studies.

Judicious use campaigns and monitoring programs, which compliment other food safety programs such as the Food Safety Initiative and the pathogen reduction program of the U.S. Department of Agriculture, should be viewed as the foundation of any considered framework for regulation of new animal drug approvals.

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We encourage the Agency to seek funding to perform a risk assessment to determine if the Framework document is truly risk-based. In the absence of a risk assessment, the public cannot be assured that the response is commensurate with the actual risk to human health or that the Agency's response is the most effective and efficient possible response. Also, a risk assessment may assist the Agency in evaluating the strength of the linkages between the Framework document's proposed preapproval studies to measure resistance development and effects on pathogen load, establishment of threshold levels, post-approval monitoring, and the actual public health protection provided by those concepts.

In the Statement of Purpose of the Framework document, it is stated, "FDA is charged with the regulatory responsibility of ensuring that the use of antimicrobial drugs in food-producing animals does not result in adverse health consequences to humans." As stated, the FDA has a zero tolerance or "no harm" policy; no adverse health consequence is allowed. The rest of the Framework document is designed to reach zero tolerance or no harm. This is the standard if resistant bacteria are to be regulated as food additives, however the more appropriate classification is as a food contaminant. Food additives are those substances deliberately incorporated into foods, and, for legal purposes, includes animal drugs. The second group, "food contaminants," includes anything not specifically approved for food use. Food contaminants are those substances which are unavoidably present and whose presence is tolerated. This group includes non-chemical contaminants such as rodent hairs. According to the Food, Drug, and Cosmetic Act, in general, FDA may not consider values other than safety in approving additives. If a substance is judged "reasonably certain" to produce "no harm" when used as intended, FDA is supposed to approve its use. Conversely, for contaminants, FDA must balance several objectives, including safety, food costs, and practicality of the regulatory action. These legal requirements engender very different regulatory concepts. For additives, FDA reaches a judgement on an intake level that will be without effect. For contaminants, FDA needs to know the likelihood of harm, given different regulatory approaches. USDA has the primary responsibility for regulating microbial contamination of meat and poultry and the USDA is not proposing regulations to establish zero tolerance for antimicrobial resistant human pathogens on meat and poultry. We suggest that the Agency reevaluate its regulatory approach to consider if microbial safety is more appropriately regulated as a food contaminant. This suggestion was addressed, but superficially and inadequately, at the VMAC meeting. We urge that the Agency thoroughly evaluate the appropriateness of regulating resistant bacteria as a food contaminant.

We are disappointed that the literature citations in the Framework document are not balanced. However, we will refrain from evoking a listing of citations that counter the arguments presented in the Framework document. Instead, we again urge that all information be considered in the context of a risk assessment.

An area that we wish to emphasize is the human health benefits resulting from the use of antimicrobials in food animals. The 1981 Council for Agricultural Science and Technology report stated, "The benefits to animals and humans associated with overall therapeutic antibiotic use in food animals outweigh the risks of use because the development and spread of pathogenic organisms are held in check." The 1998 NRC/IOM report states, "The benefit to human health in

the proper use of antibiotics in food animals is related to the ability for these drugs to combat infectious bacteria that can be transferred to humans by either direct contact with the sick animal, consumption of food contaminated with pathogens from animals, or proliferation into the environment." The NRC/IOM report also states, "Some level of risk is involved in the practice of giving antibiotics to animals but the ranking of risks and benefits cannot easily be accomplished because of lack of validated data and controlled studies." The report concludes that antibiotic use in farm animals is largely beneficial and presents a summary of data and studies that suggest that conclusion. This information on the human health benefits of antimicrobial use in food animals needs to be incorporated into a risk assessment.

We recognize the following comments refer to Docket Number 98D-0969, Guidance for Industry: Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals. We also recognize that written comments on Docket 98D-0969 should have been submitted by December 18, 1998. However, the Guidance document is directly applicable to the concepts of Docket 98D-1146. Also, Docket 98D-1146 states that comments regarding the draft guidance may be submitted at any time.

The Guidance document proposes to evaluate, in pre-approval studies, two separate factors in assessing the human health impact of the microbial effects of the intended uses of all new antimicrobial new animal drugs: (1) The quantity of antimicrobial drug-resistant enteric bacteria formed in the animal's intestinal tract following exposure to the antimicrobial new animal drug (resistance), and (2) changes in the number of enteric bacteria in the animal's intestinal tract that cause human illness (pathogen load). The intention of the proposed pre-approval studies is to allow the Agency to predict the human health impact related to the quantity of resistance and changes in the number of human pathogens in the target animal's intestinal tract following exposure to the antimicrobial when used as intended. The scientific data required to evaluate the two factors and assess the human health impact is the same type of data that can be used to perform a risk assessment.

It is apparent that the Agency intends to de facto regulate pathogen loads in the intestines of food animals. The U. S. Department of Agriculture which has primary jurisdiction for the safety of meat and poultry does not, nor does it intend to, regulate pathogen loads in food animals; why is the FDA attempting to do so? The USDA has established performance standards for *Salmonella* on animal carcasses as adequate public health safeguards. We suggest that, if the FDA continues to evaluate resistance and pathogen load in assessing the human health impact, the FDA consult with the USDA to evaluate a third factor, the quantity of resistant pathogens resulting from the intended use of the antimicrobial that are transferred through meat and poultry to humans.

The AVMA offers to cooperate with the FDA to develop the concepts of the Framework document into a regulatory approach that will adequately safeguard the public's health while providing for the safe use of antimicrobials in food animals. Please contact us for assistance or clarification of our recommendations.

Thank you for the opportunity to comment on this discussion paper.

Sincerely,

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

Bruce W. Little, DVM  
Executive Vice President

BWL/LPV