

IOWA STATE UNIVERSITY
OF SCIENCE AND TECHNOLOGY

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Reference: Review of Docket No. 98D-1146, Draft Guidance for Industry #152, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

Dear Sir or Madam:

On behalf of the American Association of Bovine Practitioners (AABP) and the Academy of Veterinary Consultants (AVC), I submit the following comments on Docket Number 98D-1146, Draft Guidance for Industry #152, entitled Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern.

The AABP and AVC, consisting of over 6000 and 500 member veterinarians respectively, are dedicated to serving the interests of both human and animal health. The AABP represents veterinarians involved in all areas of bovine practice, especially dairy and beef production. The AVC focuses on beef production, with an emphasis on the cattle feeding and cow/calf production segments. Common goals of AABP and AVC members include preservation of livestock resources, supporting the economic viability of our clients, ensuring food quality and safety, and promoting the welfare of livestock through sound production practices. All of these goals require aggressive preventive programs and the judicious use of antimicrobials to address disease challenges. In the spirit of working with the FDA/CVM to support human and animal health, we offer the following comments on the guidance document.

1. We are concerned about the drug ranking process. Ranking of drugs based on human importance for infections with no demonstrated food animal link could lead to a result of restricting veterinary use of antimicrobials due to misuse in the human health professions.

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The guidance document is stated to focus on food-borne resistance transfer, yet many of the examples cited in the ranking discussion involve human-specific challenges such as MRSA infections, tuberculosis, *Legionella pneumophila*, and *Pseudomonas*. A ranking system that results in Penicillin G being assigned a high human-importance rank in a document that focuses on food-borne resistance transfer illustrates the need for transparency and discussion in the ranking process.

2. It would be helpful for the FDA/CVM to define both broad and narrow spectrum classifications and to propose the categorization of the ranked drugs as such for purposes of use in this document. In discussing the spectrum of activity of antimicrobial drugs, the document refers to "broad spectrum" activity. These definitions are used quite often in the literature with great importance put on selection of a narrow or broad spectrum drug, but little effort has been put toward standardizing the definitions.

3. We ask the FDA/CVM to discuss the pharmacokinetic/pharmacodynamic (PK/PD) models they feel are currently validated for application as predictive models in colonic contents and/or discuss the modeling that would be acceptable for use in the release assessment.

The document calls for evaluation of antimicrobial pharmacodynamics in relation to the potential for resistance development. Specifically, the guidance document states "... pharmacodynamics might be ranked low with regard to impact on resistance if the same drug did not enter the target animal intestinal tract at concentrations shown to have an effect on resistance development". Does the agency intend to accept PK/PD based studies as sufficient evidence? If so, extensive discussion needs to occur concerning these PK/PD models. The models currently available are heavily biased towards prediction of efficacy in specific drug/pathogen combinations. The increasing body of knowledge related to mutant prevention concentrations and mutant prevention windows is primarily based on limited in-vitro work.

4. We feel the document is designed to be heavily biased towards human health without recognizing that antimicrobial application in food animals can benefit both animal and human health. The AABP and AVC support efforts to protect human health, and we ask the FDA/CVM to consider the benefits to human health of antimicrobial use in food animals.

As the document is currently written, if a sponsor finds the qualitative outcome to be unacceptable, they are relegated to either unspecified pre-approval studies or to a quantitative risk assessment. Either option must achieve the challenge of proving a negative (i.e., there is no effect on resistance). So in essence, the document achieves the precautionary principle by requiring only generalities to block drug use or approval, but requiring unspecified detailed data to remove limitations on use.

5. We are concerned that the document suggests an imminent widespread ban on extralabel use of antimicrobials in food animals. The lack of effective antimicrobial approvals for many diseases encountered in food animals requires that veterinarians prescribe extralabel uses in some cases within the scope of veterinary practice. This practice is regulated under the Animal Medicinal Drug Use Clarification Act (AMDUCA) that includes the requirement that extralabel use occurs only within a valid veterinary-client-patient relationship (VCPR).

In addition to their professional training, veterinarians have other resources to aid in extralabel antimicrobial use decisions. Supporting information for practicing veterinarians includes the Food Animal Residue Avoidance Databank (FARAD) which supplies withdrawal information for extralabel use so that veterinarians may design appropriate exaggerated withdrawal times. The Veterinary Antimicrobial Decision Support (VADS) system is also nearing availability to food animal veterinarians. This web-based system provides antimicrobial regimen selection support to veterinarians starting with labeled applications and working through extralabel alternatives relying on efficacy-based PK/PD modeling. Information on antimicrobial resistance development will also be included in the system. In addition to the FDA/CVM's support of the VADS System project, industry commitment to the judicious use of antimicrobials in food animals is demonstrated by financial support from the following organizations.

American Veterinary Medical Association
Academy of Veterinary Consultants
American Association of Bovine Practitioners
American Association of Swine Veterinarians
National Cattlemen's Beef Association
National Pork Board

We caution the FDA/CVM that removal of the ability of veterinary practitioners to use antimicrobials in an extralabel manner has the potential to severely hamper our ability to respond to diseases for which an effective, labeled alternative is not available. Removal of this ability based on drug ranking for human diseases not related to food animals, or as part of an initiative to simply reduce antimicrobial use in food animals, may have the unintended result of increasing pathogen carriage of animals going to slaughter. The extralabel use of antimicrobials in food animals is currently regulated, with a support system for residue avoidance in place and a support system for regimen construction soon to be available.

6. We urge the agency to consider the input given on commodity consumption estimates used in the exposure assessment portion of the document. Examples of the need for refinement include adjusting for cooked vs. raw product and considering quantity distribution of bacteria within a commodity instead of just a generalized prevalence estimate.

We thank the FDA/CVM for the opportunity to comment on guidance document #152.

Sincerely,

A handwritten signature in black ink, appearing to read 'Mike Apley', written over a horizontal line.

Mike Apley, DVM, PhD, DACVCP
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Iowa State University