



AMERICAN VETERINARY MEDICAL ASSOCIATION

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

**Reference: Review of Docket No. 98D-1146, Draft Guidance for Industry #152,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:

The American Veterinary Medical Association, on behalf of its 68,000 members, provides the following comments on Docket Number 98D-1146, Draft Guidance for Industry #152, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern.

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. The overarching objective of the AVMA is to advance the science and art of veterinary medicine, including its relationship to public health, biological science, and agriculture. In furtherance of that objective, we submit these comments.

We urge the Agency to review the transcript of the public meeting on October 2, 2002 where the Guidance document was discussed. The attendees and speakers provided valuable, constructive advice regarding FDA's approach. Most of the meeting participants provided a healthy, scientific debate. The perspective provided by the Deputy Commissioner of the Food and Drug Administration, Dr. Lester Crawford, in his welcoming remarks, should be especially noted. He emphasized that FDA is seeking an approach that will control or reduce antimicrobial resistance and "yet enables us to proceed with the use of drugs to treat animals". He also warned against making the same societal mistakes that occurred with pesticides where the objective simply became reducing usage of pesticides without applying the science of risk assessment and risk management. Also, the introduction to Draft Guidance #152 states, "The use of antimicrobial drugs in food-producing animals is important in helping to promote animal

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health, welfare, and productivity.” The use of antimicrobial drugs in food-producing animals may also be an important tool to promote safe food as a consequence of promoting animal health. Therefore, additional requirements for new animal drug approvals, and retention of current approvals, must be applied prudently to balance the needs of public health, and animal health and welfare. The aim cannot be simply to reduce usage; if so, we risk making the same societal mistakes that occurred with pesticides.

The Guidance introduction states, “[F]ood-producing animals can serve as reservoirs of both commensal and pathogenic bacteria that *may* be transferred to humans by consumption of contaminated food products. With the use of antimicrobial drugs in food-producing animals, these bacteria *may* become resistant to drugs that *may* also be used to treat human illness, *potentially* making human illnesses more difficult to treat. In addition, bacteria pathogenic to humans *can* acquire resistance traits from non-pathogenic bacteria originating in food-producing animals by mechanisms that *allow* the exchange of their genetic material in the human gastrointestinal tract.” [Emphasis added] The unstated extension of this theory or hypothesis, and the basis of Guidance #152, is that the transfer of resistant bacteria or resistance traits occurs frequently enough to cause treatment failures in humans to an unacceptable extent, thereby justifying restrictions on the approval and uses of food-animal antimicrobials, while recognizing the consequent negative animal health and welfare, economic, and possible food safety impacts. We urge the FDA to consider these negative impacts while establishing the acceptable risk associated with antimicrobial drug approvals, and while deciding on the appropriate risk management strategies. Just because commensal and pathogenic bacteria *may* transfer to humans, and these bacteria *may* become resistant to drugs that *may* be used to treat human illness, doesn’t mean that the level of human illness that is more difficult to treat will occur to an unacceptable degree. [We note that Guidance #152 discusses only 2 parts, risk assessment and risk management, of the 3 portions of risk analysis. The third part, risk communication that can be used to determine societies’ level of risk acceptance, is not addressed in the guidance document.]

Ranking of antimicrobial drugs according to their importance in human medicine

We have a significant concern with the ranking of antimicrobial drugs with regard to their relative importance in human medicine. Our concern is heightened since this area of Guidance #152 is especially critical because the rankings are considered when completing two parts of the three-part qualitative risk assessment outlined in Guidance #152 – hazard identification and consequence assessment. And as stated by FDA during the public meeting on October 2, “There is also a degree of subjectivity in these [ranking] determinations”. We request that the justification of the assigned rankings of the drugs be made fully transparent prior to finalization of the guidance document.

We also believe that the rankings should consider only those bacteria or resistance determinants that are foodborne. The guidance document expresses FDA’s belief that human exposure through the ingestion of resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to resistance determinants or

resistant bacteria that have emerged as a consequence of antimicrobial drug use in animals. Therefore, FDA's strategies focus on food-producing animals. FDA defines the hazard "as human illness that is caused by a specified antimicrobial-resistant bacteria, *is attributable to a specified animal-derived food commodity*, and is treated with the human antimicrobial drug of interest". [Emphasis added] The guidance document also states, "FDA's overriding concern is that the effectiveness of antimicrobial drugs is decreased or lost in humans as a consequence of human exposure to resistant bacteria (or resistance determinants) resulting from the use of antimicrobial drugs in food-producing animals". Risk is defined "as the probability that human illness is caused by a specified antimicrobial resistant bacteria, *is attributable to a specified animal-derived food commodity*, and is treated with the human antimicrobial drug of interest". [Emphasis added]

Because the objective of the guidance is to manage the risk that is attributable to animal-derived food commodities, the drugs included in the ranking of antimicrobial drugs according to their importance in human medicine should be only those drugs used to treat human illnesses that are caused by bacteria or resistance determinants attributable to animal-derived food commodities. Thus, drug rankings justified on the importance for treatment of other than foodborne bacteria or resistance determinants should not be included in the Guidance document. Examples of inappropriate inclusion that are provided in the Guidance or at the public meeting include third-generation cephalosporins for the treatment of acute bacterial meningitis, penicillin-G for the treatment of neurosyphilis in pregnant women; spectinomycin for the treatment of gonorrhea in pregnant women; streptomycin for the treatment of tuberculosis; erythromycin and azithromycin for the treatment of pneumonia caused by *Legionella pneumophila*; vancomycin and linezolid for the treatment of endocarditis, osteomyelitis, or pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA); ceftriaxone or cefotaxime for the empirical treatment of bacterial meningitis, rifampin for post-exposure prophylaxis of invasive disease caused by *Neisseria meningitides*; and aminoglycosides and fluoroquinolones for treatment of *Pseudomonas aeruginosa* infections.

Release Assessment – Probability that factors related to the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the animal

There are several factors suggested for consideration in the release assessment, including the baseline prevalence of resistance. FDA recommends that the sponsor provide available epidemiological data outlining the existing prevalence of resistance to the drug in target pathogens and commensal gut flora. The Guidance document states that the data may be obtained from National Antimicrobial Resistance Monitoring System (NARMS) data, but this is not correct. NARMS does not perform surveillance on target (animal) pathogens, except for some species of Salmonellae. The lack of the data from other sources, such as current literature, may create a requirement for the sponsor to initiate cost-prohibitive baseline studies. Otherwise the most conservative significance must be assumed.

Several other factors are often unknown or extremely difficult to obtain with a required degree of certainty. An example is the occurrence and rate of transfer of resistance determinants. The requirement to consider these unknown factors or to assign the most conservative significance will result in application of the precautionary principle and the cessation of new animal drug approvals.

Exposure Assessment – Likelihood of human exposure to the hazardous agent through food exposure

Factors to consider in exposure assessment are a) the probability for humans to be exposed to given bacteria via a particular food commodity and b) the probability that bacteria of interest (to which humans are exposed) are resistant to particular antimicrobial drug or possess associated resistance determinants.

The probability for humans to be exposed to given bacteria via a particular food commodity is expected to be estimated by considerations of 1) the probability of contamination of the food product by the bacteria of interest and 2) the per capita consumption of the food commodity. Unfortunately most of the available information regarding food contamination, as shown in Appendix B of the Guidance document, only provides estimates of prevalence in the commodities and does not provide quantification of the relative contamination among the commodities. A relatively high prevalence of contamination does not necessarily equate to high concentrations of contamination in the commodity. Nor does a prevalence estimate provide any information about the distribution of contamination on individual units of product. Disparately high concentrations on relatively few carcasses or portions may be more important than low concentrations on many carcasses or portions because the high concentrations may be necessary to achieve the infectious dose after cooking. Also Table B1 needs to be adjusted to consider the relative per capita sale of raw versus further processed (e.g., cooked) product. Over 50% of both pork and chicken is further processed and, except for seasonal variation, the majority of turkey (75%) is further processed. Cooking and other processing, such as irradiation, will reduce the contamination of the food product to zero. Therefore, the exposure risk is low or non-existent in cooked or otherwise processed meat and poultry products.

Risk Management

The Guidance document states, “The qualitative antimicrobial resistance risk assessment process provides for the ranking of proposed antimicrobial new animal drugs with regard to the level of risk that their use will cause an adverse impact on human health. All elements of the risk assessment process (i.e., release, exposure, and consequence assessments) should be integrated and considered as a whole when assigning the risk. This integration process, described previously as the risk estimation, qualitatively assigns a high, medium, or low risk ranking to the proposed new animal drug. This risk ranking can be used to help identify the steps necessary to manage the risks associated with the approval of a given antimicrobial drug.”

However, even though the risk estimate integrates and considers as a whole all elements of the risk assessment process (i.e., release, exposure, and consequence assessments), the Guidance document deems that it is necessary to introduce additional considerations into the risk management step, such as “extent of use”. Proposed conditions of use are included in the pertinent factors evaluated as part of the release assessment. Therefore, why is additional ranking for “extent of use” needed when considering risk management conditions?

Also, the scientific basis of the assigned rankings in Table 4 need to be provided by FDA if low, medium, and high extent of use is equated to low, medium, and high risk of resistance. Where is the research that shows that short treatment of individual animals results in less resistance than long treatment of flocks or herds of animals? If the regimen is inappropriate, short treatment may be more problematic than long treatment with an appropriate regimen, even if the treatment is given to flocks or herds. Where is the evidence that shows that select groups or pens of animals cannot be treated for short, medium, or long periods with a resultant low risk of resistance? Where is the evidence that 6 and 21 are the correct number of days to segregate the extent of use categories?

Extra-label use prohibition is listed as one of the appropriate risk management steps or conditions based on the outcome of the qualitative risk estimation process. We caution against an overly conservative approach where extra-label drug use is often selected for risk management as a condition for approval. Veterinarians depend on extra-label drug use, under conditions specified by FDA regulations, to prevent death and relieve animal suffering because of a lack of approved drugs for all diseases and conditions, especially for emerging diseases. It appears that implementation of Guidance #152 will not relieve the shortage of approved drugs and, in fact, will cause continued and additional shortages. Therefore, retention of veterinarians’ ability to utilize drugs in an extra-label manner, under the ELDU regulations, is essential. Adequate support, through systems such as the Food Animal Residue Avoidance Databank, is available to veterinarians to ensure responsible extra-label use. Soon the Veterinary Antimicrobial Decision Support system will also be available to food animal veterinarians to provide antimicrobial regimen selection support.

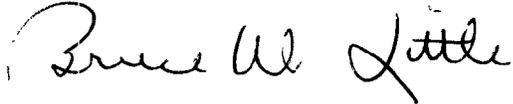
Antimicrobial NADAs for food-producing animals that may not be subject the Guidance #152

We support the exclusion of NADAs for minor species or minor uses when there is an existing approval for the new animal drug in a major species. In those cases, the safety information regarding potential microbiological effects can be obtained from the major species NADA. We also believe that, with some minor uses and minor species, an abbreviated qualitative risk assessment may be all that is needed to evaluate the potential microbiological effects because of the limited consumption by humans of food from the treated animals. Also some minor species, such as aquatic animals, have comparatively less transfer of bacteria to humans. These factors lower the probability for humans to ingest resistant bacteria or resistant determinants and lower the exposure assessment.

We also support the exclusion of generic (abbreviated) NADAs, NADAs for antimicrobial drug combinations, and for certain supplemental NADAs.

Thank you for the opportunity to comment.

Sincerely,

A handwritten signature in black ink that reads "Bruce W. Little". The signature is written in a cursive style with a large initial "B" and a distinct "Little" at the end.

Bruce W. Little, DVM
Executive Vice President

BWL/SCAR/LPV