



November 14, 2002

**Re: Docket Number 98D-1146**  
Dockets Management Branch (HFA 305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

To Whom It May Concern:

The enclosed comments address particular aspects of the 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of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern* ("Draft Guidance Document").

Thank you for the opportunity to submit these comments. Please feel free to contact me if APUA can be of assistance to CVM in the future.

Sincerely,

Kathleen T. Young  
Executive Director

CC: Stephen J. DeVincent, DVM, MA, Director of Ecology Program  
Stuart B. Levy, MD, President

Enclosures: Comments of APUA; Policy Recommendations

98D-1146

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**Comments of the Alliance for the Prudent Use of Antibiotics  
Re: Docket Number 98D-1146**

Submitted on 14 November, 2002

The Alliance for the Prudent Use of Antibiotics (APUA) is an independent nonprofit organization dedicated to improving public health through more appropriate use of antibiotics and reduction of antibiotic resistance.

The following comments address particular aspects of the *Draft Guidance for Industry #152: Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern* (“Draft Guidance Document”).

**I. Recommendations of the APUA “FAAIR Report”**

In a 2002 report (the APUA “FAAIR Report”), a panel of experts convened by APUA demonstrated that nontherapeutic use of antimicrobials in agriculture contributes to the emergence and spread of antimicrobial resistance in environmental bacteria, which can negatively impact human health.

Policy recommendations of this report included the following:

- Antimicrobial agents should not be used in agriculture in the absence of disease;
- Because of their critical role in treating human disease, fluoroquinolones and third-generation cephalosporins should not be used in agriculture except to treat refractory infections in individual animals.
- Antimicrobials should be administered to animals only when prescribed by a veterinarian.<sup>1</sup>

APUA believes that antibiotic use in animals that does not meet these criteria can never be consistent with the “reasonable certainty of no harm” standard. APUA urges CVM to incorporate these and other Policy Recommendations of the “FAAIR Report” (see attached) in formulating policy on antimicrobial use in agriculture.

**II. Ecological considerations and precautionary principle**

In Section II.B.1, the Draft Guidance Document notes that:

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<sup>1</sup> FAAIR Scientific Advisory Panel, 2002. Policy Recommendations. *Clinical Infectious Diseases* 34(Supp 3):S76-77 (see attached).

FDA believes that human exposure through the ingestion of resistant bacteria from animal-derived food 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.

APUA appreciates the acknowledgement by FDA that “human exposure to resistance determinants is complex and often involves the [sic] contributions from other sources of exposure” (Section II.B.1), but we suggest that FDA should consider explicitly incorporating other pathways of exposure in its strategy for managing antimicrobial resistance via the new animal drug approval process. An exclusive focus on direct transmission of resistance determinants from food animals to humans via ingestion of foodborne pathogens in exposure assessment will tend to underestimate the risk to human health.

If current science does not allow for adequate assessment of risk via alternate pathways, risk management procedures should acknowledge their omission by treating risk assessments based exclusively on foodborne transmission as underestimates of the true health risks posed by antimicrobial use in agriculture. In general, APUA favors strategies for risk management that are consistent with the “precautionary principle.”

## **II. Exposure assessment**

In section V.B.2.b of the Draft Guidance Document, CVM identifies the “probability that bacteria of interest (to which humans are exposed) are resistant” as one of two factors to be considered in exposure assessment (the other factor is the probability that a given pathogen will be present in food). APUA believes this condition to be problematic because it will tend to underestimate the level of risk associated with classes of antimicrobials to which resistance is not yet widespread. Ironically, these are often precisely the classes of antimicrobials that are most valuable in human medicine.

## **III. Qualitative approach**

The qualitative approach to risk assessment described in the Draft Guidance Document is both more flexible and less burdensome to industry than a quantitative approach would be. APUA agrees with CVM that flexibility is necessary to ensure adequate protection of human health. As described in the Draft Guidance Document, APUA agrees that CVM’s final risk management decision should depend on “consideration of all information available for the specific drug application in question” (Section VI). APUA urges CVM to employ a conservative approach consistent with the “precautionary principle” in making all risk management decisions (see above).

## **IV. Consideration of new data**

APUA also appreciates efforts by CVM to recognize the ecological dimensions of the antibiotic resistance problem and to incorporate new types of data into qualitative risk assessment procedures. In particular, APUA supports the inclusion of ecological

considerations such as resistance selection pressures (Section V.A.2.h) and baseline prevalence of resistance (Section V.A.2.i) as components of release assessment. Ongoing research efforts by APUA, including the Reservoirs of Antibiotic Resistance (ROAR) II Project, will substantively contribute to knowledge in these areas. APUA will strive to make the results of its research available to industry representatives and CVM officials. APUA further offers technical assistance in implementing the procedures outlined in the Draft Guidance Document.

#### **V. Need for re-evaluation of existing approvals**

Finally, APUA wishes to stress the importance of re-evaluating existing animal drug approvals in a timely fashion. As outlined in Appendix C of the Draft Guidance Document, CVM's priorities for re-evaluation seem appropriate; APUA agrees that those drugs deemed most important in human medicine should be among the first considered for re-evaluation. Given the immediacy of the antimicrobial resistance threat, however, APUA urges CVM to set and adhere to a more specific timetable with respect to re-evaluation of existing approvals.

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