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President & CEO

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May 3, 2000

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

Re: Comments to FDA Docket No. 98D-0969, "FDA Workshop on Pre-Approval Studies in Antimicrobial Resistance and Pathogen Load"

The Animal Health Institute provides these comments concerning the workshop on "Pre-Approval Studies in Antimicrobial Resistance and Pathogen Load" held by the FDA Center for Veterinary Medicine on February 22-24, 2000.

AHI is a national trade association representing manufacturers of animal health products – pharmaceuticals, vaccines and feed additives used in modern food production and the medicines that keep pets healthy.

The animal health industry shares with FDA the concern for the potential development of resistance from the use of antimicrobial drugs in food animals and appreciates the opportunity provided by the Agency for open and frank discussions on how best to address this issue. The workshop on pre-approval studies to evaluate the potential for bacterial resistance to develop with food animal antimicrobials provided an excellent forum for experts from academia, the pharmaceutical industry, animal production, veterinarians, diagnostic laboratories, various government agencies and consumer groups to evaluate and discuss the types of information that might be useful to enable the CVM to approve safe and efficacious new animal drugs. The following is a synopsis of the key issues discussed and the conclusions presented by the expert breakout groups:

1. There was consensus that *in vivo* models, at least by current scientific knowledge, were not considered of value in predicting the rate and extent of resistance development and the impact this might have on public health. Numerous problems and limitations were identified in the presentations given by several experts in the breakout discussions for determining objectives, designing protocols, and in trying to validate the results of such models. Issues such as duration of studies, age and health status of the target animal, selection of bacterial species (strain, serotype), and, in

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particular, lack of sound interpretive criteria were discussed. It was generally agreed that multiple confounding variables associated with such model studies are too complex for them to be able to provide valid conclusions, which can be used to predict potential selection of resistant organisms or determinants in actual practice and their ultimate impact on public health.

2. There was a clear and resounding consensus by all of the four breakout groups that pathogen load studies were of no value in evaluating the potential adverse impact on human safety due to the use of food animal antimicrobials. The breakout groups reasoned that post-harvest activities in slaughter and processing of food animals have by far the greatest impact on the prevalence of pathogens on raw meat and poultry and that any effects, either positive or negative, of an antimicrobial on pathogen shedding are inconsequential. Additionally, pathogen load studies have the same limitations described above for resistance selection studies. Given this, we see no benefit in having an additional workshop on pathogen load as was suggested in the CVM summary at the conclusion of the workshop.
3. The experts did support expanding the types of data that should be submitted as part of a New Animal Drug Application (NADA) for food animal antimicrobial products. It was suggested that baseline information be provided on aspects of antimicrobial susceptibility testing such as appropriate methods, quality control, etc., that would enable establishment of monitoring programs for the new animal drug. (Alternatively, if the agent is a member of an existing class, comparative studies on cross-resistance might be sufficient to use an existing agent as a class representative.) In particular, baseline susceptibility information on selected foodborne pathogens would be important information in order to evaluate prospective MIC changes over time post-approval. This could be accomplished by enhancing the NARMS program (as discussed below) and possibly eliminating the need for sponsors to conduct their own monitoring programs.
4. There was also general consensus that additional basic information on what is known about the resistance potential of the compound be provided in the NADA. It was concluded that this could be accomplished by a thorough review of published literature to document such parameters as:
 - the mechanism of action of the compound;
 - known mechanisms of resistance, if any;
 - cross resistance to other antimicrobials;
 - bacterial species that are currently known to carry resistance determinants;
 - any surveillance data on current incidence of resistance; and
 - information on mutation frequency of selected bacteria to the compound.

Additional information on target pathogens, spectrum of activity, susceptibility testing parameters including data relevant for the establishment of interpretive criteria

(i.e., breakpoints) and pharmacodynamics is already provided in the efficacy section of many NADAs.

5. In most of the breakout groups there was very strong support for the idea that the emphasis should be placed on post-approval surveillance of slaughter plant isolates for evaluating antimicrobial susceptibility changes, rather than pre-approval studies. Most participants agreed that the current NARMS program should be enhanced to include more representative (i.e., statistically-based) sampling of meat and poultry production, adding additional bacterial species and compounds for testing as needed, and expanding the number of overall isolates to the database.

On April 5, 1999, AHI submitted comments to FDA Docket No. 98D-1146, “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.” These comments included a comprehensive section on pre-approval studies, which addressed the complex nature and uncertain predictive value of animal studies to predict public health impact due to resistance selection and pathogen load. The workshop attendees confirmed many of the concerns expressed in these comments.

Therefore, based on the conclusions of the experts attending this workshop, we believe it would be appropriate for FDA to revise Guidance for Industry #78, “Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals” by eliminating the need to evaluate resistance development and pathogen load in pre-approval studies. It was clearly concluded from the discussions at the workshop that such studies are not predictive and would only add an unnecessary burden to the approval process with no resulting benefit.

AHI agrees with the conclusions of the workshop. Since additional *in vivo* studies conducted pre-approval are not needed, we strongly encourage CVM to resume approving antimicrobials that are otherwise found safe and effective for use in food animals. Post-approval monitoring over time is clearly the most effective means for evaluating the development of bacterial resistance and provides important information needed to assess any potential impact on public health.

We are disappointed to learn that the discussion on thresholds will be delayed for 6-9 months. However, this should not prevent the agency from approving antimicrobials since this is a post-approval tool which, if determined to be scientifically valid and appropriate, could be implemented following such determination. We do encourage CVM to provide the same type of opportunity for an open forum discussion about thresholds that was provided for pre-approval studies. Such discussion and open comment period should take place prior to issuance of any guidance document. It is very apparent from the Pre-Approval Workshop, that without the opportunity for all appropriate experts to discuss these concepts, policy may be implemented that does not achieve the desired goal of protecting public health and could even be counterproductive.

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We also wish to point out, once again, that any proposed requirements for addressing food safety must be tied to a valid analysis of the risk. CVM has taken the first step in this area with the draft risk assessment for the use of fluoroquinolones in poultry and the effect on campylobacter. This work needs to be completed utilizing input from the CVM workshop on this subject and comments submitted to the docket. In this regard, we consider it critical that CVM first substantiate that a significant risk exists, prior to implementation of additional requirements in the drug approval process.

Essential to this whole discussion, of course, is determination of the appropriate risk standard and what constitutes an acceptable risk. It is not possible to manage risk effectively without first making these determinations. AHI looks forward to being part of these discussions.

AHI commends the agency for providing the workshop forum to discuss the complex issues associated with the development of resistance. We believe this is an appropriate and effective means for addressing this subject. We encourage CVM to continue the process of open discussion with further workshops as needed to address additional issues such as the threshold concept, categorization of antimicrobials, risk and risk standards.

Sincerely,

A handwritten signature in black ink, appearing to read "Alexander S. Mathews", with a long horizontal flourish extending to the right.

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