

April 28, 1999

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20853

Re: Docket Number 99N-0386 – Talking With Stakeholders About FDA
Modernization

Comments by the Animal Health Institute:

On behalf of the Animal Health Institute and the Coalition for Animal Health I appreciate the opportunity to discuss the challenges that we believe face the Center for Veterinary Medicine as they review and approve animal drugs. As you know AHI represents the companies that research and develop the drugs and vaccines that protect the health of both food and companion animals. Today I plan to discuss the overall effectiveness and operation of the drug approval process both as it pertains to the Food and Drug Modernization Act (FDMA) and to the current efforts by CVM to alter the existing process for review of antibacterials.

As you are aware, AHI and the members of the Coalition for Animal Health have voiced strong concerns with the failure of CVM to base new safety requirements for animal antibacterials on quantitative risk assessment. These concerns were addressed directly in comments to the Veterinary Advisory Committee and amplified in the AHI comments filed on the proposed framework document in early April. It continues to cause concern that while the Office of Epizootics and recently the World Health Organization as well as other scientific bodies continue to point to documented risk assessment as the appropriate tool to develop and refine policy for animal and human safety, CVM seems to have subjectively established a zero risk policy.

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Throughout the debate on antibiotic resistance AHI has vocally supported the collection of national data to provide a meaningful overview of the prevalence of resistant food-borne pathogens. Specifically, we believe that the National Antimicrobial Resistance Monitoring System should be expanded to provide a more robust picture of change in susceptibility. We look forward to the opportunity to work directly with USDA and FDA to improve and expand the NARMS system. We believe CVM shares our goals in this area, and we believe that within AHI and the Coalition we have expertise that will be valuable if utilized in a positive manner. I hope CVM will take the opportunity to involve industry in workshops and symposia on this and other key element of the effort to better understand the potential for resistance development.

We have already begun work with CVM to develop a workshop on the concept of thresholds that is broadly laid out in the framework. Again, while this is a positive step CVM must make every effort to ensure that workshops and other efforts to gain public input allow balanced participation and open input. This was not the case in the VMAC hearing, the only previous opportunity for scientific review and public comment. In that case the format narrowed the range of questions that VMAC Committee members were allowed to pursue and the public comments in many instances seem to have been overlooked. We hope that the CVM will carefully review these and subsequent comments to the framework document when preparing revisions.

All the members of the Coalition for Animal Health have been active participants in the American Veterinary Medical Association efforts to develop judicious use guidelines. We

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believe those efforts to combat the development of resistance are a key part of meaningful strategies to protect animal and human health. We were disappointed when the judicious use guidelines did not figure predominately in the proposed framework or in the CVM presentation at VMAC. We would encourage CVM to make judicious use guidelines the cornerstone of the framework.

The member companies of AHI believe that the approval process for animal drugs should be based on science and the actual assessment of risk, not on assumed risk. Furthermore, the approval process should be certain and predictable. In many ways the current approval process at CVM fails to meet these standards. In October, 1998 AHI filed a Citizens Petition with the Food and Drug Administration asking that CVM refrain from imposing additional requirements on individual applicants until the legal and scientific justifications for these requirements were clarified. We believe that the approval process continues to be disrupted by the uncertainty of these product specific requirements. AHI looks forward to CVM's review and response to this petition.

AHI and the Coalition for Animal Health have always been committed to working constructively with CVM and attempting to address issues of concern in a positive and proactive manner. The record of cooperation with CVM established during the development and passage of the Animal Drug Availability Act of 1996 is a testament to that commitment. We believe that spirit of

cooperation can and should be brought to the table as the issue of antibiotic resistance is addressed.

Turning to comments relative to FDMA, AHI would like to focus on five areas or concern with regard to impact and implementation.

◆ Section 116 – Manufacturing Changes

We welcome the fact that Congress and FDA are moving to implement a more streamlined procedure for making changes in the manufacturing process and or specifications of new human and animal drugs particularly for those changes considered minor. However, we want to point out that long before FDMA, AHI and CVM had worked out a procedure for the agency review of Category I manufacturing changes called the Alternate Administrative Procedure. This allowed firms to submit many changes considered minor as biennial reports to the agency both expanding the current list of changes that do not need prior approval and also reducing the paperwork burden for documenting such changes. AHI co-sponsored a workshop with CVM, to introduce the procedure for the AAP. We viewed this as a highly productive exercise with many of our member firms participating in the program. With passage of FDMA our initial reading was that the law should not change the basic tenets of the AAP, but feedback from the agency indicates that may not be the case. In particular Section 116 requires annual reporting, while the AAP permits biennial. The major concern

with our members is that we are unable to get any guidance from CVM on this issue. We hope that the benefits gained from the AAP are not lost because of the new legislation.

◆ Section 130 – Reports of Post- Marketing Approval Studies

A new provision of the law requires reports of post-marketing studies on new drugs and presumably new animal drugs. AHI has several questions regarding this new provision. What was the intent of this section and how is it applicable to animal drugs? What types of studies will it apply to? Could it potentially apply to antimicrobial resistance monitoring which may not be a study per se but rather the ongoing collection of data? We are also concerned with the public release of information from such studies. The law indicates only identification of the sponsor and status of the study will be released. Could that be potentially interpreted to allow release of data and results to the public? Finally, will there be a lead office for reporting information to the public and to Congress or will each Center be responsible?

◆ Section 402 – Expanded Access to Investigational Therapies and Devices

An important section of the law allows greater access to life saving therapies that may not be available commercially but are under investigation. This is clearly aimed at human

therapeutics, but could it be applicable under similar circumstances to animal drugs?

Currently, CVM has a compassionate use policy that permits the use of certain unapproved drugs for treating animal disease conditions where there may be no approved drug. However this policy is tied to the INAD in that the veterinarian wishing to use the drug must be engaged in an active investigation. Furthermore, it is uncertain whether or not the company would be able to recover costs for providing the drug and must maintain specific records of the distribution and use. Companies may get requests for investigational drugs that have data showing them to be safe and effective but are not yet approved. They have a difficult time honoring those legitimate requests unless they are willing to assume the costs and responsibilities. We would encourage the Center to consider applying the intent of this section to animal drugs.

◆ Section 403 – Approval of Supplemental Applications for Approved Products

This section covers new criteria for approval of supplemental application. AHI would like to know when guidance on implementing this provision would be available for animal drug manufacturers. We note that FDMA encourages the companies to submit supplemental applications based wholly or in part on published literature or data already submitted to prevent duplication of research. This seems at odds with the proposed regulation published last year on the new definition of “substantial evidence of effectiveness” under the Animal Drug Availability Act (ADAA) of 1996. In that

proposal the agency appeared to be discouraging the use of published literature as a demonstration of substantial evidence as well as previously submitted data considered less than contemporary. We wonder how the ADAA and the intent of FDMA will be reconciled on this matter. How will supplements be designated as a priority for review? What kinds of submissions will qualify? Will important new uses of approved antibacterials to treat bacterial infections in animals be considered a priority while at the same time getting caught in the web of antibacterial resistance? Finally, is it to be assumed that the process for dealing with supplements under Section 403 will be handled separate and apart from the manufacturing supplement policy?

◆ Section 415 – Contracts for Expert Review

This provision recognizes that due to a need for specialized expertise or for resource constraints FDA may consider third party reviews of certain aspects of new drug or new animal drug applications. AHI would like to endorse the principle of third party evaluations but only if it improves the efficiency of the process and doesn't result in duplicative reviews. Does the Center have any plans for pilot testing the utility of such an approach? At one time we were led to believe the Center was seriously considering non-food animal efficacy studies as good candidates for third party review. More recently, contracting out toxicology study review mentioned. Where is the Center's

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current thinking on this and can AHI provide assistance in identifying appropriate applications? Finally, how will these reviews be funded?

We appreciate the opportunity to comment at these stakeholders meeting and look forward to comments by our Animal Health Coalition Partners, Joel Brandenburger on implementation of the ADAA, and Dave Bossman on Veterinary Feed Directive.