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THE REGULATORY ASPECTS OF THE DEVELOPMENT AND PRODUCTION OF VETERINARY PRODUCTS

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Everyone involved in producing quality veterinary drugs knows that the ability to produce such drug products at competitive prices is very dependent on Food and Drug Administration policies. My paper addresses FDA's recently announced or implemented policies and possible future regulatory trends that will affect the veterinary pharmaceutical industry. The focus of my remarks on the veterinary industry and the FDA are divided into three parts: (1) regulatory changes that are occurring; (2) regulatory issues that need resolution; and (3) future legislative issues. Let us start with regulatory changes that are occurring or have occurred.

It is difficult not to begin any present day discussion without recognizing the administrative law judge's (ALJ's) determination to ban nitrofurazones for use as drugs in animal feed. On November 12, 1986, Administrative Law Judge Daniel Davidson determined that nitrofurazone and furazolidone and their metabolites have not been found to be safe under conditions of use approved in the new animal drug applications (NADAs). In addition, he found that furazolidone, based on new evidence, induces cancer in man or animal and, therefore, these NADAs were revoked under the Delaney (cancer) clause. Now everyone recognizes that these drugs are not the first animal drugs to be withdrawn, nor will this withdrawal have a major economic impact in the marketplace. The interest in this particular proceeding is its historical longevity and the ALJ's ruling on Delaney. Those who have been in the field for a number of years will remember that the FDA's Notice of Intent to Withdraw these drugs was first published in March 1971, over fifteen years ago. The final hearing notice was published in the Federal Register in 1984 and the first pre-hearing conference was held in November of 1984. Finally, in November of 1986,

two years after the final hearing notice, the administrative law judge has announced a decision.

One of the major issues in the decision was what risk factor will form the basis for invoking the Delaney clause. The manufacturers had argued that the risk factor should be 1 in 100,000 based on benefit, but the ALJ determined that the risk factor should be 1 in 1,000,000 because the FDA's policy regarding poisonous and deleterious substances is 1 in 1,000,000 when substances cannot be avoided by good manufacturing practices (GMPs). The ALJ then pointed out that there was no reliable method of detection to measure the metabolites in edible tissue. The statute §512(b)(7) requires that the metabolites be measureable. You realize, of course, that the ALJ's determination is not final agency action and the decision can be appealed to the Commissioner. In fact, the manufacturers involved in the hearing requested 75 days in which to prepare a response to the ALJ's written opinion. The 75 day request was denied and the Commissioner allowed only 30 days. The point you should keep in mind is that it has taken almost 16 years, and the administrative procedure is not over. The actual hearing process before Davidson

took two years. One can also expect that whatever decision is made by the Commissioner, i.e., to accept the ALJ's decision or modify it, will be appealed to the Court of Appeals. Manufacturers who have spent 16 years battling the agency are not likely to stop until they have exhausted every avenue of redress.

On a second front, the agency has abandoned the cyclic review of animal drugs as not being in the public interest. During what some might call the "socially active" days of the early 70's, the agency created a cyclic review of animal drug data to be sure that human safety data was adequate to support the animal drug's approval. The agency's recent determination that the cyclic review of the animal drug's food safety data is not in the public's best interest has been called into question by a government report entitled "The Human Food Safety and the Regulation of Animal Drugs Report" prepared by the House Committee on Government Operations. The report became available in January 1986. The point made in the Congressional report was that the abandonment of the cyclic review program was not in the best

interest of the consuming public because there were unapproved new animal drugs such as methylene blue in the marketplace, unapproved uses for species and unapproved dosage levels, and investigational new drug applications (INADs) that were over five years old and still being marketed. The agency's determination to abandon the cyclic review was based on a decision to implement a "causal review" re-evaluation of new animal drug applications (NADA's). This new policy - FDA Staff Manual Guide 1240.3542 (9/19/85) - requires FDA to review basic animal safety and efficacy data when FDA has information that identifies a possible problem that may be severe enough to support withdrawal of the NADA. The fact that FDA is withstanding the congressional pressure of Congressman Weiss (D-NY) suggests that the agency's decision is well thought out and that Congressman Weiss has failed to find the agency's Achilles heel. Whatever, the Center is to be congratulated for terminating a program which it thought no longer benefited the American public.

In another matter, the Center stepped forward in a new area and will allow drug manufacturers of

approved new animal drug applications to state on their labels and to refer in advertisements to the FDA approval. The Center for Veterinary Medicine (CVM), where the agency's veterinary decisions are made, has stated that the label approval statements may be made only after the NADA has been amended by requesting a supplemental NADA. The agency published its standard in the Staff Manual Policy Guide (1240-4000) dated 2/21/86. CVM concluded that the prohibition against referring to approval in labeling in §301(l) of the Act relates only to human drugs and devices and that there was no prohibition from providing such information on animal drug labels. It is interesting to note that the manufacturer is only allowed to make the statement "NADA #_____ approved by FDA" in the label and it can only appear on the front panel on the bottom of the label of the immediate container. If a statement appears in the drug's insert, it must be at the very beginning or at the very end of the insert. As to advertising and other "promotional material", any statement may only indicate that the NADA is approved, it cannot characterize the basis of the approval. However, in promotional material, the manufacturer may cite

to FDA's FOI Summary of the drug and the Federal Register citation for the drug approval.

You are aware, I am sure, that the animal drug regulatory system differs from the human drug regulatory system in that the statute requires, under §512(i)of the Act, that the drug approval for the animal drug be published in the Federal Register. This information will then appear in the Code of Federal Regulations (CFR) (21 CFR 520-558). Therefore, it is relatively easy to determine by the Code of Federal Regulations whether a particular new animal drug can legally be produced by a particular sponsor (manufacturer). The list of sponsors is at 21 CFR 510.600. The Federal Register publication is not done for human drugs, and, therefore, there is no publication in the Code of Federal Regulations listing the sponsors (manufacturers) and the approved human drugs. You should not be overly alarmed about the failure to list human drugs in the CFR because there is presently an official FDA publication listing all approved human drugs called the "Orange Book".

The fourth current issue of significant importance is the medicated feed policy. The agency, for a number of years, has been unsatisfied with its medicated feed policy and the handling of the approval of medicated feed applications. Recently, FDA adopted what it calls the "new second generation medicated feed regulation". The proposal for the new procedure was published in July 1983 following a report from the 1978 Medicated Feed Task Force. The new medicated feed procedure the agency adopted (51 Fed. Reg. 7382 March 3, 1986) is designed to create two classes of medicated feeds: Category I feeds, which will not require the feed mill or farm to register; and Category II feeds, which are animal drug-containing feeds with required residue withdraw times, and which require registration of the mill or farm with FDA by filing a Form 1900. The 1900 Form replaces the old Form 1800. The agency also plans to withdraw the form 1800s held by firms that have failed direct inspections. The actual procedures for withdrawing the Form 1800's to be used under 21 §512(m)(4) of the Act have not, to the best of my knowledge, been determined, nor do I expect them to be announced any time soon.

The agency notes that there are over 10,000 commercial feed mills. Many produce only Category I feeds and will not be required to register with FDA. For enforcement purposes, these feed mills will be regulated by the state. Some mills will seek FDA approvals, but since they were not in compliance at the conclusion of their last FDA inspection, their new Forms 1900 will be denied. The applications for the new forms are due and the agency intends to review those submitted prior to June 13, 1986, prior to the March 3, 1987 deadline.

These new procedures being used by the agency should improve FDA's ability to take action against violative medicated feed mills, but the basic regulatory process and the procedures by which the agency is operating have not changed materially with this new regulation for those firms required to obtain Form 1900s. The major change occurs for the feed mill that once needed a Form 1800 to manufacture what are now Category I feeds. This process is real government deregulation.

The last matter that I would list under present regulatory action is FDA's efforts to

prevent the illegal distribution of veterinary drug products. As you are well aware, for most veterinary drugs, the manufacturer seeks approval for one or maybe two species and, after the drug enters the marketplace, veterinarians and farmers often determine that this new drug will be effective in other species. A new, "extra-label" use for the product occurs. This has been a matter of concern for sometime at the agency, but the issue has been highlighted because of recent Congressional pressure from Congressman Weiss. "The Human Food Safety and Regulation of Animal Drugs Report", issued by the Weiss subcommittee in January 1986, stated that the agency was permitting a violation of the pre-market approval section, §512, of the Act because these extra-label uses were occurring.

In response to Weiss' allegation that there were a significant number of prescription veterinary drugs involved in illegal drug sales, the FDA has devised methods to combat the problem. First, the agency, at the American Association of Veterinary State Boards meeting in Atlanta, invited state enforcement of illegal veterinary

prescription sales. The agency also has noted that it has increased signifcantly its resources to combat these illegal activities over the next couple of years.

While the agency is in the process of increasing its own resources and seeking state assistance, it also is working with the Association of Food and Drug Officials (AFDO) to create a Model Veterinary Drug Code that would license all purveyors of veterinary drugs, unless the drug was being used for dogs, cats, or household pets. AFDO's Legislative committee, in response to FDA's request, has proposed a Model Veterinary Drug Code which it plans on adopting as a final code at its June 1987 meeting. The major provisions of the model code would: (1) license all purveyors of veterinary drug products; (2) require recordkeeping (not dissimilar to that required of pharmacists for physicians' prescriptions); (3) exclude from licensing purveyors of medicines for household pets; and (4) control the sale of both prescription and over-the-counter veterinary drug products under the same license. The AFDO's Code's failure to distinguish between prescription and over-the-

counter veterinary drugs does appear to create a third class of drugs in the veterinary field. Such a third class, i.e., drugs not requiring a prescription but not generally available, is not present in the human drug area.

The agency recognizes the high level of extra-label use that is occurring. In fact, in a survey of feedlots, FDA found that 25% of the feedlots routinely stocked drugs which had not been approved for the particular species of animal in the feedlot. Many of these illegal products were prescription drugs. It also is, as far as FDA is concerned, a common practice to see the advertising and selling of illegal animal drugs directly to the livestock producers. FDA attempted to resolve the issue of extra-label use by stating in 1983 that all unapproved uses of new animal drugs in food producing animals, including those drugs used by veterinarians, would be actionable under the Food, Drug and Cosmetic Act. In other words, FDA took the position that a veterinarian, unlike a physician, could not use any drug that he or she chose as the best treatment for the patient (animal). That was one of former CVM Director

Crawford's policies and it met great opposition from the AVMA and the majority of practicing veterinarians. After much discussion and consideration, the agency modified the 1983 position to the present policy that allows veterinarians to use new animal drugs extra-label under certain circumstances, but limits such circumstances to situations where there is a veterinary-client-patient relationship.

With respect to extra-label use of medicated feeds, on November 1, FDA revised its Compliance Policy Guide (PFD CPG-7125.06) to say that a new animal drug may be used in medicated feed only as specifically permitted by the regulations. It was an attempt to stop fairly wide-spread abuses, but, in particular, it was aimed at the use of dimetridazole (DMZ) which is approved for use in turkeys as an aid in the control of blackhead. DMZ evidently is being used extensively by swine farmers against swine dysentery. The Compliance manual change places the agency on record as being against extra-label use of drugs in animal feeds. The extra-label drug use in species for which the drug is not approved is an issue which is difficult

for FDA and one which I will discuss in more detail later in my remarks.

I have not attempted to discuss all the past regulatory events and some might even suggest that I have not chosen the major ones, but I believe that the ones discussed represent significant matters in relationship to FDA's control of veterinary medicine. One item that has not been discussed which I feel should be commented on, is the agency's choice of a Director. After Lester Crawford left FDA to become Don Houston's deputy at USDA, FDA spent time reviewing the situation and made an excellent choice by appointing Dr. Gerald Guest as the Center's Director. Dr. Guest is a regulatory professional of the highest caliber who has spent a number of years at FDA and is extremely well qualified to provide the Center and the agency with the leadership that it so desperately needs at this time. Dr. Frank Young and the Department of Health and Human Services are to be congratulated on their choice.

Let me turn from the actions that are involving the agency day-to-day and move to issues

that the agency must seek to resolve in the coming year. The first of those is tied, in some degree, to the last issue that I talked about, the illegal use of veterinary drug products. The agency has historically allowed injectable veterinary antibiotics both as prescription and over-the-counter veterinary drugs. Many of FDA's decisions were practical ones, in that the agency recognized that the dairy farmers and professional breeders were able to diagnose many conditions and treat their own animals without the intervention of a veterinarian. In fact, some rules as to prescription status for veterinary drugs in the past were made on that basis. The drug would be over-the-counter as to dairy cattle and prescription as to horses. The rationale was that dairymen were dealing with a docile animal, the cow, who they worked with daily, while many of the horsemen were weekend enthusiasts who were not skilled or trained to either diagnose or administer medications to highly spirited animals. Because of the illegal use issue, the agency has raised the question of whether or not all injectable products should be prescription-only. CVM's Advisory Committee, to which this question was addressed,

was able to demonstrate that the drug products in the marketplace were inconsistently labeled. There were products containing prescription legends being sold beside identical drug products available OTC with appropriate OTC labeling. There is also the issue that the Food, Drug and Cosmetic Act, does not contain explicit authorization for veterinary prescription drugs. There is no Durham-Humphrey Amendment, §503, in the veterinary provision §512 of the Act. Section 503 applies only to human drugs. The issue of OTC versus precription use was given to the CVM Advisory Committee to obtain their guidance and also reduce congressional pressure on the agency. The Committee was of little assistance because it could not reach a consensus. In fact, they recommended that the agency stop using the "human drug" prescription labeling statement "Federal law prohibits..." and instead adopt the word "restricted". The Center for Veterinary Medicine, at the October CVM Advisory Committee meeting, rejected the idea of the "restricted use" language and stated that it wished to retain wording modeled on the human drug legend. Therefore, the agency has progressed no further with this matter than when it requested the CVM

Advisory Committee's advice almost a year ago. It is an issue which the agency needs to resolve.

Even though the agency has sought to limit extra-label use, FDA recognizes the extensive extra-label use, particularly of a product such as dimetridazole (DMZ) against swine dysentery. In fact, the agency targeted DMZ for enforcement action, but that decision was severely criticized by the CVM's Advisory Committee, which noted that DMZ was approved for swine dysentery in Canada and much of Europe. In fact, the CVM Advisory Committee went on record as saying that it believed the agency was taking enforcement action as to DMZ not based on a health-safety issue, but based on the fact that Congressman Weiss was exerting political pressure. Whether or not it is political pressure is really moot to Salisbury Laboratories, because on December 17, 1986, FDA published in the Federal Register (51 Fed. Reg. 45245) a Notice of Opportunity for Hearing on a proposal to withdraw the approved NADA for DMZ. FDA cannot ignore the political pressure, as can be seen by the fact that Congressman Weiss, in November of this past year, asked Commissioner Young to review FDA's policy as

to extra-label use. Weiss has taken the position that the current extra-label use policy which allows a veterinarian, under limited circumstances, to use the drug of his or her choice, does not comply fully with FDA's statutory authority. Weiss states that CVM intended extra-label use as a privilege to be restricted to rare circumstances in which the animal's health was in severe jeopardy, but that some in the veterinary profession have misread the agency's statements to be an approval of extra-label use.

The next matter I want to discuss also begins with a comment concerning Congressman Weiss. He exerts the major congressional focus on veterinary products and is making FDA's Center for Veterinary Medicine either miserable or visible, depending on your perspective. Weiss has gone on record requesting documents on whether the low level use of penicillin and tetracycline in animal feed should be banned. He did that in early 1986. Meanwhile, the Commissioner has taken the position that the agency has not reached a decision on its long standing proposal to ban subtherapeutic uses of antibiotics. Weiss is well aware that the

agency, in 1977, proposed a ban on the low level use of penicillin and tetracycline. That proposal was set aside, in part because of congressional pressure counter to Weiss' position. Recently, CVM Director Guest noted that recent CDC studies strengthen the agency's argument to ban the use of low level antibiotics. He thought that, in six to eight months, the issue might be resolved. Recent comments suggest that, while Guest may be convinced, others in FDA and HHS are not prepared to articulate a final decision without additional peer review. It is interesting to note that one of the major arguments against banning the use of low level antibiotics is the economic impact it will have. It has been argued by some that the consumer could see an increase of up to $3 billion in animal food costs due to the loss of improved feed efficiency if the subtherapeutic penicillins and tetracyclines were no longer available. Some argue that the 3 billion dollar number considers all antibiotic uses and that the economic impact caused by removing the low level tetracyclines and penicillins would be significantly less. The economic impact issue can probably be argued forever.

Now I would like to turn to what I would call future issues, matters that the agency must consider but on which they have not, or cannot, reach policy decisions. Both of the issues I am listing are in the area of legislation. The first one I will just mention, because my fellow panelist, Bill Pendergast, will discuss it in detail. During this past congressional session, a Pharmaceutical Export Amendment (S.1848) was passed that permits the export from the United States of new animal drugs that have not yet been approved for marketing in the United States. Bill will explain what that legislation provides and, I think, something about it's impact. I would like to note that, if you are talking about regulatory developments, it will have a major impact in the future.

The other piece of "legislation" is the bill that did not pass when everyone thought it had such an excellent chance to pass. That was the Animal Drug Amendment and Patent Term Restoration Act of 1986 (S.2407). That legislation closely paralleled the human drug version, The Drug Price Competitioon and Patent Term Restoration Act of 1984. Because

it was similar to the human bill, it was thought that there would not be a significant problem with passing the animal drug amendment. The Senate bill was introduced by Orrin Hatch in May 1986 and, in June 1986, Henry Waxman introduced H.R.5069, which basically paralleled the Hatch legislation. The major differences between the two were the transitional periods during which drugs could be approved or the lengths of marketing exclusivity to be allowed. The legislation required measurements showing bioequivalency in the listed animal drug species, it required major species to be used for bioequivalence testing, some labeling requirements and it eliminated the requirement in the Food, Drug, and Cosmetic Act that every veterinary drug approval be published in the Federal Register and then appear in the Code of Federal Regulations.

The legislation ran into trouble in relationship to bioequivalences, an issue that has raised a significant number of problems in interpretation for the Human Drug Patent Term Restoration Act. The "research firms" do not believe that the agency's standards of bioequivalency as to "generic firms" are strict

enough and the generic firms believe that the agency is still requiring too much testing and is being unduly pressured by the research firms. In October, Senator Hatch thought he had a compromise, which was an amendment to the legislation which stated that FDA should consider requiring certain types of testing and that the agency could decide what species tests were appropriate. However, that provision was, while a compromise, not totally amenable to everyone. Senator Metzenbaum was particularly concerned and, it appears, has had second thoughts about how necessary The Drug Price Competition and Patent Term Restoration Act of 1984 legislation really was. He is not about to repeat the same error. Hatch had obtained a final legislative version that was okayed by the Animal Health Insitute, the Generic Pharmaceutical Industry Association and FDA. Even with all that harmony, he was not able to obtain passage of the legislation and the session ended with the Animal Drug Patent Term Restoration bill dying. It is believed by many that that whole issue will be brought up again and that industry and FDA will again seek patent term restoration legislation in the animal drug area. Because Hatch has been

replaced by Senator Kennedy as the head of the Senate Health committee, the future of any legislation, and whether it will be possible to fashion compromises, and, in fact, whether compromises will be necessary, remains an interesting issue that will deserve significant attention from those in the animal drug industry.

I have briefly attempted to give you an overview of the issues before the Center for Veterinary Medicine, some that they have resolved, some that they have to respond to and a reminder of the legislation both actual and proposed, that is the driving force for any regulatory agency.