

SUMMARY MINUTES
FOOD AND DRUG ADMINISTRATION
VETERINARY MEDICINE ADVISORY COMMITTEE

MEETING
May 14, 1997
Holiday Inn, Gaithersburg MD

These summary minutes for the May 14, 1997 meeting of the Veterinary Medicine Advisory Committee were approved on November 14, 1997. We certify that we attended the meeting and that these minutes accurately reflect what transpired.

/signed/
Donald H. Lein, D.V.M. Ph.D
Chairperson,
Veterinary Medicine Advisory Committe
Committee

/signed/
Richard E. Geyer
Executive Secretary
Veterinary Medicine Advisory

VMAC Participants

MEMBERS

Steven Barker, Ph.D.
Sue Hudson-Duran, R.Ph., M.S.
Diane Gerken, D.V.M., Ph.D.
Oscar Fletcher, D.V.M. Ph.D
Ling-Jung (Kelvin) Koong, Ph.D.
Gary Koritz, D.V.M. Ph.D.
Donald Lein, D.V.M. Ph.D
Keith Sterner, D.V.M.
Alice Wolf, D.V.M.

CONSULTANTS

Janis Cleland, D.V.M.
Ruth Francis-Floyd, D.V.M.
Douglas T. Kemp, Pharm.D.
Vernon C. Langston, Ph.D.
William R. Ravis, Ph.D.

Questions for the Committee

1. How should the term "clinical ineffectiveness" be defined for purposes of the Animal Medicinal Drug Use Clarification Act?
2. How should a veterinarian go about determining whether a drug is clinically ineffective for a labeled indication? What steps should he or she take in making that determination?

Dr. Steven Sundlof, Director of the Center for Veterinary Medicine

The proposed regulations for the Animal Medicinal Drug Use Clarification Act (AMDUCA) did not include clinical effectiveness as a criterion for allowing veterinarians to use drugs in an extralabel manner. This contrasted with the previous Compliance Policy Guide, which recognized a need for extralabel use when a drug is clinically ineffective. The AMDUCA language does not specifically mention clinical ineffectiveness as a criterion. However, FDA was able, with support from the numerous comments we received, to interpret the Act to allow for extralabel use where a drug is clinically ineffective.

Now we need to define clinical ineffectiveness and describe how a veterinarian would determine that it exists, because the regulation does not do so. There is concern about this in the veterinary profession. We do want to have some assurance that the clinical ineffectiveness determination is made for legitimate reasons, so we need some fairly solid guidelines.

CVM will on occasion approve drugs that we know will not be effective in all cases. Also, drugs may lose effectiveness over time. We require firms to test drugs under field conditions, but they cannot test under all conditions and sometimes the conditions change.

Dr. Linda Tollefson, Director, Office of Surveillance and Compliance, CVM

Dr. Tollefson reviewed major provisions of the AMDUCA regulations. The regulations require that the veterinarian have a basis for determining that the use of an approved new animal drug is clinically ineffective. The provision applies both to food and nonfood animals. The circumstances for ELU based on clinical ineffectiveness are intended to be defined narrowly, to avoid undermining the animal drug approval process or jeopardizing the approved products that are on the market. Relevant issues to consider are:

- o Is actual clinical experience necessary to determine that a drug is clinically ineffective?

o How frequently should a finding of ineffectiveness be considered or reconsidered?

o Should the guidelines be different for different classes of drugs?

o What is the status of the specific intended use? For example, a drug might work for one labeled indication but not for another.

Dr. Steven Vaughn, Director, Division of Therapeutic Drugs for Food Animals, CVM

Dr. Vaughn discussed factors that the Center considers, in the preapproval context, in determining whether a drug is effective. The statutory standard is that there must be "substantial evidence" of effectiveness for approval. Factors include: a reasonable claim or claims; whether the response can be reasonably measured; a dose-response relationship; assumption that there is a repeatable effect; qualification of investigators; form of the drug; and the inferential value of the data. The last factor includes whether the data would apply to the entire population, for the majority of animals, etc. CVM includes restrictions to define the inferential value, e.g. age, class of animals, physiologic class. Data to support effectiveness of a prescription drug will differ from that for an over the counter drug. The class of drug (e.g. anthelmintic, systemically absorbed antimicrobial) will have a bearing on the data requirements, as will the species of animal.

At the time of approval, CVM is fairly confident that the drug is effective for the labeled conditions of use in the majority of clinical situations. Studies are not done to determine clinical ineffectiveness.

Dr. William Keller, Director, Division of Surveillance, CVM

Establishing the active ingredient, dosage form and concentration needed to provide successful treatment seems fundamental to a determination that the available approved product would be clinically ineffective. In the field, however, the busy practitioner selects treatment based on information from a wide variety of sources including local colleagues, textbooks, academia and industry, that identify agents thought to be clinically ineffective or clinically superior. When does clinically superior become of sufficient weight to relegate the clinically inferior product to clinically ineffective status? The usual approach is through a peer-reviewed journal, although drug sponsors may disseminate that information only in response to an unsolicited request. That limitation should have a dampening effect on the amount of extralabel use under the clinical ineffectiveness concept.

Two fundamental concepts underlying the Food, Drug and Cosmetic Act as they related to AMDUCA are the "lack of substantial evidence" provision of the Act and the "clinically ineffective determination" under the AMDUCA regulation. Scientifically, the two lie on the same continuum and ultimately must be rationalized. Although a large number of approved animal drug products have been withdrawn from the market in recent years, virtually none were removed solely on the basis of lack of substantial evidence. Most of those withdrawn were old, and not active in the market. A determination of clinical ineffectiveness under AMDUCA does not necessarily constitute grounds for withdrawal under the substantial evidence provision of the Act. Also, the set of approved clinical indications is not static.

For a number of approved products, there is information in the textbooks or other source indicating that the products are more effective when used at a more frequent or higher dose than on the label.

From a post approval perspective, decisions by veterinarians that approved products are ineffective carry a responsibility to base the decisions on supportable science. This science could range from simple clinical tests such as culture and sensitivity or other clinical pathology results, to published scientific information.

Committee Discussion

- o Dr. Sterner: Expressed concern that a few individuals could contaminate large volumes of food with drug residue through extralabel use.

- o Dr. Fletcher: the continuum between ineffective and effective can be identified by the number of veterinarians finding a drug to be clinically ineffective.

- o Dr. Kemp: FDA is going to react to notoriously bad outcomes (ineffectiveness), and there may be notoriously good outcomes, but in the middle is a gray area that will have to be based on professional judgment by the veterinarian.

- o Ms. Duran and others: Expressed concern that cases of clinical ineffectiveness be reported to FDA or USP.

Public Comments

Dr. Butch Baker, AVMA Drug Advisory Committee, Swine Practitioner (Kentucky)

We have many diseases that no longer respond to drugs labeled for those purposes. We frequently see more pigs that are ill at one time and at one site than all of the research that was done to get the product approved, so the field veterinarian may actually understand the disease and clinical ineffectiveness better than anyone else. Frequently we don't have any prior records to fall back on. It is extremely important for us to have flexibility.

Speakers in specialty group meetings report about their trials, but very little of the information can be found in refereed journals. With regard to situations where there is a potential for drug residue -- many times large numbers of animals are involved and decisions involving treatment must be made quickly. However, information on withdrawal times is readily available from FARAD.

Dr. Gatz Riddell, American Association of Bovine Practitioners (Alabama)

In making clinical ineffectiveness determinations, practitioners need to be able to use their training, experience and possibly laboratory work that they have available. The observations and intuitions of the veterinarians are going to be very important. Information obtained in a meeting, or from published literature or from other sources will be useful. There needs to be flexibility in determining clinical ineffectiveness. There may be valid data in some cases, but in many instances practitioners will not have data on which to base their determinations.

The input of a veterinarian who is familiar with environmental stresses, background of the animals, disease processes, pharmacology, microbiology, and all the animal variables are going to be important in treatment decisions. Supplementing with data compiled by laboratories as to the effectiveness of particular drugs would be helpful.

Dr. Mel Pence, American Association of Bovine Practitioners (Iowa)

There is considerable variation between the management abilities of individual clients, and this has a bearing on clinical effectiveness. Sensitivity patterns of infective organisms varies by region. There are a number of examples of disease conditions for which particular drugs may be clinically ineffective.

Dr. Tom Burkgren, American Association of Swine Practitioners

The situations we deal with in the field are complex. The definition of the term "clinically ineffective" should be left up to the discretion of the primary care veterinarian. Practitioners know clinical ineffectiveness

when they see it. There is variation in effectiveness within a farm in addition to farm to farm; determinations have to be made on a case by case basis.

Dr. Richard Carnevale, Animal Health Institute

Determination of clinical ineffectiveness should be an independent decision by the veterinarian based on personal experience and evaluation of scientific data. A veterinarian should not resort to a drug that is not approved for the indication simply based on anecdotal reports (without scientific support) by others that a drug has not worked for them, or only because a drug is less costly than the approved drug. A decision that a drug is clinically ineffective should be able to withstand a peer review test.

Criteria should be developed to guide the veterinarian and, in some cases, the agency. Because of differences in pharmacologic activity of drugs and the varied disease conditions being treated, the criteria would need to be very general, at least initially. A conscious and supportable decision should be made and documented. One approach could be a decision tree (with a list of questions) that is developed along with the criteria.

The goal of the animal drug industry is to keep extralabel use at a minimum because of an abundant supply of effective, approved drugs. Until that goal is reached, extralabel use should be approached cautiously. The veterinary community can be helpful in providing guidance.

Richard Wood, Food Animal Concerns Trust

It may be possible for a veterinarian to determine that a particular drug is clinically ineffective but, in our view, it is inappropriate to allow the extralabel use of a drug in food animals, particularly where questions of drug residue and resistance are at stake.

Committee Discussion

Dr. Lein suggested that VMAC's recommendation might be referred to AVMA's Council on Biologic and Therapeutic Agents, specifically its Drug Availability Committee, and then also to specialty groups such as the associations of swine and bovine practitioners. There was general agreement with that suggestion.

Ms. Duran suggested that standards might be established for different categories of drugs as a guide to determining whether the drugs are effective.

Dr. Koritz questioned whether a restrictive definition of clinical ineffectiveness is needed in absence of evidence of a general problem with drug residues in food.

Dr. Wolf noted the discussions that recognized that certain drugs seem to be more or less effective for various indications, depending on conditions, regional differences, etc.

Dr. Sundlof stated that CVM did not want to use the clinical ineffectiveness provision of the regulation as an enforcement tool, except as a last resort. The profession should be making the determination, but there should be some basis for making the clinical judgment that a drug is ineffective. CVM would like the profession to define in very general, flexible terms what "clinically ineffective" means, then discuss the definition with CVM to determine whether CVM can endorse it. There was discussion to the effect that it is not just that the drug doesn't work, but that it does so only marginally. So, definition of what is "clinically ineffective" is the first step, and that can be followed by the decision process to get to the definition.

Dr. Wolf pointed out that there may be circumstances in which the drug approved for the indication might be effective given enough time, but the particular presentation of the disease requires use of a drug that acts faster. Dr. Sterner noted that in that kind of case practitioners should use their scientific training, experience and clinical judgment to determine when a product is clinically ineffective. There also should be recognition that there is an extraordinary scope of species, and circumstances which are subjective.

Dr. Fletcher stated that the definition of "clinical ineffectiveness" can be viewed on several levels: (1) case by case use of professional judgment based on education, experience and supporting data (e.g. laboratory data) along with information from other sources: consultation with colleagues, meetings, publications and the like; (2) at the level of the species or specialty, where there is a collective opinion by many practitioners that a product is clinically ineffective.

Dr. Sundlof stated that if the definition is written broadly enough, each of the specialty organizations could develop their own guidelines. In defining what is optimal, there are three different missions related to the patient, client and food safety.

Dr. Sundlof stated that if a drug is blatantly ineffective CVM would take action to remove it from the market. But if it is ineffective in certain circumstances but not in others, CVM might ask for relabeling or take other

steps.

After further discussion, the committee adopted the attached statement.

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