To Use or Not to Use - The Regulatory View Point

Terence Harvey, *D.V.M., Deputy Director*
Bureau of Veterinary Medicine
Food and Drug Administration, Rockville, Maryland 20857

The practice of veterinary medicine is clearly an art guided by, among other things, the principles of biomedical science, analytical reasoning, and informed choices. The primary goal of the training and experience of veterinarians and other health professionals is to instill learned judgement into complex clinical situations. Notice I said *judgement* and not certainty. How many times have you, as practitioners, seen the truly "text book case"? On the contrary, the art in practicing veterinary medicine requires cerebral analysis of many disparate and sometimes conflicting facts - all of which must be reasoned into a practical diagnosis leading to a safe and effective and timely remedy.

The FDA policy on the unapproved uses of drugs in veterinary medicine (and by unapproved I mean not in accord with label directions, e.g. changes in species, disease, dose, schedule, etc.) is that a veterinarian may use any product he can legally obtain. Let's tease this statement apart into the practicalities for and responsibilities of the practitioner.

First, the operating phrase of this policy statement is "what he can legally obtain." The product or agent could be an approved or authorized new drug, a drug that is generally recognized as safe and effective, or a chemical compound that has some recognized non-drug and drug uses such as a laboratory reagent. (Examples: methylene blue, technical grade DMSO). The key to understanding this latter category of product is the way in which the product is labeled. If a chemical reagent is labeled with drug claims, then it would be regulated as a drug, perhaps subject to FDA pre-marketing approval. Labeled solely as a reagent, the product would not require FDA pre-clearance. However, when you try to order chemicals labeled as reagents and these agents also have known drug uses, some supply houses may ask that you obtain FDA clearance before your order is filled.

Secondly, a licensed veterinarian is viewed by FDA as a learned health professional who in the course of his professional practice can write prescriptions for and obtain drugs labeled for use in humans. By my prior statement of FDA policy, such use of a human labeled drug in domestic animals is, of course, an unapproved use. In this instance, the Agency has relied on and continues to rely on the judgement of the veterinarian to use such products to the best advantage of clients, their animals, and the public health.

Third, a veterinarian may become involved in the use of an investigational drug to either generate data in support of a new drug approval or to treat selected cases of a disease on a random animal or herd basis. In this scenario, the veterinarian or drug sponsor must receive authorization from the FDA before the drug may be legally sent to him for clinical use. We frequently issue such "compassionate" authorizations for individual practitioner to deliver otherwise unavailable animal health care to the public. A recent example of making investigational drugs available on a broad scale is the emergency authorization of albendazole use for treating liver flukes. In the Spring of 1980, FDA authorized the investigational use of albendazole, a Smith-Kline/Norden product, in parts of the U.S. where liver fluke disease is endemic. This investigational drug can only be used under the supervision of a licensed veterinarian and it bears a 180 day withdrawal period. Additional record keeping requirements on drug use are placed on the veterinarian's shoulders. A compelling stimulus for this first time broad scale approach for an investigational drug was that no drug is approved in this country for this disease.

Occasionally, FDA is asked about the availability of drugs in other countries and asked if these products may be imported for clinical use in the U.S. The law requires that to legally import a new animal drug substance or product, it must receive prior clearance by FDA. Consequently, if you desire to utilize and import a foreign drug, I encourage you to contact BVM before you make arrangement to bring the product into this country so that border and customs complications are avoided.

As to the use of other types of therapeutic agents, I will remind you that pesticides applied topically for external parasites and biological products are not licensed or approved by FDA. While FDA has some regulatory involvement in these areas, the Environmental Protection Agency (EPA) is responsible for pesticide registration and USDA for animal biologicals licensing which includes vaccines, serums, and bacterins. I would encourage a dialogue between you and these agencies for specific guidance on the use and importation of these products.

I will now update you on the regulatory status of veterinary prescription drugs and recent significant events concerning the availability of these drug products. The Federal Food, Drug and Cosmetic Act does *not* have specific language for veterinary legend drugs. It does provide for prescription drugs for use in humans. Since 1938, FDA has provided for veterinary prescription drugs

by regulation. In 1980 FDA took legal action against IBA in Ohio, for distributing veterinary prescription drugs to the laity. IBA was able to convince a federal judge that since the law did not contain specific language providing for the prescription legend, the prescription animal drug restriction could not be enforced. FDA quickly appealed this initial decision because contrary to the view that such a decision, if allowed to stand, would make prescription drugs available over-the-counter, it would in fact result in the withdrawal of many prescription veterinary drugs from the market -- one basis being that these products would be unsafe unless used under veterinary supervision. An appellate court on December 11, 1980 overturned the initial judge's ruling and essentially affirmed from a judicial standpoint the validity of FDA regulating prescription veterinary drugs by the existing regulation. The IBA case itself was remanded back for trial on the illegal distribution issue. This important ruling will permit us to continue to make prescription veterinary drugs available to the profession.

Another recent unapproved drug issue involves the withdrawal of approval of diethystilbestrol (DES) implants and DES use in feeds effective November 1, 1979. Several veterinarians have encountered FDA personnel who have asked that the DES implants be returned to the manufacturer or destroyed after the use cut-off date. This has resulted in some confusion in the minds of practitioners as to the sanctity of the drug inventory in their hospitals. Let me clarify the issues involved.

I previously said a veterinarian can use any drug he can legally obtain. Many veterinarians and animal producers legally obtained DES implants prior to the banning. However, that legal acquisition of DES implants terminated with the withdrawal of approval and subsequent use cut-off date. Therefore, the product was no longer legally approved nor could it be legally obtained or sold, even to a client. Although FDA's request for recalls by the manufacturers were denied, the product became illegal no matter who possessed it. Veterinarians should have no fear of bureaucracy swooping down upon them to confiscate any product they can legally obtain or retain.

Once a veterinarian decides to use a legally obtained product for an unapproved use utilizing his best professional descretion, certain additional responsibilities are inherited. If the drug is used in a non-food producing animal, the veterinarian assumes the usual civil and professional responsibilities to the client. These would include due and diligent care and justification of the use to the client or perhaps even in a civil court should adversity arise.

If the drug is used in a food producing animal, a very important responsibility in addition to those mentioned for non-food animals is taken on by the practitioner. The animal will eventually enter or contribute to the food supply and the veterinarian must be concerned with the persistence and presence of drug or drug metabolite residues. From a clinical perspective, questions arise such as how long should the drug withdrawal time be? What kinds of residues persist? Are those residues safe? What pharmacological interactions may occur? These questions will, of course, not be answered by reading the product labeling. The practitioner must use other means to provide himself and his client with necessary answers and advice. These means may include colleague consultation, review of scientific literature, and comparison with like drug substances for which there are approvals. But in no case is the veterinarian more assured that the withdrawal time is correct and the residues, if any, are safe than by using a product in accord with label directions.

Furthermore, the veterinarian and the animal owner are both potentially liable for a violation of adulterating the food supply should the residue in the contaminated foods be detected.

Let us now turn to some pharmacologic considerations in selecting a product for unapproved uses in animals. Concerning drug withdrawal times one only has to look at the need to lengthen withdrawal times for injectable oxytetracyclines (10 to 18/22 days) and dihydrostreptomycin (10 to 30 days) in past years. These withdrawal times increased based upon experimental evidence of persistence rather than the often criticized chasing of the vanishing zero with improved sensitivity of analytical tissue residue methodology.

The whole arena and risk of drug reactions and interactions is opened up to veterinarians with empirical use of drug products. In 1969 when I first came to FDA, little was known about reactions and interactions. Few publications in the veterinary literature were occurring on this subject. Since that time there has been a *knowledge explosion* in this area which almost surpasses our professional capability to acquire and comprehend. I will cite a few examples for your reflection: the clinical use of certain organophosphorous anthelmintics in dogs resulting in widespread disablement and death; the increased pentobarbital sleeping time in dogs receiving chloramphenicol; the abortifacient warning on steroid products used in the third trimester of pregnancy and on and on.....To help you digest this information explosion, BVM publishes each year a summary of reported adverse reactions and interactions. If you are not already receiving it a personal copy of this annual publication can be obtained by you by writing to the Bureau of Veterinary Medicine (BVM) in Rockville, Maryland.

One suggestion that has been advanced to solve the problem of having veterinarians turn to unapproved products is to make more approved veterinary products available. This is an admirable objective but one that must be considered in the socio-economic environment in which we live. I believe no one really wants to return to the pre-1962 environment where many ineffective and unsafe products were in the marketplace. Consequently, I envision a continuing requirement for some demonstration of safety and effectiveness prior to drug marketing.

BVM has taken this challenge very seriously and in concert with the AVMA, the Animal Health Institute and

others who are in the process of critically assessing the drug petitioning and evaluation process to improve it. An innovative step taken by BVM this year is the Fast Track system. This strategy permits a sponsor to request and obtain a priority review of drugs that truly add new therapeutic dimensions such as a new chemical agent for therapeusis in treating a disease for which no drug is available. Fast Track status does not mean a relaxation or lessening of scientific standards but does mean a more rapid review by FDA.

Another important facet of drug approvals and availability is the economic practicality of new animal drugs. Many veterinary pharmaceutical manufacturers have over the past 3-5 years become but a small part of multi-national firms and conglomerates. The animal health divisions are now viewed primarily as income and profit centers rather than research and development centers. To give you a better understanding of what this means to you as a practitioner, let me quote some figures presented by Dr. George Scott (SK) at the Animal Drug Session of the Food and Drug Law Institute Meeting in December, 1980. According to Dr. Scott, for a cattle drug administered in feed it requires approximately $11 million to develop the new drug substance from beginning to end; it takes approximately 8½ years from original isolation of the agent to approval; and perhaps most revealing, the annual gross sales volume must be no less than $25 million per year. As you can see the economic hurdles are very rigorous. Consequently, we may be seeing the end of the availability of the traditional service (but non-profitable) type products for the profession. However, I believe that American industry and the FDA can do much to eliminate economic waste in drug development by doing a better job of planning and conduction research so that various wheels are not continually being re-invented; by abandoning the historical approach of large quantities of repetitive but not informative data collection; and by focusing the nation's scientific and regulatory resources on drug products and issues that truly impact favorably on the public health.

Lest you feel my preceding remarks tend to completely discourage the unapproved use of drugs in veterinary practice, I want to re-emphasize my previously articulated counsel to you. The practice of veterinary medicine is truly a mixture of art and science in its finest form. Were it not for innovative and informed entrepreneurship by veterinarians, regulators and industry, this country and veterinary medicine would not have progressed nearly so rapidly. We are all familiar with the demands of clients and our own consciences to relieve suffering and save animals from the ravages of diseases. You need, however, to consider not only that part of the oath you took to faithfully serve your client and his animals but also the impact of your actions on the nation's food supply and the public at large. After all, the most important mantle veterinarians assume in our society, be it in public or private practice, is to safeguard and protect the public health of all animals including man.

This paper was prepared for presentation at the 1981 Western States Veterinary Conference, Las Vegas, Nevada, February 16, 1981. (the meeting was cancelled due to hotel fire)

For Your Library — Textbook of Veterinary Ophthalmology

Kirk N. Gellatt, *V.M.D., Editor. 21 Contributors.*
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Lea & Febiger, Philadelphia, Pa.

In this important new book, the editor has collected and distilled into one reference source the current status of veterinary ophthalmology. It is a comprehensive text of ophthalmic diseases and surgery in domestic and laboratory animals. Each chapter provides in-depth information, supplemented with outstanding illustrations and references for practicing veterinarians, veterinary medical and graduate students, veterinary ophthalmologists and visual scientists. Of particular interest to the visual scientist are the large number of potential biomedical animal models for vision research.

Ophthalmic diseases and surgery are fully discussed in the dog, cat, horse, and food and laboratory animals. Clinical signs, pathogenesis, etiology, gross and microscopic pathology, prognosis and treatment are emphasized for each ophthalmic abnormality. Each chapter is abundantly illustrated and fully referenced. The text is made up of three major sections. The first section on basic sciences and examination covers embryology, anatomy, genetics, physiology, pharmacology and therapeutics, and ophthalmic examination and diagnostic procedures. The second section is devoted to canine ophthalmology and includes chapters on the orbit, eyelids, lacrimal and nasolacrimal systems, nictitating membrane and conjunctiva, cornea, anterior uvea, the glaucomas, lens and posterior segment. Special ophthalmology is discussed in the concluding section, with full discussion of feline, equine, food animal and laboratory animal ophthalmology, neuro-ophthalmology, and ocular manifestations and systemic diseases.