

A PERSPECTIVE FROM ACADEME

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In 1975, a symposium was held in Fort Collins, Colorado to examine the status of pharmacology in the animal health sector and to establish a dialog among scientists in schools of veterinary medicine, in the pharmaceutical industry, and regulatory bodies of government. A section of that symposium was devoted to the subject of drug evaluation in animal patients. I would like to review briefly some of the accomplishments that have been made since that meeting.

At that symposium, Dr. Huber discussed the interface existing between industrial, academic, and regulatory scientists; and suggested several actions that would strengthen the cooperative interaction among the three sectors.¹ He suggested the establishment of a professional organization with a membership of people working in the three sectors. The American College of Veterinary Pharmacology and Therapeutics was organized during the 1976 meeting of the AVMA and was officially founded in 1977 with the following objectives:²

1. To support and promote education and research in comparative pharmacology, clinical veterinary pharmacology, and other aspects of pharmacology of interest to the veterinary profession.
2. To sponsor a periodical journal which will publish reviews, summaries, and original treatises on all aspects of veterinary pharmacology and therapeutics (The Journal of Veterinary Pharmacology and Therapeutics was first published in March 1978, and has continued since that time).
3. To sponsor and conduct workshops, symposia, and other scientific and educational meetings in veterinary pharmacology and therapeutics.
4. To enhance the exchange of educational materials and ideas among veterinary pharmacologists.
5. To organize committees of experts to research and make recommendations to the profession on current problems in veterinary therapeutics.

The present Academy is comprised of Fellows and Associate Fellows from the FDA, industry, academia, and private practice.

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Another action suggested by Huber was to facilitate scientific exchange among the three sectors on problems of mutual interest. Since that time, the Academy had held four biennial symposia and has participated in two colloquia sponsored by the AVMA. Additionally, the present symposium is the fourth of a series of programs designed specifically to facilitate discussion among participants from the three sectors.³⁻⁵

A third suggestion made at that meeting was to establish a research center for minor species supported by government, industry, and academia. This attained fruition last year with leadership provided by CVM/FDA. The Consortium for Research on Minor Use Animal Drugs was established as a cooperative agreement between CVM and four colleges of veterinary medicine. This consortium had already provided a framework for active collaboration of scientists from the three sectors. The primary objective of this work is to develop comparative pharmacologic data to facilitate the transfer of information derived from studies conducted in major food-producing animals to the minor species. It is to be hoped that this matrix-type of organization of manpower might serve as a model for tackling complex problems facing our profession in the future.

We have accomplished much in the decade following that symposium. Most importantly, an active forum has been established which fosters the rational discussion of scientific issues surrounding the development of new drugs for the benefit of our animal population.

The relative roles of the three sectors in the development and clinical assessment of new drugs have changed considerably over the past 80 years. During the first 50 years of this century, most new drugs were discovered and evaluated within the academic environment. Familiar examples of drugs discovered and investigated by academic scientists during this period include insulin, dicoumarol, heparin, penicillin, epinephrine, liver extract, and many of the vitamins. It may be noted that nearly all of these compounds were derived from natural products and did not require the teams of research scientists that exist today in the pharmaceutical industry. Up until the early 1950's there existed little control over new drug development by federal agencies, but there were many abuses to the public welfare noted during this period. Uncontrolled entrepreneurial activity produced the so-called "toadstool millionaires" at the expense of the citizenry. With the restrictive legislation enacted by Congress in 1951, 1958, 1962, and 1972; the complexity of the regulatory environment increased dramatically. This, coupled with the fact that routes for new drug discovery shifted to fermentive and synthetic processes necessitated the shift away from the individual academic investigator to teams of highly trained people who could only be supported within highly-capitalized industries.

If the general welfare of the nation and its animal population is to be preserved, there needs to be a balance maintained among the three sectors. We must examine in a critical, objective manner, the impact of changes that have occurred in each sector on the health of our animal population

and on our profession. I am not at all convinced that the tremendous increase in regulations, guidelines, and legislation which has occurred over the past 35 years has improved the safety and efficacy of drugs sufficiently to justify the enormous expense which has been incurred, nor do I believe that it has protected the public health. I have to believe that one of the most misguided legislative acts was the stipulation of the Durham-Humphrey Amendment that antibiotic drugs for animal use be made available for OTC use, as adequate instructions cannot be written for such use by the laity. We have seen the incidence of penicillin allergy in the human population increase almost ten-fold over the past 25 years, and many pathogens have become multiply-resistant to a number of antimicrobial drugs. Changes have taken place in the pharmaceutical industry which have made it less responsive to the needs of the veterinary profession. Formerly, we were served by a number of small companies which were highly responsive to the needs of the profession and were competitive with each other. The majority of these have merged with several large multinational corporations which are highly diversified. This process was probably accelerated by the regulatory climate. Lastly, the academic environment has changed from a value-oriented to a fiscally-driven organization at most institutions. This has produced excesses and violations of trust which were nearly unheard of 20 years ago. I hope that we can explore some of these issues during the course of this symposium.

To return to the subject of this symposium: one of our outstanding industrial pharmacologists--Dr. Karl Beyer--stated:⁶ "Today, the clinical assessment of a new drug is the most expensive, most time consuming, most exciting, most frustrating, most complex, and most regulated aspect of new drug development--by far." It is appropriate that we are devoting this two-day symposium to this topic. I would like to review the steps involved in the development of a new drug⁷ (Figure 1), and discuss some of the reasons why I believe that we need to redefine the meaning of clinical evaluation as applied to new animal drugs.

Following discovery of a new chemical entity, the compound is subjected to pharmacologic screening and toxicologic studies in laboratory animals and *in vitro* systems. If the substance shows promise as a potential product, an NDA is prepared and filed with the FDA. For a drug intended for use in people, phased clinical studies are conducted. During the phase I and phase II clinical pharmacologic studies; human toxicity, dose-range, pharmacokinetic, metabolic, and initial efficacy studies are conducted in healthy volunteers and limited numbers of patients. These investigations are the most rigorous aspect of the process in terms of establishing relative safety and efficacy of the drug. These studies are followed by phase III clinical trials by a number of investigators in a large population of patients. The NDA is then prepared and filed with the FDA. After approval by the NDA, the drug is marketed and is subject to continued surveillance in phase IV. This provides the ultimate definition of relative safety and efficacy of the product.

There is a need to examine language used to describe certain aspects of the study of new drugs. The term "animal studies" which is frequently encountered in the pharmacologic literature usually refers to preclinical studies of drugs being developed for human use. The term does not have a precise meaning when applied to the development of drugs for treatment of animal patients. This has assumed a connotation that animal studies are not as good or as relevant as the clinical studies in people, and are not deserving of as careful a consideration.

An important feature of clinical trials of animal drugs by veterinarians is that of ethical constraints when dealing with target animal species for which a new drug is being developed. Many of our problems in this area devolve from the failure to recognize that these subjects of our investigation are the same animals that we are duty-bound to care for as veterinarians. Our approaches must be modified in such a way that we respect the fact that the drug is being developed for safe and effective use in the target species, rather than that the animal is simply being exploited as a test object to meet some regulatory requirement. The ethical implications are entirely different from those of preclinical animal studies required for clearance of a drug for human use. There has probably been more wastage of animal life and creation of suffering to meet some regulatory requirement than would be necessary to establish relative safety and efficacy of a new drug. The clinical investigator must be an advocate for his or her patient.

Times have changed rapidly. Many of our traditional bearings are being lost, we seem to be wavering at the brink of social and economic chaos in the world, and we are having to cope with an increasingly coercive federal bureaucracy and special interest groups. The judicial system seems to be out of control, which adds greatly to the problems we are facing. One of the significant social movements of the 1980's has been the increased concern for animal welfare. The animal right's groups have become increasingly vocal, militant, and effective. Various explanations have been given for the development of this phenomenon, but it is part of the reality with which we must deal in the 1980's. The veterinary medical profession should play a leadership role in this movement rather than merely reacting to the increasing militancy of some of the groups of laypersons and to the animal welfare bills which have been introduced in the Congress of the United States, e.g., Walgren, Dole, Brown, Torricelli, Broyhill-Madigan, Hatch-Kennedy. As a discipline of veterinary medicine, these events provide an unprecedented opportunity for veterinary pharmacologists in academia, industry, and FDA to participate in the development of more rational approaches to drug therapy in animal patients and more humane and less wasteful methods for the evaluation of safety and efficacy of new drugs. The greatest strength of veterinary medicine lies within its generality. In an age⁸ characterized by narrow specialization, high technology, decentralization, an exponential increase in quantity of information, and fragmentation of the "big picture", there is a vital need for generalists who have been trained to synthesize information derived from a wide variety of sources, for the improvement of health and health-

care of animals.⁹ The veterinary pharmacologist and clinical pharmacologist should endeavor to meet this societal need.

For the past 15 years, administrators of veterinary colleges have yielded to political pressure for expansion of the size of veterinary classes and for the establishment of new colleges. This has produced a glut of veterinarians with a concomitant decline in opportunities for new graduates in the private-practice sector. Accordingly, we need to expand the post-graduate training opportunities for veterinarians. This may take the form of traditional graduate programs in comparative pharmacology leading to the M.S. and Ph.D. degrees to prepare the student for a research career. However, the number of years already spent in formal education, and the burden of financial debt incurred¹⁰ would seem to militate against the general attractiveness of this option to many veterinarians. Innovative approaches should be sought for intensively educating veterinarians in pharmacology and toxicology so as to preserve and expand their clinical expertise while, at the same time, providing them with a depth of scientific understanding. Such individuals would be of value in academic, industrial, and regulatory positions. A corollary would be the development of intensive, short-term, post-graduate training programs at veterinary colleges for veterinarians who plan on making mid-career shifts or who already are employed by the pharmaceutical industry or federal government. Perhaps these programs could originate from a network or a consortium of several veterinary colleges to most efficiently utilize the limited manpower which is available for such training.

An important activity of academic veterinary pharmacologists is research. The fruits of our laboratory or clinical investigations provide the basis for future advancement of our discipline. We have made good progress, but have become too narrow in our perspective. Virtually our entire collective effort has been focused on problems concerning the disposition of drugs in the various domesticated animals. We now should seek to provide a broader base for understanding the pharmacologic effects of drugs in these same species. We must investigate the pharmacodynamics of drugs employed in veterinary therapeutics and elucidate the effects of various disease processes on both drug-disposition and drug-action. There is a need to investigate the drug concentration-pharmacologic response relationship for a number of drugs to make our pharmacokinetic knowledge more applicable to the solution of problems inherent in drug therapy. Finally, newer research techniques and knowledge of basic science developed in basic pharmacology departments of medical and pharmacy schools should be applied by veterinary pharmacologists, to the diverse problems encountered in veterinary therapeutics. In doing so, we can maintain the generality of our understanding, fully utilize our veterinary medical training, improve the quality of veterinary care, and develop more sophisticated methods for evaluation of safety and efficacy of drugs.

In the arena of professional service, veterinary pharmacologists serve in a pivotal role which has become more important as a result of rapid changes in our society. Regulatory bodies have become increasingly

coercive and the American populace has become more inclined toward litigation in recent years. In order to minimize the damage done to the profession as a result of these trends, we must maintain the dialog which has been established among academia, industry, and regulatory agencies. Continued active communication is essential if we are to mitigate the negative effects of sometimes overzealous regulation of the pharmaceutical industry and veterinary practitioners. At the same time, we academicians should extend greater efforts toward the continuing education of veterinarians. Many cases of malpractice actions against veterinarians have been the result of inappropriate use of drugs. Increased knowledge of pharmacology will serve as a basis for better therapeutic decisions in the course of veterinary practice. Indeed, the Center for Veterinary Medicine of the FDA has established the doctor-patient-client relationship as the necessary basis for the extra-label use of drugs in veterinary medical practice. This is as it should be, as the person in the best position to assure safe and effective use of a drug is the attending veterinarian, who is in a position to make a responsible therapeutic decision relative to a particular case. This person must have the necessary information to be able to make appropriate risk/benefit assessments regarding his or her choice of therapy. Efforts by veterinary pharmacologists to provide current concepts and knowledge through available vehicles for continuing education will assist the practitioner in his task.

How might we reconcile these considerations with the need to establish relative safety and efficacy of a new drug entity before it is approved for marketing? I believe that we can begin by defining the term "clinical trials". For animal drugs, all studies conducted in the target species of intended use should be included within the definition. Thus, the preliminary studies of acute and chronic toxicity, metabolism, pharmacodynamics, etc., performed in laboratory animals, chemical studies, development of analytical methods, etc., would be termed preclinical studies and would provide information essential to the planning of the clinical investigations. The clinical trials themselves would be conducted in four phases as for human drugs. Phase I would be concerned with defining routes of elimination, pharmacokinetic behavior, dosage range, minimal toxic doses, and other such essential information in healthy animals of the target species. Phase II would utilize this information to design trials for evaluation of safety and efficacy in a limited number of animals with the disease for which a claim is sought, or in animals with an experimentally-induced disease similar to that seen clinically. Phase III trials would be conducted in an appreciable number of patients in a variety of settings to confirm the generality of the information acquired in Phases I and II. Following approval of the NADA, Phase IV would involve the long-term surveillance of the product during widespread clinical usage in the field. This is the ultimate test of safety and efficacy, as adverse drug reactions which have a low incidence may require years of use to become apparent and to be placed within a useful clinical perspective.

Phased clinical trials would permit us to acquire information germane to safety and efficacy considerations without wasteful sacrifice of life and the imposition of needless suffering. It would allow veterinarians participating in the drug approval process to utilize their clinical training and expertise in a manner which would be ethically and aesthetically acceptable to the profession and others who are concerned with the welfare of animals.

The following stipulations are made in the Code of Federal Regulations-- "substantial evidence, consisting of adequate and well-controlled investigations, including field investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the new animal drug will have the effect it purports, or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling" and that the NADA "contains full reports of adequate tests by all methods reasonably applicable to show whether or not the new animal drug is safe and effective for use as suggested in the proposed labeling". These requirements could be met more economically, expeditiously, and with greater scientific rigor by emphasizing the importance of well-controlled Phase I and Phase II studies. The Phase III field trials would confirm the generality of these results and would reflect the conditions of therapeutic use of the product.

In summary, there currently exists an open discourse among veterinarians from industry, CVM, academia, and private practice. As a result, discernible progress is being made toward the resolution of once seemingly insoluble problems. We need to continue to examine the changing roles of each of the sectors concerned with new drug development and to adjust our modus operandi to the realities of the 1980's and beyond. An important aspect of this effort should be a redefinition of what is meant by the clinical evaluation of drugs intended for use in target animals.

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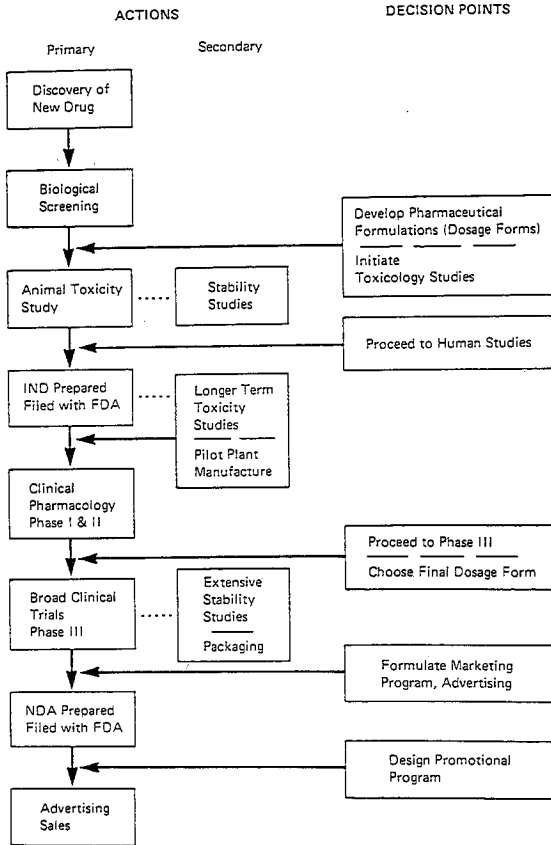


Figure 1. Steps in the development of a new drug for human use. From Reference 7.