

American Academy of Veterinary Pharmacology and Therapeutics

Task Force Report and Recommendations for the
Symposium on Clinical Trials

held at Alexandria, Virginia, April, 1985

This is the third task force report from the AAVPT symposia organized for the purpose of studying the developmental and approval process of new drugs. The first task force report is given on pages 138-143 of the book entitled Topics in Veterinary Pharmacology (1982) and the second task force report is included in the book Determination of Doses of Veterinary Pharmaceuticals (1984), pages 254-258.

As in the previous reports, this report was assembled at the conclusion of the symposium on Clinical Trials and contains the information that was derived from the papers presented, from the open discussions from the floor of the meeting, and from the deliberations of the special task forces. In addition, the conclusion from a special panel of veterinary practitioners was given thorough study by the Task Forces.

A. Statement of Concern

Although these special symposia have greatly increased communication between FDA-CVM personnel, industry, academicians and practitioners, a need was expressed for some method of continuing dialogue among these groups involved in the development of pharmaceuticals.

●● Special Recommendations

Formation of a standing advisory committee to the FDA-CVM from the ranks of the AAVPT members. This concept was later approved unanimously by the council of the AAVPT at its annual business meeting (1985) held in association with the AVMA meeting.

B. Statement of Concern

The FDA-CVM currently requires clinical trials involving a minimum 20 treated cases which have a system or tissue infected by the same organism in order to develop a label claim for a new antimicrobial product. This requirement prolongs, unnecessarily, the time needed to assemble sufficient numbers of patients, without adding to the degree of certainty that the product is effective for its intended use. The need for control patients doubles number of clinical cases required. This limitation, imposed for each organism to be claimed, requires the sponsor and the investigators to study hundreds of patients before they are able to fulfill the requirement. This causes an inordinate expenditure of funds and manpower time which contribute little or nothing to the development of the label claim. Furthermore, the claim for efficacy against a single organism may greatly restrict the utility of the product in practice because of

the possible legal implications of the restricted labeling to the veterinarian.

●● Special Recommendations

1. The label claims for the drug should be supported by pharmacokinetic data obtained from animals of the target species for which the label claim is being made together with in vitro bacterial susceptibility data for applicable pathogens.
2. The clinical trials could then be conducted in patients having infections of the system caused by any bacterial pathogen which has been shown to be susceptible to the drug being studied.
3. The label claim would then be for treatment of a system (e.g. bacterial cystitis, pneumonia, metritis, mastitis, gastroenteritis, nephritis, etc.) infected by organisms susceptible to the product.

C. Statement of Concern

A need was identified for the development of a consortium for the purpose of conducting in-depth clinical trials.

●● Special Recommendations

Establish a cooperative agreement (consortium) between FDA-CVM, industry and academic clinical pharmacologist for the purpose of conducting in-depth clinical trials. This could have many perceived benefits including: a) maintaining and updating pharmacokinetic data on commonly used drugs in species of concern with diseases of concern, b) allowing application of sensitive population pharmacokinetic techniques to be applied to veterinary species, c) documenting in vitro susceptibilities (MICs) and clinical responses to specific antimicrobial drugs on a regional and national basis, d) integrating pharmacokinetic, microbiologic and pathologic data on clinical cases of animal diseases, and e) providing a training opportunity for residents and graduate students in clinical pharmacology.

We recommend that FDA-CVM host a Feasibility Study Group of interested individuals.

D. Statement of Concern

The definition of what is entailed in the term "clinical studies" has been interpreted by CVM personnel in too limited a manner in certain situations in the past. That is, basic pharmacological studies in normal and diseased target animals, as well as studies in both induced and diseased states may be classified as clinical studies.

●● Special Recommendations

The Task Force recommends the following as general definitions for (1) Nonclinical Laboratory Studies, (2) Clinical Investigations, and (3) Clinical Field Investigations:

1. Nonclinical Laboratory Study means any in vivo or in vitro experiment in which a test article is studied prospectively in a test system under laboratory conditions to determine its safety. Examples are: toxicology studies, tissue residue studies, residue metabolism studies. The term does not include clinical investigations or clinical field investigations. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.
2. Clinical Investigation is a study usually conducted in the target species to determine basic physiologic/pharmacologic effects or the potential field effectiveness of a new animal drug in normal or diseased animals. Examples are: drug disposition studies, pharmacokinetic evaluations, induced disease studies, bioequivalency/bioavailability studies, etc.
3. Clinical Field Investigation is a study conducted on the new animal drug in the target species under the proposed actual conditions of use to confirm safety and/or effectiveness.

Statement of Concern

Protocols for clinical trials must be designed so as to be valid, flexible, interpretable, and capable of being complied with under different clinical situations.

●● Special Recommendations

The Task Force recommends that the following components of the protocols used for clinical trials should enjoy particular attention:

1. Protocol design. The experimental design of each protocol to be used for a clinical trial should be such that the specific objectives of the study should be attainable under reasonable circumstances. Whenever possible the design for the trial should be developed well in advance, taking several key elements into consideration. These include statistical validity and analysis, the use of blinding techniques for the investigators, the necessity of repeated studies in different geographic locations and the selection of appropriate control animals or cases. The importance of

control studies cannot be overemphasized. The choices include no controls, historical controls, positive controls or the administration of a placebo. The type of drug on trial, the disease condition and the animal species will determine in large measure which type of control study that should be conducted. The statistician's role in this context is extremely important. The need for repetitive studies in different geographical areas will depend upon the particular pharmacological agent method of administration (e.g. feed vs parenteral) and the claims being sought. In most cases such trials will either be absolutely necessary or at least highly desirable.

2. Flexibility of design. It is clear that the design of a clinical trial will depend to a significant degree on the class of drug being studied, the claims that are being sought and the type of animal that is the target species. Because there will almost inevitably be so many confounding factors associated with the clinical investigation of a new drug intended for veterinary use, it is recommended that, although guidelines would be helpful, there should always be a degree of flexibility permitted in the design of clinical trials. Specific stringent regulations governing clinical trials for each class of drug are not necessary or warranted under the circumstances.
3. Compliance. A critical component of any successfully conducted clinical trial is the absolute requirement to follow the predetermined protocol without unnecessarily jeopardizing the life or ultimate well being of a patient. The careful and comprehensive training of investigators and the scrupulous monitoring of clinical trials that are underway, represent the only satisfactory way to ensure acceptable compliance. The incorporation of concurrent therapeutic regimens into a clinical trial, although often highly undesirable, may be required or even essential under some conditions. The compliance of the investigator to remain within the limits of this additional or supportive therapy is equally important. Moral, legal and ethical considerations may apply and if concurrent therapy is employed, the same approach must be used for the treatment as well as the control group.
4. Evaluation of results. In most instances the design and development of a protocol should permit the satisfactory statistical analysis of the results obtained by using standard tests of the predetermined hypotheses. However, it must be emphasized that when conducting drug trials, clinical evaluations sometimes do not lend themselves to quantitative analysis. Thus allowance should be made for reporting qualitative medical responses when deemed appropriate.

F. Statement of Concern

There was a concern expressed by both industry and FDA-CVM regarding the heterogeneous manner in which NADA's are submitted. This lack of uniformity results in additional time required by the reviewers to locate necessary information for approval.

•• Special Recommendations

A summary prototype should be developed which describes typical contents of statistical summaries for each study within the NADA. In addition, an outline for an overall summary should be constructed.

G. Statement of Concern

The fact that certain drugs (for example, aminoglycosides) have extremely long withdrawal times due to their selective binding in specific tissues limits their clinical value in food-producing animals.

•• Special Recommendations

Adoption of a policy of selective condemnation of organs of food-producing animals would allow marketing of livestock carcasses containing persistent drug residues confined to a single organ. For example, an animal which has been treated with gentamicin or another aminoglycoside could be slaughtered after depletion of the drug from muscle has occurred and the kidneys alone would be condemned. We recommend that FDA support adoption of this policy in discussions with USDA.

H. Statement of Concern

Because of its great importance and since the problem still exists, the following concern is repeated from our second task force report of 1984.

"1. Despite the diligent and well-meaning efforts of the drug industry and the Bureau of Veterinary Medicine, the dosage recommendations on the labels of veterinary prescription drug products, as well as their package inserts, have become excessively restrictive and consequently are interfering with the practice of clinical medicine.

2. Associated concerns include such factors as frequency of dose; lack of latitude to select appropriate dose ranges; dosage for specific clinical cases and for selected veterinary drugs; doses that are considered on the low side of recognized effective dose levels or ineffective dose levels; and inadequate information relating to the characteristics of the target organisms and their sensitivity profiles.

The issue of the extra-label use of drugs poses a considerable concern and potential hardship to the practicing veterinarian and the veterinary profession. Recently the Agency has acknowledged that extra-label use is necessary in the course of veterinary practice.

Recognizing the complexities of this issue, the AAVPT suggests several special recommendations for consideration:

●● Special Recommendations

- a. Sponsors of new veterinary prescription drugs should be encouraged/allowed, but not required, to include the following clinical pharmacology data, relating to drug dosage, on product labels, and/or package inserts:
 - 1'. A therapeutic dose range, as well as a recommended dose level.
 - 2'. A therapeutic window which encompasses the factors of target animal safety (drug toxicity) and human food safety (drug residues in food animals) as its upper limits and minimum effective doses at its lower limits.
 - 3'. Pharmacokinetic parameters important for dosage adjustment such as biological half-life, volumes of distribution, percent bioavailability for relevant drugs, and drug clearance. This would permit the tailoring of doses to meet the needs of critical clinical cases.
 - 4'. Major target organisms, along with their susceptibility spectra including relevant drug dose/serum concentration relationships. Use of charts or graphs to display this information should be considered. Minor but important etiological agents should be encompassed in the general term of "organisms susceptible to . . ." in the case of antibiotic drugs.
- b. Drug labels and package inserts, with full disclosure, should be developed so as to assist the practitioner in making clinical judgments, rather than hinder his/her judgment."

I. Statement of Concern

The NADA review process is still perceived to be slow and cumbersome in many cases as was first recognized in the 1982 task force report and reemphasized in the 1984 report.

●● Special Recommendations

" Problem--NADA review process is perceived to be slow and cumbersome.

Solution--Recommend that the Bureau of Veterinary Medicine consider implementing a program of segmental review (phasing) of data submission to support an NADA with specific decision points established as milestones. This program would have several characteristics:

1. Encourage INAD protocol development and review.
2. Protocols should be specific and should carry optional approvals.
3. Review and evaluation would occur in specific phases, eg:
 - a. Efficacy and safety data (dose determination and safety studies: acute; reproductive; 1X, 3X, 5X and for 3X duration of recommended dosing regimen), including target species, human safety and assay validation would be completed by sponsor and submitted early in the process for review and approval. (Potential time saving: 6-18 months.)
 - b. Clinical efficacy study: while safety data are under review, sponsor would continue to develop the necessary clinical efficacy data. Deficiencies in safety data can be communicated during the process.
 - c. Labeling submitted for review, refinements and modifications. (Potential time savings: 12-24 months.)
 - d. After approval of safety and effectiveness data by the Center for Veterinary Medicine, the sponsor could proceed to market the drug while the notice of approval was being published in the Federal Register. (Potential time savings: 2-15 months.)
4. Protocols would need to be definitive, with appropriate expert opinions incorporated early, and the sponsor would need to complete the data in a given segment prior to submission for review. "Dribbling" in data after a segment was completed would defeat the program."

The preceding Task Force Report (190-196) was prepared by the following committee:

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