

American Academy of  
Veterinary Pharmacology and Therapeutics

TASK FORCE REPORT AND RECOMMENDATIONS  
FOR THE SYMPOSIUM ON DOSE DETERMINATION WITH ANIMAL DRUGS

This title encompassed the essence of this Symposium which was primarily focused upon *antibiotic and prescription veterinary drugs*. In accordance with the precedent established at the Third Symposium on Topics in Pharmacology, co-sponsored by The American Academy of Veterinary Pharmacology and Therapeutics, a number of issues concerning the profession and the practice of veterinary medicine have been identified. It is from the papers presented, the ensuing discussions, and the task force deliberations, that the following statements and recommendations are embodied.

A. Statement of Concern: 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*.

Associated concerns include such factors as frequency of dose; lack of latitude to select appropriate dose ranges; lack of desirable pharmacokinetic parameters which allow dosage determination for specific clinical cases and for selected veterinary drugs; dosages 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 specific recommendations for consideration:

\*\* Specific Recommendations:

1. 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:
  - (a) A therapeutic dose range, as well as a recommended dose level.
  - (b) 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.
  - (c) Pharmacokinetic parameters important for dosage adjustment such as biological half life, volumes of distribution, percent bio-availability for relevant drugs, and drug clearance. This would permit the tailoring of doses to meet the needs of critical clinical cases.
  - (d) 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.
2. 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.

B. Statement of Concern: The Food, Drug and Cosmetic Act makes reference to the need for "*substantial evidence of efficacy*" without imposing any specific criteria or procedures on methodology or scientific judgment. This general area remains a source of intense discussion and sometimes disagreement between the regulated industries and regulatory agencies. While this area was addressed in a previous symposium, it was determined that this topic should be readdressed and defined further.

\*\* Specific Recommendations:

1. "Substantial evidence of efficacy" for a new drug may/should be obtained from a variety of sources:
  - (a) Historical and previous use data, regardless of country or species in which the drug has been used.
  - (b) Its basic pharmacological activity. *In vitro/in vivo* studies.
  - (c) Efficacy studies done in controlled clinical or target species models, where available.
  - (d) Clinical trials.
2. It should be obvious that value weighting for any or all of these types of studies must remain in the domain of clinical and scientific judgment and not legal judgment. In any given case, any *one or all* types of studies may have to provide the bulk of evidence for the efficacy of the drug. Usually a "blend" or "mix" of studies will be required. To *insist that all types* of these studies are required for *every* drug is inappropriate and wasteful.
3. Clinical trials, while perhaps the most imprecise of all, contain valuable data in terms of the actual use of the drug.
4. Clinical trials on client animals should, from an ethical and moral basis, be conducted whenever possible with positive controls rather than negative controls.

C. Statement of Concern: There was much discussion regarding methods and means of studying and defining differences between normal and diseased animals, species specificity and cross-referencing, extra-label use of drugs, human food safety, drug metabolism, and animal drug safety. While the discipline of pharmacokinetics represents a powerful tool to address these issues, it should be recognized that additional and continuing research needs to be done in this area.

\*\* Specific Recommendations:

1. The regulatory agencies, academia, and the drug

industry should focus more support on research designed to address these important issues, with particular emphasis on the *development of research and interpretation techniques* which are repeatable, practical, and have a significant predictive value.

D. Statement of Concern: The Proceedings of the 1982 Symposium (pages 138-142) make reference to a number of issues for which there is still considerable interest and concern. These issues are:

1. The *unnecessary use of animal resources*.
2. Implementation of a *segmental review process* and perhaps a consideration for some sort of phase review process for new animal drugs.
3. *The use of guidelines for the purpose of general direction and guidance rather than regulation or legal requirements.*

\*\* Specific Recommendations:

1. The Academy remains in a posture of support for these recommendations and suggests that the regulatory agency maintain them on an active agenda for further discussion and action.

We, as members of the American Academy of Veterinary Pharmacology and Therapeutics Scientific Task Force, agree with the contents of the report and endorse it with our signatures. No official support or endorsement by any academic institution, industrial company, or federal agency is intended or should be inferred.

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