

DR. ARONSON: Our next two speakers will be offering comments on the clinical trials. The first of these speakers is Dr. Donald Gable. He is a graduate of The Ohio State University, having received his D.V.M. degree in 1960. His current position is that of Director of the Division of Therapeutic Drugs for Food Animals at the Food and Drug Administration. With pleasure, I introduce Dr. Gable...

## COMMENTS ON DOSE-RESPONSE AND ANIMAL EFFICACY STUDIES

Donald A. Gable, D.V.M.

To establish the effectiveness of an animal drug product, it is axiomatic that it is necessary to quantify the relationship between the administration of the drug and the biological responses that it produces in the animal. The magnitude of effects produced by an antibiotic is, in general, determined by the amount of the antibiotic administered, the toxicity to the animals evaluated, and its action on the disease, i.e., host-parasite relationship. This relationship can be established in a dose-titration, i.e., dose-response, study. Further, the biological responses to the antibiotic are graded; the responses will continuously increase with dosages up to a maximum level. The dose-response study quantifies the magnitude of the biological responses in a limited number of test animals, at a set number and level of doses, and in a specific experiment.

The Bureau's requirements for the dose-response studies include the following: (a) a minimum of three non-zero dose levels, (b) levels properly spaced so as to define the optimum dose, and (c) for therapeutic uses of antibiotic drugs, that the selected doses be administered on the basis of unit(s) of drug per unit of body weight. If the antibiotic is to be administered after clinical signs are shown in the animals, i.e., treatment of disease, dose-response studies should indicate that the antibiotic is effective when clinical signs are present. For control of disease, the antibiotic is administered to the herd or flock at the time of diagnosis or when a disease outbreak is likely, e.g., for control of bovine respiratory disease complex, the antibiotic is administered as cattle enter the feedlot. Subsequently, the optimum dose must be tested in controlled clinical field studies.

From the data collected in the limited population of test animals in the dose-response study, the conclusion is reached that the tentative optimum dose established in the dose-response study represents the relationship between the dose of the antibiotic and the response in all members of an animal species. Obviously, it is unlikely that such limited data precisely determines the wide variability in responses for all animals in the species. That is, the optimum dose established in a dose-titration study may be less than the optimum dose for all conditions of field use of the antibiotic. However, by proper consideration of the major components (test animal, disease agents, and the environment), the dose-response study remains a very practical and useful requirement for the preclearance of antibiotics for animal use.

For dose-response data to be reliable, certain deficiencies must be avoided. These include the following:

1. Population not representative of animals' environment and/or disease.
2. Nonrepresentative test microorganisms, e.g., atypical serotype, highly sensitive strain or isolate.
3. Testing too few animals to draw valid conclusions.
4. Variables other than the parameters being measured are not kept to a minimum.
5. Failure to adequately investigate the dose in pre-clinical studies so that the dose-response study fails to delineate an optimum dose.
6. Using method of administration not proposed by labeling: drug formulation not representative of the product to be marketed.
7. Multiple categories of subjective parameters not permitting consistent reporting of observations by investigators.
8. Investigators not qualified and/or dedicated to the conduct of the study: support personnel not diligent in caring for animals or reporting experimental errors.

The reliability of the current efficacy requirements for antibiotics could be improved by including, prior to marketing, one or more of the options listed below:

1. Conduct multiple dose-response studies in different geographic locations, e.g., different management practices.
2. Conduct dose-response studies against severe natural outbreaks of the disease.
3. Conduct comprehensive in vitro and in vivo sensitivity testing to determine minimum inhibitory concentration for causative microorganisms in natural outbreaks of the disease. This could include isolates from animals in all efficacy studies.
4. Determine the half-life of the antibiotic in the target animal species and utilize the half-life of the antibiotic in establishing the dosage regimen.
5. Investigate the differences in pharmacokinetic parameters, if any, between healthy and sick animals.

6. Perform resistance profiles (both chromosomal and extrachromosomal) on isolates from animals used in efficacy studies.
7. Investigate the effects of the antibiotic on the normal flora of the animal species: document the inherent resistance of the animal species to exogenous microorganisms and to overgrowth of endogenous microorganisms.
8. Conduct a pharmacokinetic analysis of all phases of physiological drug disposition associated with single and multiple dosing of the antibiotic in the specific animal species.

In conclusion, we acknowledged that current efficacy data requirements for an antibiotic in animals do not fully explore its pharmacokinetic and pharmacodynamic characteristics. Nevertheless, current data requirements are reasonable and adequate to document efficacy. However, alternative options which are reasonable and sound will always be considered.