

## SECTION II

### PHARMACOLOGICAL BASIS OF DOSE DETERMINATION OF ANTIMICROBIAL DRUGS

#### Chairpersons

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DR. PAUL: The chairperson for the second half of Section II will be Dr. Rich Carnevale who is the Deputy Associate Director for Scientific Evaluation at the Bureau of Veterinary Medicine. Leading off Section II as chairperson will be Dr. Bill Miner who quite recently joined the Continental Grain Company.

DR. MINER: I'll introduce this section only by saying that those of us who have struggled with the new drug development process, and in particular with the bridge that must be built between the classical preclinical studies that we conduct in the pharmaceutical industry today and the need for adequate well-controlled clinical studies, have recognized and continue to recognize that there's a strong need for improved models to assist in our decision making, and to assist in our protocol design. I think we can look forward this afternoon to a fine series of presentations and hopefully to a lively discussion period which will help us to identify some new opportunities in the development of models and the utilization of these models for predictive ability. Additionally, we'll hopefully recognize some of the limitations that must be placed on what conclusions we can draw from these models.

Our first group of presentations will focus on the value and limitations of pharmacokinetics in predicting dosage regimes

and will be given by Dr. Richard Teske of the Food and Drug Administration, Dr. Gary Koritz of the University of Illinois, and Dr. Jim Riviere of North Carolina State University. Dr. Teske is going to open the presentations to lead off the discussions with an overview and then yield the floor to the other two individuals to develop. Dr. Teske, as I indicated, is with the Food and Drug Administration, Bureau of Veterinary Medicine, and is Associate Director for Veterinary Medical Research.

DR. TESKE: Good afternoon. The importance and value of pharmacokinetics in the dose determination process is obvious from the discussions this morning; however, because it is so important, perhaps some of the points that were made this morning bear repeating.

## The Value and Limitation of Pharmacokinetics in Predicting Dosage Regimes

Richard Teske, D.V.M., M.Sc.

I will discuss briefly the complex nature of the question of dose determination from a regulatory point of view as an introduction to the presentations by Dr. Koritz and Dr. Riviere both of whom are eminent authorities in the area of pharmacokinetics and are therefore well qualified to discuss the value and limitations of pharmacokinetics in predicting dosage regimens.

As you know, the application of pharmacokinetic principles in the research and development, application, and regulation of veterinary drugs and feed additives is a relatively new and rapidly expanding phenomenon. The use of mathematical models to quantitatively describe dose response characteristics and to provide mathematically precise end points that have pharmacological and/or toxicological significance in biological systems would seem to have broad applications in supporting judgments concerning the safety and efficacy of drugs and chemicals.

It has already been pointed out that these concerns go far beyond the simplistic "how much" to include the total therapeutic strategy encompassing timing, site of action, clearance--all directed towards disease resolution. To disease resolution we can add disease prevention, alleviation of pain, increased production, modification of behavior, enhancement of performance, and a myriad of other medical claims for which we administer drugs to animals. The focus at this point, in terms of dose determination, is on the therapeutic window, that range of concentrations between minimally effective and minimally toxic that is the target of the dose determination process.

As Dr. Koritz will explain, the concept of defining the "therapeutic window" within a particular individual is, in itself, a complex process. Even without considering the clinician's preferences and biases, the picture is complicated by the fact that we are dealing with a widely diverse biological system that, even within a particular species of given age and sex, is still highly variable depending upon complex determinants such as nutritional status, pathophysiological state and concurrent disease and/or therapy. The question of veal calves is a case-in-point. Among the various classes of veal calves we have: (1) bob veal calves -- those generally marketed by 10 days of age; (2) normal veal calves -- those raised on a concentrate/roughage diet and marketed at 250-350 lbs. body

weight; and (3) fancy veal calves which are also marketed at 250-350 lbs. body weight, but which receive a diet consisting only of milk or milk replacer.

In the case of companion animals, variables such as nutritional status and pathophysiology can, in a clinical sense, generally be handled on an individual animal basis. Dr. Mercer earlier outlined the process that the clinician might follow in a given case and showed how the therapeutic regimen might be modified in a case involving a single animal. In the case of food producing animals however, we are dealing with the ranges that are inherent in a herd, pen or flock. In this connection, Dr. Riviere will discuss recently developed pharmacostatistical techniques termed population pharmacokinetics, that may be applicable in such situations.

From a regulatory point of view, many of these same questions and concerns must be addressed in the context of combination drugs, bioequivalence determinations and generic products, and residue control and human food safety. The dilemma in all of this is that it is impossible to determine directly the effects of all of the possible variables or combinations of variables on the safety and efficacy of every drug product. Thus, there is a great need for methods by which this seemingly infinite variety of variables can be classified and categorized according to quantitative effects impacting on the physiological, pharmacological and/or toxicological end points of drugs and chemicals. Predictive models might then be constructed which would allow us to describe the effect of specified changes in a given quantitative data set without actually demonstrating the effect in the animal. Models characterizing a given variable or set of variables might enable the investigator to predict therapeutic outcomes on the basis of reduced numbers of data points or to project the effects of alterations in metabolism, distribution or elimination rates.

Pharmacokinetics will also find important applications in the development of animal drugs for minor species under the Bureau's minor species policy. For example, by demonstrating either comparability of absorption, distribution, metabolism and/or elimination or by providing a mathematically definable basis for extrapolation decisions.

In conclusion I believe that the solution to the problems we are addressing is not simply a better understanding and application of pharmacokinetic principles. However, pharmacokinetics does represent a powerful tool that can be more effectively utilized in addressing the questions that have been raised.