

DR. MINER: Dr. Jerry Brunton who will comment next is currently Vice President for Scientific Activities for the Animal Health Institute and is well known to all of us. He is a graduate of the University of Pennsylvania, receiving both his V.M.D. and Ph.D. degrees from that institution. We'll ask Jerry for his comments at this time.

COMMENTS ON PHARMACOKINETICS

DR. JERRY BRUNTON

One of the principal purposes of this Symposium is to review the recent advances in the pharmacokinetic approach to the study of drugs and to consider specifically how these new approaches and models can be utilized in establishing the appropriate dosage regimen for animal drug products. The three previous speakers agree that the pharmacokinetic approach should have application in determining dosage regimens. Drs. Koritz and Riviere have provided excellent accounts of how these elegant techniques and pharmacokinetic models might be applied in veterinary medicine. However, when a drug industry scientist considers use of these techniques to generate data that would be used in support of approval of an animal drug product, he must remember that animal drug products, as regulated by FDA, must be developed within a framework of science and law.

The industry scientist finds that the need to meet FDA's legal test of substantial evidence affects his approach to gathering scientific data. For example, the same experimental data of a drug's usefulness that would be used to convince top company management to invest millions of dollars into developing a new product, would not be likely to meet FDA's criteria of substantial evidence of efficacy. Thus, when the industry scientist is asked to incorporate a new scientific procedure, such as pharmacokinetics, into an information-gathering process that is designed to meet formal FDA requirements, this request will be met very cautiously.

When the current procedures and models for developing dosage regimens are examined, there is no problem agreeing with Dr. Koritz's feeling that the use of pharmacokinetic approach would help to determine a dosage regimen for an antimicrobial with greater speed, less expense and better understanding of the underlying mechanisms than is provided by the empirical approach. However, after listening to the limitations and variations of pharmacokinetic models as discussed by Dr. Riviere, one realizes that a great deal of developmental work must yet be done before many of these models could be utilized effectively to establish a data base for regulatory approval.

This points out the need for the drug's sponsor to insure that whatever pharmacokinetic model is utilized, the investigator

must feel confident that the data generated would provide a good possibility of answering the questions being asked. Protocols and pharmacokinetic models should be developed to the point that there is a well-established basis for interpreting the data that would be generated. Basic research with new pharmacokinetic models as part of information-gathering for an animal drug application is a very risky business and should only be performed as part of a sponsor's desire to solve a problem that can't be solved otherwise.

Many of the more sophisticated pharmacokinetic models need to be developed and tested further prior to their routine introduction into gathering regulatory data. However, there is no doubt that use of the pharmacokinetic approach will provide, in many cases, an improvement over the current empirical approach to dose determination. We must also recognize, however, that because of the complex handling of the drug by the animal, there will be times that the empirical approach is still better than any of the available pharmacokinetic models to demonstrate therapeutic effectiveness. Industry, I'm sure, has some concern that the use of pharmacokinetic models might turn out to be an add-on requirement to the current empirical approach rather than a replacement for an inefficient process. This should not be allowed to happen. Use and defense of the appropriate pharmacokinetic model should always remain the option of the drug sponsor.

I am impressed, as I am sure you are, by the wide variations in kinetic profiles of the same drug between normal animals and in various disease and production conditions. I feel that these wide variations which occur normally are an indication that there should not be a bright line indicating a particular dosage regimen above which there is too much drug and below which there is too little. Such variations indicate a much broader need for utilizing dosage ranges in the use of animal drugs.

While I have taken some time to express my concerns about the application of pharmacokinetics to meet drug approval requirements, I am certain that pharmacokinetic-derived data is already playing a crucial role in answering safety and efficacy questions, and I am optimistic that this use will be expanded. Certainly, many of the poor animal disease models currently used can adequately be replaced with pharmacokinetic models that will more adequately reflect the onset of disease, the disease condition, the appropriate route of therapy, and a more reliable measure of therapeutic efficacy. The pharmacokinetic approach certainly offers the ability to obtain a

good data base on a limited number of normal and diseased animals that may be effectively used in selecting dosage regimens for field-trial testing.

The developers of animal drugs need to have much greater flexibility in determining the appropriate dosage regimes for their products while the basic research on more effective methods and pharmacokinetic models should develop in a cooperative interchange between scientists from industry, government, and academia.