

SECTION III

EXPERIMENTAL DESIGN OF DOSE DETERMINATION  
STUDIES WITH ANTIMICROBIAL DRUGS

DISCUSSION PERIOD

(PART I)

DR. ARONSON: At this point our program offers us an opportunity for discussion and I'd like to have our previous speakers join Lloyd at the table and we'll open the floor for discussion of the papers that have been presented. Once again, I'll ask that if you do come to the microphone, please state your name and affiliation before asking your question. Thank you.

### SECTION III - PART I - DISCUSSION PERIOD

DR. PAUL: Harlan, you certainly took an interesting approach to discussing the use of clinical trials for dose determination of topical drugs, but I can appreciate why you took that approach. If I heard you properly, you said that it is very difficult to determine dosages of topical products in a clinical setting and that you thought that models were much more valid for that purpose.

DR. BIGBEE: Yes, that's correct.

DR. PAUL: And I think I further heard you say that clinical trials then should be used to prove efficacy.

DR. BIGBEE: You are correct.

DR. PAUL: May I then ask this question: Do you think that because of the variables that you are confronted with in the clinical setting with topicals, that you could also prove efficacy in a valid model?

DR. BIGBEE: Yes, I think you're going to get a lot of efficacy data out of a valid model. I don't believe that I would totally throw out the clinical cases, providing there is some semblance of a positive control. You get a lot of base information out of your model.

DR. PAUL: Would you think that there would be any merit in trying to establish the efficacy of topicals and possibly some other drugs with models and then seeking a waiver for controlled clinical trials?

DR. BIGBEE: There is a definite place for a waiver of controlled clinical trials if you do not have another appropriate or similar type of drug to compare to. If this type of situation should come up, then a request for waiver I think would be very valid.

DR. PAUL: That would be a good example, but what I'm really getting at is, I guess it's my opinion, I'm wondering if you are agreeing with me but I don't think you are entirely (and I was hoping you would!).

DR. BIGBEE: State your question clearly.

DR. PAUL: I'm going to make a comment instead of asking any more questions. I think we can derive more definitive efficacy data in certain situations with models than we could with clinical studies.

DR. BIGBEE: Oh I agree with you. If you're going for extreme, or very finite data, the clinical trial is not the place to obtain this at all, you're going to get some comparative data and you're going to get some judgmental data. As far as it being very finite in the clinical condition with topicals, I don't think you're going to receive it.

DR. PAUL: I want to make it clear that I'm not generalizing, I'm talking about certain specific situations.

DR. MUSER: Believe it or not, it took me until today to realize that Tom Powers started out as a microbiologist; I knew I had something in common with you, Tom! I would like to pick up on what Wally Brandt said about his experience in the field trying to evaluate antimicrobials against Pasteurella infections, and I would like to illustrate it further with one of my favorite stories about scientific arguments. It involved German scientists who sometimes get quite intensive in their arguments. Pettenkofer was one of the prominent epidemiologists in Germany around the turn of the century and one of his specialties was cholera. To prove a point, he assembled a number of scientists and friends and gulped a culture of vibrio cholerae in front of everybody. He survived to tell about it and didn't even have symptoms. This illustrates further what Wally said, there are some diseases, bacterial disease in particular, whose outcome depends on many factors.

I don't have a question, I have a comment on what was said so far and what was said yesterday, too. I think it would behoove us all if we tried to reduce the variables in all the studies we do, dose titrations in particular. I suggest that we try to see what was common to all the things we have heard and one thing they had in common. In one case it was a clinical study that made it easier to find a dose and in another it was a model study and in still another it was a clinical model if you will -- so I would suggest that a good

conclusion from this meeting would be very fine if we say we need to reduce the variables wherever we can, be it in clinical or be it in model studies. Let's try to find the best way to do it. I would be very unhappy if we came out of this conference saying we have to do pharmacokinetics with each drug, or we have to do a model study with each drug, or we have to determine a dose in the clinical studies with each drug. Let's try to be flexible in what we do. Thank you.

DR. CSUBAK: I have a question for Dr. Keefe and then I'd like Dr. Gable to comment on it also. Yesterday we heard Dr. Jean Powers suggest that perhaps the use of historical controls might be appropriate. You've done five NADA's on antibiotics for mastitis; would you comment on whether or not you think a historical control might be appropriate for any future studies which you might be doing for this type of product. Then also, if Dr. Gable would comment on whether or not he thought that might be appropriate from an FDA standpoint.

DR. KEEFE: The thought of doing a study without controls is somewhat strange to my thinking process; you've got to have controls. I would not rely on historical data. If nothing else, an active control protects your drug from an abnormally poor result in a given herd. So I think it's to the company's advantage as well as the Agency to have a control and not rely upon historical controls.

DR. GABLE: I agree with what he's said; I don't think you can tell from herd to herd, or year to year, what the incidence of mastitis is on a historical basis.

DR. BRITT: I'm a practitioner from Kentucky but you can hold the applause. I want to make a couple of comments and ask some questions concerning intermammary fusion products. I represent the American Association of Bovine Practitioners and Dr. Paul, we appreciate the invitation to be here. We've already heard some real good practical things that we can take back and use in our practice.

One reason we're here is the practitioners' concern over the new extra-label drug policy. For you that are not aware of this, and although the policy has been well-publicized this is one aspect that has not been publicized, our AVMA liability trust that covers our malpractice insurance has stated that under the new policy they will not cover us if we use extra-label drugs. They would cover us under the prior existing FDA policy, so we're all in jeopardy if we use anything out of label right now as far as malpractice is con-

cerned. Two or three comments for Dr. Keefe on mastitis: I certainly agree with you on the higher dose rates; whether we want to put the higher dose rate in the syringe or have the client use three syringes, they're already using 2 or 3 many times of the initial dose. And, Dr. Baldwin, I would think that from a practical standpoint in the field, it would be more efficacious and less dangerous from the standpoint of multiple infusions to put a higher dose rate in that initial syringe than it would be to use three separate syringes on that cow. You mentioned that coliform mastitis is a minor problem and I think we need to readdress the need for antibiotics that are effective against coliform mastitis. This was an important topic at the National Mastitis Council this year, in many herds that have been using dry cow therapy and good hygiene for several years, coliform mastitis is the predominant subclinical mastitis problem. We do have a need there for a future product that is effective against coliforms on a practical basis. And finally, Dr. Brandt, we work two stockyards at our practice, too; we haven't had any stockyard inspections but our clinic had suffered two FDA inspections this last year; perhaps you would want to compare notes sometime. I think that someone should give FDA inspectors a lecture in integrity, if nothing else, because they certainly caused havoc at our practice for a couple of days.