April 18, 1985

Section II - 4:00-4:30 Open Discussion

Dr. George Washington: If the four speakers will come up, we will open the floor up to discussion.

Dr. Bob McDowell: I want to thank Dr. Muser for those kind words. It is someone elses turn now. I think I will pick on Beecham, Tom Keefe. This is not his drug so I am not specifically picking on him. I have been working recently with some applications that are dealing with urinary tract infections. What I am finding, this is not unique, I have encountered the same situation previously but I have encountered it recently so I will mention it. There will be criterias for excellent or an improvement which the drug company will combine and say excellent and improvement will constitute 85-95% of the animals tested and then there will be 15% or whatever is the remainder, is a failure. And what I am finding is the excellent will be based, and I think it is based entirely on a clinical response that can be observed and not looking at scientific issues such as in the case of these urinary things, whether it is bacteria, casts, protein, pH, lack of ability to concentrate urine, albumin, anuria or things like this. Frequently you will see improvement is an observable clinical improvement that you can eyeball but there will be a failure of microbiological elimination.

I think this system is unfair because you have two criteria that they are combining and the only thing left is failure. I just wonder why one, why there is not a fourth category where to give recognition to something less than total failure but they do give recognition to the albumin area, lack of ability to concentrate urine and things like this. I have recently seen, and this is no stretch of the imagination, I have seen numerous cases where there was classifications of excellent and/or improved classifications where there was a 2+ pretreatment protein in the urine, a post treatment 2+ albumin in the urine and it still classified, you see them both as excellent or improvement. I do not think that this is really, --it is no wonder that we have some ifs in some of the types of cases that are coming in. I hate to saddle you with that but I guess I would like to have some type of response.

Dr. Keefe: Bob, I have the same problem you do. If the investigator calls a case excellent, that is how I have to report the case. There are cases that I would like to change but I cannot change the investigator's evaluation. It does create a problem. This is why we looked at the various parameters individually. If the majority of the pivotal parameters add up to a favorable response, you have got to consider that as positive evidence of efficacy. These evaluations are often subjective, not objective.

Dr. Urbeck: (small animal practitioner/clinician/investigator) I noticed during the afternoon that a number of you have been removing your coats and it has been a little warm in here. I apologize for this because it definitely was me getting hot under the collar after listening to the statisticians. The reason is because I interpreted their statements to

mean and I thank Terry and Stirling very much for cooling me off because I have my jacket back on again. I interpreted their statements to mean that as a clinical investigator, that I do not really have the ability to diagnose a disease condition that has a predictable end. I must remind these statisticians that there is a disease condition that they are expecting me to diagnose and treat and try to have some type of response from this. The people at the table now, I thank you for exonerating we clinicians from this bind that these statiticians tend to put us in. It all goes back to the idea that we do have a responsibility for the animals welfare. Besides finding these cases for the people that we are working for in the drug industry and treating them with the drugs that they are giving us to treat. So I guess I got to say to the staticians, I recognize the problem but it goes right back to putting some degree of creditability to my 1) diagnosis and 2) observation of results that are occurring within the animal.

Dr. Harvey: I would like to move the pace a little bit to anyone in the FDA or all of them relative to the hastening the approval process with a more vigorous monitoring program than mere term, marketing situation.

I have given fishing stories in front of this group before. The bait was out but nobody rose.

Dr. Gable: I work in the food animal area; I have yet to see the NADA submission where modifying the requirements for clinical trials would have been a great time eliminating step. In the food animal division, we have nothing to be gained by the proposed system. I have a rather warped mind and this morning, while the speakers were talking about phase four studies, I was thinking that one way to get good phase four information is to reintroduce an "animal drug lag" in the U.S.; then you have all the marketing experience from foreign countries. This happened, for instance, with invermectin in cattle. We had very good information regarding phase four data in cattle from its foreign use. But at least to respond in my area to your question, I really do not see the advantage of approval prior to the collection of clinical field data. I will let the nonfood people speak for themselves.

Dr. Harvey: I got you there. What is the most, great eliminating step for clinical trial material in food animals. We heard about nonfood from Bob this morning.

Dr. Gable: It is generally the toxicity data needed to establish a tolerance and the validation of the methods for measuring that tolerance. Recently, more in the forefront as a time intensive step has been the environmental data.

Can I make a comment rather than ask a question? My comment pertains to the issue of geographic locations. I tend to be somewhere between Dr. Muser and Dr. Keefe on this. I think this has become one of the "set in concrete" requirements associated with guidelines. That is, if you have this guideline recommendation, you apply it to every drug product. Personally, I can see little or no justification for three or more geographic locations for physiological drug products. For antibacterial drugs, if

you can measure the range of the susceptibility of the organism without running to the west coast or the east coast, you can probably satisfy the geographic requirement. I can't speak to the coccidiostats or the anthelmintic drug products as well as Dr. Muser, but you can quantify the variability and the susceptibility of the etiological agent, you have addressed a major justification for geographic locations. For S. aureus mastitis, quantifying susceptibility of the organism is probably more meaningful than geographic location. In addition, the extreme in husbandry practices can occur within as well as across geographic locations.

Where you do need geographical information, and the initial reason or driving forces behind this requirement, has been drugs which are administered in the feed or the water, you have variables introduced by diet, consumption, temperature, humidity, etc., on top of the susceptibility of causative agent. In addition, there has been a reluctance by the animal drug industry to label the product to be administered by feed or water on a unit of drug per unit of body weight. Many sponsors continue to have a preference to treat the feed or the water rather than providing a dosage regimen.

Dr. Muser: I would like to comment on the anthelmintic studies. Let us remember what we said before, what we perceive clinical trials to be. We are not establishing efficacy with them. We establish that with critical studies. What we are doing in clinical field trials is taking the drug and testing it in a larger population. There are some variations, there are different diets, there are different management conditions. You do not want to transport a feedlot just because it is conveniently close to home. So I think there are many different reasons why testing an anthelminthic in different geographic locations is appropriate.

Dr. Washington: Any other questions.

Dr. Gable: Dr. Muser is right. In the development of anthelmintic drug products, usually what we (CVM) get out of the clinical studies is use information and some assessment of safety.

Dr. Keefe: I would like to make a comment regarding the regulatory requirement for geographical distribution studies with antibiotics. When a company has volumes of information on in vitro susceptibility, then I do not feel it is necessary to have widespread geographical clinical studies. If it is sensitive in vitro, the antibiotic will work in a dog in Iowa, New York or California.

The second comment I would like to make is the duplication of effort and cost in considering each species (dog and cat) and each indication (skin, UTI, etc.) essentially a new NADA. The same applies to different dosage forms (drops versus tablets). Is there not some way to extrapolate some of these data from one species to the next, particularly in the case of antibiotics where you have equivalence in the pharmacokinetic area and in vitro sensitivity.

Without some modification to existing guidelines, or rather interpretation of them, we are going to have fewer new drugs for dogs and cats with

veterinary labels. If we have new ones, they will be what I call "one label" drugs, which means the veterinarian will have to extrapolate dosages, indications, etc. These "one label" drugs will cause our profession problems, including malpractice. I think this group needs to consider this subject.

Dr. Gable: I took a vow of silence this morning. I just broke that vow. I would like to echo what Dr. Keefe says. I am responsible for drugs in food animals. There is probably 20 drug manufacturers represented at this meeting. We see new antimicrobial drugs, we see new anthelmintics, we see the prostaglandins. We do not see any other drugs in food animal medicine. We have major orphans out there in all the other areas of food animal therapeusis. There is little or no drug development in the other areas of food animal medicine.

Dr. Griffith: Tom, if I understand your question, I think it is entirely possible that we would be able to approve the drug with considerably less number of clinical case reports in a cat if it was already approved in the dog and we had the basic preclinical data in both species. I think there is a real good chance that we might well approve that drug with considerably less data.

Dr. Keefe: I would love to talk to you right after the meeting. Bob, I appreciate your comment and I know you are serious and sincere. But I think it is something we really must take into consideration in future work.

Dr. Griffith: I agree with you and, quite honestly, I think we are doing that now. I think maybe, well, Dr. Dawley, would you want to comment on that. I think we have had some discussions recently with regards to extrapolating from going from dogs to cats.

Dr. Dawley: Yes, I know that, the fact that we go to CVM, let us talk about what the problem is, what the situation is, they can not do anything for you if you do not come and talk to them. They can help you if you do it. We take protocols down there. I resist the fact that it takes 90 days to look at a protocol but I have been in their position and sometimes, it takes 90 days. We both are working for the same cause. So, by all means, I think if you can demonstrate to yourself that you should be able to extrapolate from the dog to the cat, and you do it honestly, then you will have no problem demonstrating or getting cooperation from CVM. That is my own opinion.

Dr. Washington: Any other questions in this part? OK, thank you speakers.