

April 18, 1985

Section I - 9:00-9:30 Open Discussion

**Dr. T. Powers:** I will start the discussion. Dr. Griffith, I think you deserve a right to respond to Dr. Gingerich's comments regarding clinical trials. Could you respond as to: "Are they really needed or are they needed as a requirement for the Center of Veterinary Medicine?"

**Dr. Griffith:** Dr. Vail has just pointed to a good example where an additional large number of clinical trials may provide information to avert unacceptable post approval drug reactions. Extensive clinical testing is sometimes the only practical means available to sample the total population and identify a small subpopulation of animals that has some type of unique drug susceptibility. For example, in the case of the canine organophosphate anthelmintics, extensive clinical testing is necessary to identify the small subpopulation(s) that is apparently predisposed to serious adverse reactions.

**Dr. T. Powers:** Following that line of reasoning, Bob, suppose you wanted to determine the incidence of the idiosyncratic reaction to chloramphenicol. How many clinical trials would you have to do? Is there not an answer that some of these clinical trials could be done after the package insert is approved, after the drug is approved so that you could really obtain adequate numbers? After all, are thirty animals in each of six locations adequate numbers?

**Dr. Griffith:** A drug is approved on the basis that it is, in fact, safe and effective at the time of approval. I'm not aware of a mechanism that permits conditional approval before the safety and efficacy have been conclusively established. Adequate clinical data to document safety and efficacy is a prerequisite for approval. Some factors that are considered in determining an adequate number of clinical cases are the nature of the disease, the acuity or chronicity, the severity, the incidence, the lack of or availability of other therapeutic agents, familiarity with the compound or drug classification, the persistence and type of adverse reactions, and the magnitude of response to treatment. All these factors determine the number of clinical cases needed.

**Dr. Gingerich:** Before we leave that point, I would just like to say that I agree with both Dr. Vail and Dr. Griffith that extensive clinical trials are needed to determine some of those idiosyncratic things. What I contend is not to disagree with that but to say that we will never have extensive clinical trials if they must be conducted under 514.111. You are not going to get thousands and thousands of cases controlled that way. That is all I am saying. If you can recognize a clinical trial for what it is supposed to be, which is evaluation of a drug under conditions of actual field use, then we can get hundreds or thousands of cases but not under 514.111.

**Dr. Griffith:** I previously suggested in some cases using a two phased approach to clinical studies where initially a relatively small, well controlled study is conducted to conclusively document the effectiveness.

Then in the second phase, continue the study and get more easily acquired, large numbers of uncontrolled data to confirm the safety.

**Dr. Muser:** My name is Rainer Muser, I am with American Hoechst in Somerville. I have a couple of thoughts to offer which may help us to focus our discussion. Some of the things I wanted to say already have been said just now. We have difficulty to do well-controlled studies in large numbers of animals in veterinary medicine or with animal health products in general. If we continue with the train of thought that Dr. Dan Gingerich has followed in his paper, we should ask where we come from. One answer may be we have this situation because of regulations which if you will remember, are mainly targeted at human drugs. In the evaluation of human drugs, it is not possible to kill a human patient after treatment to determine the results which may be the ultimate control. In veterinary medicine we added animal models to clinical evaluations because they give us real criteria for developing some safety and efficacy data. In addition to that, clinical studies according to human standards are also required. I think that is a waste of money, of resources, of efforts. I would totally agree with a concept that in certain areas all the basic information is obtained with laboratory studies in a well controlled design, call it laboratory study, call it clinical study, I don't care. They could be done in a limited number of animals and a substantial number of animals could be added in studies of a less closely controlled design. This would allow us to find out some of those individual animals that are more sensitive than others. Let us remember that the clinical evaluation of a drug never ends as long as it is used in the field. Thank you.

**Dr. Griffith:** Just one additional comment - there is a provision for waiver of certain types of controls in clinical studies, if conventional controls are not feasible and there are alternative methods that convincingly demonstrate efficacy.

**Dr. Harvey:** I am Terry Harvey from Monsanto. I would like to echo Dr. Muser's comment that says the real clinical trials are after the first approval. That is when most of the problems that we have talked about, and they often are the exception, have occurred relatively rapidly as we increase the numbers. So the concept of going ahead with an efficacy standard has been suggested and implemented by CVM for anthelmintics, for example. Laboratory targets hit that to a very small, well controlled number study. And that piece, Rainer, could be like what we see in human medicine. Thoroughly diagnostic, really work them over. Then go into what I would call, user trials; less controlled, more practical.

**Dr. Mercer:** Dwight Mercer, Mississippi State University. I have a question for Dr. Vail, please. In your twenty-five years of running clinical trials from a clinicians perspective: How many times have you been involved in the design of the clinical trial protocol and if you had had the opportunity, would you have designed it differently or more appropriately to fit the field conditions?

Dr. Vail: Well, I suspect you have asked a question that you already know the answer to. And it is never and yes.

Dr. Mercer: Would you expound on that just a little, please.

Dr. Vail: Number one, I will do a bit of Pontius Pilate on it in that I do not feel that we necessarily are qualified to make a significant contribution to designing field trials. On the other side of the coin, in the early days, we did trials on colic studies where they insisted there would be no concomitant therapy. One of the reasons we still use the term "colic" in babies and in horses is that it is entirely a subjective type thing. It is a symptom and not necessarily a specific disease. I do not know what the adequate model for an equine abdominal distress syndrome field trial would be, but it certainly cannot preclude concomitant therapy. We were able to fudge that recently in our butorphanol studies and even so we had a situation where the senior partner used it with xylazine, (Rompun) and grumbled back to the staff meeting and said it would not work on the basis of three trials. I think that certainly the practitioner should be consulted in designing these trials. It is one of these things where I think it is a good idea but I think somebody else should do it besides me. I would submit, however, that practitioners in the embodiment of the American Association of Equine Practitioners which, in fact, is not just an American Association of Equine Practitioners. Number one, it is not just American. It is international. Number two, it is not just practitioners but there are several members of AAEP from industry in this room. But I think working with that organization, and working with the people who are not necessarily private practitioners but who have constant dialogue and intercourse with clinical practitioners, I think things like that can be worked out. AAEP has forty-five committees and seventy-two liaison assignments in the organization and we are more than anxious to get after these kinds of problems. So I would suggest there are resources out there to involve clinical practitioners in the design of these trials. It should be done through such an organization so that you have continuity. The yes part of my answer is, I do feel that clinical practice does have a contribution to make in designing field trials and certainly AAEP through their research committee, or through any one of several committees would be really glad to pick up that ball and run with it.

Dr. Teske: In response to Dr. Vail's comment. I am Dr. Teske from the Center for Veterinary Medicine. I would submit that his suggestion that we make more effective use of some of the national organizations that we have that really represent the expertise in many of these areas is important. We should do a lot more than I think we are now doing.

Dr. Aronson: I am Art Aronson from North Carolina State University. As a follow up to the last consideration regarding the participation of investigators doing clinical trials in designing the protocol. A clinical trial requires one to consider the patients and the client. They brought that animal to the veterinarian for the purposes of treatment. Therefore, in the design of a clinical trial one must take cognizance of the fact that what is done has to be done for the benefit of the patient first. This strikes me as being the basis for a number of these cases that get

tossed out. If the investigator who is going to carry out the trial would work together with industry and the FDA in the design of that protocol, perhaps there would not be so many of these problems about concurrent treatment. When you are dealing with a clinical patient, the needs of that patient have to come first. My wife has a dog. When she brings it to a veterinarian, she wants that dog to have first consideration and not have beneficial (concurrent) treatment denied because of a clinical study.

Dr. Paul: I am John Paul of American Hoechst. I have a question for Charlie Vail. Charlie, when you talked about one of the faces of the investigator being the clinician, you talked about certain ancillary uses that were made of investigational drugs, in your opinion, and I am asking you not only to speak only for yourself but for the clinical community as a whole, what happens with that type of information. The ancillary uses, for instance. Does that become part of the body of knowledge to have a better understanding of the drug or what happens to it?

Dr. Vail: Well, we tend to and try to get all the information applicable to back to the company that has us investigating the drug. This was the case with lasix. Certainly this was the case on butorphanol and to the extent that it is now probably used more for analgesic tranquilization purposes than it was for colic therapy or for respiratory relief. I know some veterinarians that will absolutely not use anything else in fixing a horse to the floor. It has remarkable analgesic properties in combination with tranquilizers, maybe Dan could speak to that. But that is one example where our information certainly was minimal as regards to the specific therapy they wanted investigated and yet we developed quite a bit of information on other uses. They may have known that before we did the work but certainly we report those back and it was our expectation to report them back. One other thing, and this is a private and/or organization complaint. I was a little dismayed at the advisory committee named to the CVM that there were only two practitioners on that committee and neither of them had the remotest idea which end of a horse you feed. I think that if we are going to improve the lines of communication and shorten the distance between Washington and places like Littleton, then somebody from equine practice should be considered to that advisory committee (somebody besides me!).

Dr. Chatfield: I am Ron Chatfield from Bristol Laboratories. I have a question for Dr. Vail. The historical control in clinical trials has never been embraced by FDA as a particularly attractive form of well controlled clinical study. It would seem to me that if this position were changed, we might be able to, in fact, double the number of clinical cases subjected to the test article, if we could use the historical control as opposed to a positive control or placebo control. It also implies to me the clinical investigator is possibly not able to subjectively evaluate a drug unless he has a positive control or some other control to compare. I am wondering what your thoughts are on historical control versus positive control.

Dr. Vail: Tough question. I do not have a strong position on that. You know when you start talking about controls and private practice, you

talk about the issues that have already been brought out. (1) The owner to consider. I have always felt the worst possible incarnation for any type of animal was to be owned by a practitioner because that is where a lot of our controls come from. We compare it to the poor old roping horse we keep out in back that is the blood donor and the anaphylactic shock test case and things like that. So I would tend to disqualify my opinions or my preparation in terms of how the controls should be handled.

Dr. Teske: Dr. Teske, CVM. Before we take the next question, I would like to make one comment about an earlier comment, Dr. Vail, and that is about the CVM advisory committee. Your comment is well taken and one we have heard from a number of groups. Unfortunately, the advisory committee consists of just eleven people. With that size group obviously it is not possible to represent specifically and individually every organization that can, and perhaps in many cases, should be represented. Let me say that that advisory committee membership will be changing, that is, it is designed to have a continuing, ongoing turnover and we will be announcing this summer a request for further nominations for that committee. I would certainly suggest that your organizations, as well as other organizations that feel it is important to be heard, take advantage of that nomination procedure and also perhaps in accordance with that, indicate some of your feelings regarding the importance of your particular organization involvement.

Dr. Mercer: Dr. Teske, Dr. Dwight Mercer, from Mississippi State University. Just a follow up on Dr. Chatfield's comment and Dr. Vail's response to it. They asked a question regarding clinical trials: In your opinion do you really believe that you can run an adequate and well controlled clinical trial and take into consideration the other things that a practicing veterinarian and the client relationships require.

Dr. Vail: Was that addressed to me.

Dr. Mercer: Yes.

Dr. Vail: That is an unqualified yes. I think Dr. Muser spoke to it pretty well. If I can try to quote him again without the accent, I apologize, Rainer. But that is, the clinical investigation of a drug never ends as long as it is being used. I think that is a significant enough statement for me that it ought to be framed and hung in my office. Certainly, I think, everytime a drug company is sued, some veterinarian is also sued along with it which is looking at it from the other end of the telescope but I will stand here forever and defend the ability of any practitioner to conduct those clinical trials. I think it is of critical importance and I think I have sufficient experience and evidence, with some of the calamities that have occurred in these areas to argue persuasively and strongly for the clinician.

Dr. Mercer: I am not arguing the ability to run the trials, Dr. Vail, at all. I am simply questioning the controlled aspect of a clinical trial. Do we in veterinary medicine need to face the fact that any one practitioner will see over the period of a week or month, a small number of specific clinical cases. Can we run a controlled clinical trial with the

volume of material on a specific kind of case that comes through an average clinic in a week or month or year. The key point is controlled studies. Can you realistically run a clinical trial that can or will conform to the definition of a controlled trial.

Dr. Vail: No, clearly not, in the terms of the schematics of what you are saying. But on the other side of the coin, if you select your investigators, on a broad pattern, I think and certainly Dr. Jean Powers could address this better than I could, that statistically you could do a sufficiently significant controlled study that you would come out with usable results. I am continually astounded and still a bit incredulous that they can predict election results based on a two or three or four percent sampling. Does that mean that it is possible for use, to do controlled studies in forty or fifty states and have a statistically well controlled study. Did I get anywhere close to your answer, Dr. Mercer?

Dr. Mercer: Most of it.

Dr. Vail: OK.

Dr. Kearley: I am Ed Kearley from Turlock, California. I am an investigator. I have a commercial dairy that I started eleven years ago because I had three dairy studies and none of the dairymen would cooperate with me. Right today, I really know the economics in the dairy business. I get up each morning in fear, fear of my wife, she is vice-president in charge of finance and it is a real decision of what to do now. Now back to controls. This is one thing that has always bothered me, are these control animals. If they are mine, that is fine, I can negotiate with the drug company real easy if I lose one. But if I lose a client's, which I do not have very many because I do not practice that much, that bothers me immensely. Because then you have two people to negotiate with. In relation to this, I do not practice that much so that I can give my time to research work. As an investigator, you have to give all the time you can to the project. I think you should collect most of the data because the way some of these dairymen collect data, is unbelievable. Once in a while you will hit an organization that has some herdsmen that will work with you close. But the thing that bothers me the most is the economics that surround controls. I do not mind doing it on my animals. I have 250 cows but now I think I need 400 to 500 cows. We are doing a study now where there are 4000 cows and boy, that is beautiful. You can get numbers in a hurry, but I am not going to take one chance of losing a control animal in that dairy. That is just some comments.

Dr. Keister: I am Dr. Mark Keister of Sterling Drug. I was wondering if someone on the panel might address the use of positive control studies in which there is an improved drug but has been researched with dubious thoughts of efficacy, was researched a number of years ago and which potentially it is not as efficacious as the package insert would lead you to believe.

Dr. Griffith: The issue you raise is often further compounded in the case of combination drugs where the standards for approval several years ago didn't include component efficacy data. However, if the product is approved and if the Agency has initiated no regulatory for withdrawal, the drug is considered to be safe and effective. Nevertheless, some of the older combination drugs have been considered questionable subjects as positive controls for testing the component efficacy of new combination drugs.

Dr. Teske: Thank you Dr. Griffith. Would you want to comment on that?

Dr. Gingerich: Well, we at Bristol have been in that situation a number of times. Basically I would concur with what Dr. Griffith said in that if it the positive control drug is approved by FDA, the assumption is that the positive control is safe and effective from FDA's point of view. In our experience, FDA generally agrees with those kinds of designs. The hassel we get into is not so much whether FDA agrees but whether we can find any practitioners who will agree to use a drug they perceive to be less effective than the experimental drug as positive control. If we can, then we probably accomplish what we were after anyway. We have something between a negative control and a positive control that is a control we perhaps do not quite believe in but probably makes the study worthwhile anyway. I think the world comes out a little smarter for having run such studies than if we do not have the opportunity to do them at all. It is a very real situation though.

Dr. T. Powers: I would like to extend the question, let's say you do the study now with a positive control and with your drug, then let us suppose it is a new cephalosporin that you are comparing to an older one, and the new cephalosporin does not turn out as good as the old one. Do you throw it away?

Dr. Gingerich: Do you think it should be thrown away? Basically, it has been our experience in clinical trials with good designs that we are always within a few percentage points of the positive control drug in terms of efficacy. We have never felt that clinical trials conducted under 514.111, with the drugs that we have studied, have been sensitive enough to be able to separate small differences in efficacy between drugs. I think it is the luck of the draw if you come out a little bit better. Sometimes the new drug does not come out as good but statistically, we have never shown any differences. That is the way we look at it.

Dr. Griffith: The example that Dr. Powers presented requires a judgmental medical decision. How great is the difference in drug response? Does the drug showing marginally less efficacy have other redeeming qualities? Maybe the drug is slightly less effective but is much safer than other drugs available. You just have to consider the specifics of each case and make a medical judgment.

Dr. Shotwell: I am Dr. Tom Shotwell from Dallas. I have a question for Dr. Gingerich, you were suggesting using some sort of score card which would sort of add up the information available to us from pharmacological

studies, from human clinical studies and all other sources. It seems to me that you are suggesting a great deal of judgment be exercised than by the reviewer or the team of reviewers. My question is what do you do when you get into disputes or with the reviewer or the agency in this judgmental area? The statistician resorts to the power of the test, the attorney resorts to the law, where do you resort.

**Dr. Gingerich:** I think that is a very good question. What we are saying is that suppose I think I have presented substantial evidence and my colleagues in academia think I have substantial evidence but the reviewer does not. At the present time we utilize the FDA appeal procedure to resolve such disputes. However, that is one issue that I had anticipated would be handled by the FDA Advisory Committee. I would have to confess that I am a little dismayed to see that the Advisory Committee does not appear to be positioning itself to resolve such disputes. I realize that their agenda is very important but I think we as a group in AAVPT pushed for the Advisory Committee so that we could have a body standing by to resolve those kinds of issues, but I do not see them in the picture at all. My answer to your question, Tom, is that that is where an advisory committee should come. Disputes like that should be handled by an arbitration body of some sort.

**Dr. T. Powers:** I would like to direct the same question to Dr. Griffith. When a dispute arises between the drug company and your reviewer, where does the drug company go for an appeal?

**Dr. Griffith:** The initial review results in a recommendation. The agency's position evolves after that recommendation is subjected to review by at least three levels above the primary reviewer. Then, if there is still disagreement with the agency's position, there are procedures for an appeal process. During the course of an appeal there is always the possibility of conferring with a consultant or an advisory committee, and this frequently occurs.

**Dr. Muser:** I would like to raise a little more of a friendly argument about the issue of disallowing case reports that are part of a clinical study. Obviously this changes with the nature of compounds under study. We do not have that much experience with antiinfective drugs, but we have had on occasion some limited discussion on that subject with FDA. It does not quite add up to me. I do not understand why a case report has to be thrown out completely just because it is not in agreement with the protocol in one aspect, because there is no follow up or whatever. For instance, if there is not enough efficacy information in a case, why can't it be used for the safety aspects of the study. I would like to hear more comments on that, please.

**Dr. Griffith:** We will. We will use the case to the extent possible. If it is flawed by deviation from the protocol, we will still utilize it to whatever extent we can.

**Dr. Harvey:** It looks like Rainer and I have a Fonz act going on here but not really. A question of earlier in the market place with good monitoring. Is that concept, we hear it being discussed in terms of the

human drug area. Is there anything in the animal drug area that is happening there. Not a condition approval, Dr. Griffith, but just to the group at large, Dan, or Bob's specifically. Let us get the market control and control it for that six month period, for example, and then pull our controls back. So we can broaden the base with clinicians.

**Dr. Gingerich:** I think that concept is rather good. I would point out that we already do that in a sense on the manufacturing side of our products. Many of you may not be aware of that but whenever we get a new drug approved, one of the things we have to commit to is stability studies on the first few lots that are manufactured. We have to, so we make a commitment to keep our chemical controls up to snuff. Additionally, we do have an adverse reaction monitoring program in place. I think what you are suggesting is earlier approval and greater commitment to clinical monitoring. I would be supportive of that concept.

**Dr. Griffith:** We have implemented the expedited review concept which has been helpful in obtaining more rapid approval and marketing of innovative new animal drugs.

**Dr. Teske:** I think our time is about up. I want to thank the speakers. I think our presentations this morning were exceptional and were a very excellent kick off for our program today and tomorrow.