April 19, 1985

Report & Discussion of Practitioner/Clinician Workshop to Symposium

Dr. Paul: Good morning class! We are going to start this morning's session of the symposium by having a brief report of each of the six discussion groups that met during breakfast this morning. This discussion group concept was designed to make sure that the investigators that came to this symposium--and I want each of you investigators to know that we are very pleased that you came. After all, what would a symposium on clinical trails mean if we didn't have clinical investigators here. I hope in the future that we will always try to include you in these symposia. So, along with the investigators, we asked two people to be co-leaders. In the first group, the co-leaders were Dr. Dwight Mercer and Dr. Bob McDowell. Their spokesperson is Dwight Mercer.

Dr. Mercer: I would like to say that the exercise of having the clinical investigators in an open forum make some comments extremely valuable and I would encourage us to doing that more. We tried to diligently cover the assigned questions. No way can I report on those. So I am going to try to hit some high notes and say that we really did not get consensus on these points. I may have misinterpreted a point, and if I have, may the clinical investigator stand up and say we did not say that. I shall try to capture the meat of the discussions in these few moments.

The issue of motivating animal owners is not generally a problem in large animal and in the small animal area, not really a problem from the investigators viewpoint. They did feel like that there are some aspects of screening out those clients, mainly on the basis of attitude and historical evidence, that are not going to follow the instructions. Paying those people would probably not improve the efficacy very much. So, in general, in motivating the animal owners to follow a protocol boils down to an issue of integrity with regard to that client and that practitioner. He has to make that judgment.

Interesting concept is when you start picking and selecting different clients on the basis of that integrity, instead of as those cases come in, do you create any bias? In other words, when you have five cases of cystitis coming across the table and you pick three of those because of the client's attitude rather than the disease, do we create any bias and I do not want any statistician to say anything at this point.

The practitioners viewpoint with regard to the types of trials valued most--some real polarization here in the thought process. The issue is the preclinical trials. This is those trials up to and including the experimental models. The investigator's viewpoints indicate that this is really the safety data. They look at preclinical data primarily from the safety aspect. The strength of the efficacy data is based on the clinical trial. I think from a pharmacologists viewpoint, we tended to look at that just the opposite. We simply believe to determine the mechanism, and mode and the actual pharmacological activity of a compound, we need to be involved early in the well controlled, perhaps experimental model environment. When you go to the clinical field trials, at least from my perspective, you are looking for use data, perhaps safety data. As stated, investigators do not feel that way and,

in fact, just the opposite. To the practitioner the strength of the data is based on the clinical trials. I think that is an important point. It is worth mentioning, however, that in the food animal area, we all have to realize that the real clinical trials are done after that drug is approved. Because most every integrated operator that I know of, including feedlots, are going to run their clinical trials under their specific set of very percise management procedures. Regardless of what you in industry or the clinical investigator does in getting that drug approved, those guys are not going to accept the data until they run it in their system. This is especially true in the poultry industry. It is an important point, and may lend some strength to some discussion of about post drug approval, of being able to use that data. I think there is some potentially valuable data there that we are not taking advantage of at the moment.

How to select cases was another question we looked at--Again our practitioner said that when he selected a case coming across the table it is on the basis of clinical judgment. It is going to take another 12, 24, 36 hrs to get the laboratory support, so they have to make a decision in a 20 minute interval. This aspect leads us down the road to some of the reasons for throwing out a lot of clinical cases. It is also a potential area of bias. If you are doing a urinary tract infection, or anything that requires extensive laboratory workup, means cases that come in from Friday night to Saturday evening, are not going to be included in the trial because you cannot get laboratory backup that quickly. I think this issue is a real issue that may create some bias in a number of clinical cases that are evaluated.

Availability of laboratory support--Much to my surprise, our group did not believe that this is a problem. Most investigators are located close to institutions and if they aren't, they are located close enough to an airport to get samples to some of the nationally operated laboratories. Most have good turn around times. The investigators did not feel that to be a major problem as far as they were concerned.

Kinds of controls--We do not want to spend a lot of time on that but one major point was made. It is not fair to generalize or to say it is unethical to use negative controls. There are specific conditions that our investigators feel where negative controls do or can play a part. Where they don't recommend using a negative control is in an economically damaging or life threatening condition. Obviously this situation requires positive controls. They do not feel it is fair in general to say negative controls are unethical. There are conditions that you just simply can use a negative control on. Examples: coccidiosis, flea problems, otitis externa, and certain dermititis, etc.

Strangely enough, our clinicians did not feel strongly about the values of historical controls. There are a few occasions where historical controls can and should be used which I thought was interesting.

Last, perhaps not least, a burning desire to talk more about the Rx versus the OTC issue and perhaps a need for half-day symposium on that particular issue. I truly believe that practitioners believe that to be a major problem they have to contend with and I think they are probably right.

Dr. Paul: Dr. McDowell, would you go to the microphone, please.

Dr. McDowell: It was brought up by these people that they thought the OTC designation for a drug possibly should be a matter for comment by the practitioner. And I think this is a concept that I have not heard in FDA previously, and it might be taken up for consideration.

Dr. Paul: Thank you, Dr. McDowell. And to you, Dwight, and Bob, and to your group, and thanks very much and thanks for a good report. The next group was co-chaired by Dr. Terry Harvey and Dr. Bob Griffith. Their spokesperson is Dr. Bill Kay from the Animal Medical Center in New York.

Dr. Kay: I promised I would not quote anybody. And I can not remember who said what so it would be impossible to quote. Question 1: Does the informed consent aspect with the owner pose problems? Is there really informed consent or what is informed consent? Both from large animal and small in our group, we feel that informed consent is important, and generally is used although albeit, there is variation in what informed consent means from a formal written contractual type of consent to a verbal coaxing. Perhaps there are no clear guidelines as to what consent means in that regard. Litigation has not posed much of a problem in small animal regarding vilations of or misinterpretations of informed consent. And I do not know how much there is in large animal.

Should owners be compensated?--Certainly in large animal it is probably mandatory to have compensation in a fairly defined way. In small animal, that is also important and we feel that there are varying ways to compensate. By and large, little or no economic transactions, per se, reduction of professional fees, free services, free pharmaceuticals and the like. But that compensation certainly shortens the time frame and makes it easier to get people to submit to the studies and in cases where neither the disease is a simple disease, or the drug is particularly effective, wherein followup might be important because of success. A compensation is a real additive to complete the trials.

Regarding contaminate with or enjoyment of doing clinical trials--probably this group is prejudiced about as much as any group can be prejudiced. Perhaps enjoyment is not the correct word. And again, there is a variation in reward or satisfaction or enthusiasm. Perhaps depending on the seriousness of the trial whether it is a redo, a need to, a generic or some breakthrough product so there is a variation in there.

Do you personally and professionally value clinical investigations when you consider using new drugs--In other words, how valuable is the data accumulated by the process in terms of the use of, or the assessment of a new compound or new drug, And yes, we all feel there is value in studying the data. I think there is a feeling that the process is rigorous enough that there must be merit in the compound to get through all the steps that we are here debating about.

So, as to what part of the process is the most valuable? Is it dose determination? Is it preclinical? Is it toxicology?--there seems to be some variations in our group as to what was the most valuable. There are people

who feel that clinical trials are the most valuable, that toxicology and preclinical is the most important.

Are there any redo's of clinical trials?--Or is that something that happen in clinical practice. Probably no, and at the post clearance phenomenon of assessing data, or in investigators or clinicians redoing what has been done. We did not think that was happening very commonly.

Clinical case selection--And I agree with Dr. Mercer, that is probably both an impressionistic sense, and a laboratory support sense, in many cases, and there are, depending on your support systems, either a high degree of dropout or a low degree of dropout, depending upon the kind of criteria you use.

The question of whether the FDA is a good guy or a bad guy. I am not going to answer that. Thank you very much.

Dr. Paul: On behalf of you and your group, that was a good report. The next group was co-chaired by Dr. Rainer Muser and Dr. John Quast and Dr. Dallas Horton from Wilmington, Colorado will speak for their group.

Dr. Horton: Since he finished a little early, I am going to take one minute of that to tell a story that relates well to this group. It goes like this. There are two guys in Amarillo, Texas, and one looks at the other and says, "What do you do?" "I am an international, agricultural, biological, physiological consultant." This guy says, "That is a high power term. How did you get to be something like that? And who do you consult for?" "Well," he replied, "I consult for the Food and Drug Industry, I consult to the animal industry, I consult to producers themselves and I do this all over the world." And this guy says, "How do you do something like that?" And he said, "I had to go off to school." (The moral of this story is there is a hell of a difference between education and intelligence.) And he said, "How long did you go to school." And this guy says, "Well, I went to eighth grade, then I got a high school degree, then I got a B.S. degree, then I got a M.S. degree, then a D.V.M. degree, then I got a Ph.D. degree in reproductive physiology and that is the study of sex in farm animals. So how about you?" This old boy batted his eyes a couple of times and said, "Well, I quit school in the third grade." "Well, I'll be damned, what do you do?" This guy said, "I work for a feedlot out north of town here in Texas, north of Amarillo." And pretty soon the international consultant says, "Where is the action in this town?" He said, "Hell, we have just had two beers, just you and I in here." The cowboy says, "There isn't any action. This is it." And he said, "I have got to do something more exciting than this." The cowboy says, "I am just here too, there ain't any." He said, "Well, let us play 'riddles.'" And the cowboy said, "What is 'riddles.'?" And he said, "That is where I think up some complicated deal and you figure out what it is, then you think up something, and I will try to figure out what it is." The cowboy thought for a minute and he said, "Naugh, you have been off and had all that learning and traveled all over the world, and hell, I haven't been any further than Tulia, Texas, which is just 40 miles down the road here, and I wouldn't have a chance." The Ph.D. kept edging him on and finally the cowboy said, "I'll tell you what, partner, give me two to one odds, let me be first, and I will take you on." The Ph.D. said, "You have a deal." The cowboy said, "What has eight arms, six legs,

flies upside down and backwards, and only has sex in midair." The Ph.D. grabs his vest, switches from Coors beer to a double shot, downs it, dead silence, then says "God, right in my area of specialty too, reproduction, and I am going to miss it." (And they had bet $50.00 on this question.) He orders another double shot, and still hasn't got it and finally he jerks out a $100 bill and he says, "Two to one odds, here is your $100. What is it?" The cowboy says, "Hell, I don't know either, here is your $50."

Our group discussed several things, some of them have already been discussed,--after you get so far down the program, it kinda reminds me of a cleanup bill after a successful eye program. Some of these have already been covered but I thought of one that we came up with that was real unique and we are real anxious and hope we can get something done and shared by everyone at our table from all aspects in this business and that was we feel real strong that the the Food and Drug reviewers, the fact that they do not have as large a travel budget as they need and as a result, do not get the opportunity to get out in the "real world". Like one at our table said, "It has been ten years since I have had any cow manure on my shoes." That if we could develop some method like this through some form, whether it is the bovine practitioners, the swine practitioners, the animal health institute or some other form that we could help travel for the FDA reviewers so that they could get and visit with practitioners, universities, private researchers, to develop an opportunity to see what is going on the other side of all the paper work that they have to look at day after day. It would be a real plus in the overall educational process of what we are trying to accomplish. That was one thing we came up with that we recommended.

The other one was concurrent therapy.--We felt real strong that some guidelines have to be developed to test some of these products that will allow concurrent therapy so that we can evaluate does that drug work or not, but also what is the synergism or antagonisms of it with other drugs. And we felt strongly that this would not dilute well controlled studies because we would still limit it to one variable and that all animals would get the basic therapy, whatever it may be,--every other animal or however it was set up would get experimental drug X and we would still have a well controlled study and allow concurrent therapy to take place at the same time.

We discussed management site--and we did feel that geographical locations around the country as well as different management systems, particularly in the food animal side of it, are real important aspect to evaluating the product.

The practioner involvement in guidelines and protocol were discussed--The ones at our table did feel, sometimes, if they could have a little more involvement, particularly if the trial is designed to the marketing of the product rather than just the FDA clearance that the practitioner would have lots of good practical imput into those design. Several at our table, the practitioners mentioned, would like to bet a better line of communication after the trails are overwith on the followup, how did this statistical analysis turn out, if they did not have the interpretation of the data, the type of information they thought would be real helpful.

The last thing we discussed that pretty well fits food animal was alternatives in measuring response to drug therapy for disease, in addition to just morbidity and mortality--Those alternatives we suggest are the two parameters of average daily gain and the feed conversion. In other words, we are suggesting that nutritional parameters that have been used for years to measure nutritional feed additives and nutritional programs of gain and feed conversion, if they were used in food animal models, many times we would pick up economic response that we are loosing now by just limiting it to the narrow scope of morbidity and mortality. I know myself, over the last seven years, I feel strongly that we have let several products go down the drain because we only measured morbidity and mortality and we did not measure average daily gain and feed conversion. In other words, I feel that the economics or the bottom line or whatever, is important in food animal if it does make money or it doesn't, is what it is all about. And to point an example, a 1% improvement in feed conversion has twice the economic importance that a 1% difference in death loss does--twice the economic importance. So these parameters are used to measure in, what we are really saying, gain and feed conversion utilized to measure subclinical disease. And I for one and I know my other colleagues here that represent the feedlot end of this business and we also that subclinical disease is probably much more economically important than clinical disease in food animal. So we would like to see those brought into the picture.

The other thing discussed are the clinical signs when we are doing a study--We discussed shipping fever as an example. Some of these subjective signs that we are required to evaluate in the large feedlots that we work with where we have access to large numbers are not near as conclusive as as the objective ones and so this business is the nasal exudate seruous, is it mucuoprevelent? Did it hang 3" down from the nose? Nine inches down the nose? Did he breath a little bit fast? Real fast? All of these are so subjective and when you are done to put good statistics to them are very difficult. The bottom line to us is did they live or did they die? And if they lived, how many treatment days did it take for them to get better and did they make a complete recovery or did they turn into a chronic. And anything beyond that, we are not interested of in terms of the bottom line. And those are hard core objective parameters that we can measure and put good statistics and save a lot of paperwork and get to what the root of the real situation is and that is, is it profitable or isn't it? Thank you.

Dr. Paul: Dallas, I commend you and your group on that excellent report and I think you have taken a little different approach and it was excellent. The next group, the co-leaders were Dr. Ron Chatfield and Dr. Don Gable and Dr. Jeff Davidson from Tulare, California will report for their group. Jeff.

Dr. Davidson: We have to explain a little about the makeup of our group, Three of the individuals were people that own their own in-house facilities where they ran their clinical trials, one individual was a swine practitioner, and the other was a small animal practitioner. I think most of my comments will be in the area of clinical trails and food animal medicine. Not to ignore the small animal practitioner for what was said in that area but I think it has already been covered in other reports.

The first question was what problems do you have with adequate diagnostic and laboratory support--Basically, none. What you can not get done locally, you can send off so that this is not a problem with the individuals in our group.

Describe your most troublesome variables in conducting clinical trials, followups, clinical signs, diagnosis, etc?--I think this is where we are a little bit different because of the problems that these variables do pose in conducting clinical trials. That is why the three of us went to our own in-house facility. We try and run the study, the clinical trials, within our own facilities to eliminate some of these problems. So basically, the answer to that question as far as describing your most troublesome variables is all of the above and any of the above. The problem of doing a field study are these variables and each field study is going to have its own set of problems. An important point that came out of this question is, it did point out to me the importance, or how much easier it is to do a study in in-house where you can control many of these variables. Obviously, some clinical trials cannot be done that way, the disease can't be reproduced. But whenever possible, it seemed to eleviate many problems.

How do you handle case records and subsequent report to sponsors--Everybody had their own way of handling records, I think the important thing that came out of this was the importance of good records, the importance of close contact with the sponsor and developing a record system whether you use your own, or you use their system. Everybody has to be comfortable with it and they have to be complete records. An important point was the importance of the sponsors monitor in keeping track as the clinical trial progresses, to make sure those records are complete and filled out; and if there are some questions that should arise, they can be answered immediately. As far as getting back to the sponsor with the reports, of course there is all different ways of doing it. Some people send in the raw data, some people write a complete report. One thing that came out of this is the importance of a very prompt response. To try to get it back within the first couple of weeks because if you do not get it back then, it is going to be a long time.

Does the informed consent aspect with the owner pose any problems? Do you really get informed consent? What is informed consent?--I think, the summary of that is informed consent is very important. Everyone involved indicated that they go to great lengths to inform the owner of what is going on and that in most cases, the owners know as much about the trial as we do, as much about the product and that this is very important. Most individuals had their own forms, some use the sponsor's form, but regardless of the form he used, the important point was explaining to the owner, and not necessarily just the herdsman. The owner may live 100 miles away, and he is the guy that really must know what is going on and that you have to be completely open and honest, and tell him everything.

Should the owner be compensated in some way? And how?--Yes, the owner has to be compensated. There are a lot of different ways. Whether it is done directly from the sponsor to the owner, whether it goes through the investigator. Everyone has their own formula and each owner is compensated in a different way even within the investigator.

Do you enjoy doing clinical trials? Why or why not?--Again, three of the individuals at this table were people that did it for their living, that is all they did. Whether they enjoyed it or not, I do not really know but they did it for a living. The other two, obviously, enjoy doing it both for monetary reasons and for the satisfaction of working with new products. And when a new product comes out, being able to say, "I worked on that."

Dr. Paul: O.K. Jeff, and to your group, thanks very much. The next group, the co-leaders were Dr. Bill Huber and Dr. Sandra Woods. And Dr. Ed Kurley from Turlock, California will report for that group. Here is Ed.

Dr. Kearley: We had a very small group, five of us. Dr. Sandra Woods, from the FDA was there, Dr. Bill Huber, he is kind of an old man--he had wisdom and kept his mouth shut and summarized everything. Then we had three different individuals from three different walks of life, we had Dr. Jeff Wilke from Virginia Tech, pharmacologist and he looked at the academic aspect, I'm sure, or least that is my interpretation. Dr. Bob Kohn is from Rosyln, New York who is more scientific, I think, not more scientific but lives in a more scientific world or let me explain that, and then there was me. Finally, Bob classified me and I never had been classified like this before. He said I was street wise. He grew up in New York City and he considered me street wise because I washed the manure off my boots about ten times a day. I am there every day and this is not my normal uniform. We had three different answers most of the time. Bill was very good at summarizing this because he could take all these opinions and put them in about two words.

Do you enjoy clinical trials?--It was mixed answers.

Do you want to contribute?--And this contribute, we assume was contribute to the protocol or to the study and all of them agreed we would like to contribute to the protocol some. I think, to some degree, I do contribute over the phone.

Do I like clinical studies?--Boy, I do because I have been in private practice and I do not like night calls any more and I do not take them. So I had a different outlook on this. I really like the money too.

Do you follow the protocol that the company gives you?--I figure if they are paying me, I will do what they want, that is my basic philosophy.

Do you personally or professionally value clinical investigations when you consider using a new drug?--We took this statement to mean that it was a new drug and not even on the market. I have got to look up how we answered that one. It was a modified yes, because each of us wanted to evaluate it ourselves.

What type of drug safety and efficacy studies do you value the most?--That was primarily they looking at concentration and effective data. Secondly, the range of safety at the labeled dose. And the last thing which could also be the first thing, was the drug class--how dangerous was the drug.

Number three: Does the practitioner tend to do clinical trials before he subscribes to the new drug?--This was unanimously yes. In your own mind, you redo clinical trials in your own way, until you develop faith in the drug.

Number four: How do you select your clinical trial cases? We all agreed, basically, the first thing we consider is the owner of the animals--the attitude, and the cooporation that the owner will give you. And then secondly, we consider the animals that we are working on but we believe the protocol should be followed. At least Sandra thinks we should follow it to the "T." Right, Sandra? Sandra, I would like you to come out to Turlock sometime and I would love to be your host. We had a nice discussion, really.

Question number five: If a valid model for a given disease or condition was available, what could clinical trials contribute to the evaluation of a drug? --Well, to summarize that, Bill was our summarizer as I mentioned, basically it would be safety. The model is very good for (if you have an adequate model) speeding up the evaluation of a drug rapidly. But then once you get some safety and efficacy data, the main thing that the clinical trials do is give you enough numbers for statistical data.

The last question, I think it was. How do you motivate an animal owner to follow the protocol or your instructions? Number one: it is monetary. And the other thing that I think is important is (and I am looking from large animal primarily at someone else's dairy) and that is, can that be of use on the dairy if the drug works. That is a prime criteria for me. That is all.

Dr. Paul: Ed, thanks to you and your group. We appreciate your report. The last report will come from the group where the co-leaders were Dr. Bill Jenkins and Dr. Charlie Hanes and Dr. Dave Aucoin who comes from The Animal Medical Center in New York. The Animal Medical Center is well represented this morning. Dave.

Dr. Aucoin: Thanks for the opportunity for going last. It makes the job a lot easier. Most of us agreed with some of the things, and some of us agreed with most of the things and being veterinarians, none of us agreed with everything. The group is made up of basically large animal types, I was the only small animal person here other than Dr. Davis who swings both ways. I don't mean that. Now do not take that the wrong way.

Basically, in a summary of what differences we had or some special things that were brought up--Definitely doing case reports was the biggest thing and reporting case reports requires somebody be an organizational supervisor. That is somebody in charge of making sure that all the forms are in fact filled out correctly and being on the tail of those people who actually fill in the blanks. So having an organizational supervisor was very important to one of the people in our group who has three practices and does a great deal of clinical trials.

Computerization was not mentioned before, but with people who do a large amount of clinical trials computerization becomes a very essential part of maintaing records. The FDA will not obviously accept computerized forms, but it certainly makes it easier, I think, for the person doing the clinical trials to keep track of what is going on. Maybe one of these days, the FDA will accept them. Computers can lie, however. Case reports probably lie too.

The second thing was whether or not the owner should be compensated and informed consent--Basically, we felt it is also almost in the same category, in that in order to have a clinical trial the protocol must be followed. The owner has to feel that he/she is part of the project. So, smoozing or developing that good client/doctor relationship is important. Which means if you are going to inform them of the project, you really must talk to them about it. In small animal medicine, we spend a great deal of time talking to them about the project that they are going to be involved in. And whether or not they are informed or not obviously depends on the person telling them which is the bases of why informed consent forms probably aren't very legal. But we feel the informed consent form basically tells the people what they are expecting or not expecting in the project. It is sometimes difficult to double blind a study. On the informed consent form they read the bottom line and realize that their animal may not get the drug. They are more willing to go on the project if they know they will get the drug being studied but if they do not know, they are less willing.

Emotional and monitary compensation--Emotional compensation is particulary important. You can not treat the client as if they are not a part of the project, particulary in large animal. That is where the money comes in. You are talking about spending a lot of time with these people, especially in feedlots or on dairy farms. And if you are going to spend a lot of time, it is going to cost you money. But you have to have them on your side because then they will follow the protocol. The best way is to follow the protocol is obviously have the people involved in the project.

We did have a difference in our enjoyment of doing clinical trials. The academicians did not enjoy doing clinical trials, they like doing model studies. The clinical trial once set into protocol form is basically cookbooking and not very exciting for the academician. An interesting point brought up by Dr. Davis was that perhaps the end-points that the FDA is looking for can be changed. For instance in a mastitis test, instead of doing a California mastitis test, why don't we do something like a Gamma camera analysis of the teats. By doing Gallium scanning for instance, you can test for infection sites. Now that is something that someone in industry would love to do. It would only cost about $1200 a cow. Seriously though, there is a lot of high technology available to clinicians and we are still using a lot of the techniques that we used back twenty years ago. If you make it more interesting to the academicians to do the study, they are more likely to do it. We do not have to go to the extreme of Gallium scanning but we can make use of different methodologies to make the results a little bit more intellectively stimulating.

Redoing clinical trials--It was interesting, most of the people at our table said that they did redo clinical trials. When a new drug came on the market, they retested it themselves in their own practice. Meaning that they were careful about going "gung ho" and selling it because as some of the people have said they have been burnt before. Feedlots, I must be careful, obviously, of pushing a product until one has a good feeling for the project because of the economical considerations involved in such large studies. So at least our group felt we did do clinical trials on our own after the drug was released. I think that is all we had to say.

Dr. Paul: Thanks very much, Dave, and to your group and to all the people who got up early and have put in a day's work, we really appreciate it. We are running short of time so I am going to turn it over to president-elect of the AAVPT, Dr. Bill Jenkins.