

April 18, 1985

Section I - 11:00-11:30 Open Discussion

Dr. Paul: Thanks Tom, if you and Lloyd will take a seat here at the table, we will proceed as we did with the last session, and take all questions and comments from the floor. I want to remind you to please step up to a microphone and identify yourself. So who has the first question or comment?

Dr. Paul: I will lead off. This is Dr. Paul from American Hoechst and this is for Dr. Davis. When you talked about the tremendous resource of animal patients going through the veterinary medical teaching hospitals, one thought came to my mind. That has to do with some individuals in academia who feel (if I may be permitted to say it this way) that it is beneath their dignity to conduct a clinical study for a drug company. The other problem is some of the tremendous overhead figures which the university administration adds onto the cost of a clinical study. Would you comment on those two situations.

Dr. Davis: I alluded to the second point, John. I have been known to make the comment, during some of my worst moments, that the universities have become nothing but big cash registers that process money. I am sure it has not degenerated to that point but we are seeing that emphasis. I think that in the universities, it is go out and get the buck, it does not matter what you use it for as long as you get it. So the universities are guilty of avarice. They are not guilt free, either, in this triangle that we are talking about. There is certainly criticism to be directed there.

Some of the problems that arise in the clinical trials is that many of these people, particularly some of the young people, are really sharp intellectually. It is not so much a value judgment that it is beneath their dignity to conduct a drug trial but I think what turns them off is they view this as if they are a highly skilled clinician who is being asked to serve as a technician because everything is "canned." There is no room for judgment, they are asked to just fill in the blanks. That is very boring to them. Historically, and I am not really that old that I have that enormous perspective, but I think at one time the clinical studies of drugs conducted in an academic environment were exciting. There was flexibility and freedom to really explore the potential of a drug. To learn about pharmacology and the interaction between the organism and drug. A lot of that has been squeezed out because of the need to fulfill regulatory requirements. Gentlemen, that is boring work, it really is, as compared to research where we have got a degree of flexibility.

Dr. Paul: Do you want to comment on that Tom.

Dr. T. Powers: Yes, I think again, this is another good argument for the veterinary clinical pharmacology unit (VCPU). If you can channel these studies through a unit such as this, you could give (VCPU) the opportunity not only to do the clinical trials study but also enable them to generate some money so that they could also do some of the basic research. I see a clinical pharmacologist as the one who is going to go from case to case

and monitor it several times each day probably as well as or even better than the clinician would do. If we can get more VCP units set up across the country, I think it will not only put money in several more universities back pocket but will also enable us to develop new science to be applied to clinical trials.

Now as far as the overhead on research, again, the federal agencies are the ones that dictate to us what our overhead will be. The federal agency and our Research Foundation determine what our cost were for the preceding year(s) and from this they determine what the overhead for the coming year will be. These overhead costs vary across the country, but are usually between 40 and 60% of the original budget. It can make a \$40,000 study turn into a \$60,000 study.

Dr. Paul: Thank you. What other questions or comments do you have?

Dr. Lloyd: I am Gene Lloyd from the Vetamix Corporation. Our experiences indicate that veterinarians in the field often lack objectivity, scientific approach in just keeping good records. I can comment on that because I spent over ten years in practice and ten years in academia. I would like to ask Drs. Davis and Powers if they are addressing this problem and if so, has it been successful?

Dr. T. Powers: Again, the only way you are going to obtain good studies and get objectivity from the veterinarian is to train him properly. If we have on going studies in the veterinary hospital that are done correctly, then the student has the opportunity to learn by simply observing what is being done or by actually participating in the study. When he graduates, he should have more objectivity. Another thing we have done at Ohio State, as several of the other schools have also done is that experimental design and statistics are a part of the required curriculum. We have it in the freshman year as a formal course. We need more emphasis beyond the freshman year, that is during their clinical studies in the 3rd and 4th years. I think, though, the emphasis on clinical pharmacology, that is the role model of a clinical pharmacologist and his residents in the hospital every day, is needed to solve this problem as we would like to see it solved.

Dr. Davis: I think a couple of things could be done and I am sure you probably face this at Ohio, too, Tom, that there is really a need to have assigned space in a hospital and so on to provide visibility so that this is a service just like ophthalmology, neurology and the other specialties. Just about every human clinical pharmacology unit I have visited has a ward for patients that they can involve in studies. We have never had this in the veterinary schools. So we are always in a position of having to beg for space that is generally encumbered by more classic functions of the teaching hospital.

Another place I think we find a discontinuity, and I addressed this at the dosage symposium, is that we are doing a better job of educating our students in some areas than the field is ready to accept. Well, the students I am working with right now are within a month of being inflicted upon the public. I get the last shot at them before they graduate from

school. I feel fairly confident that these students can go out and individualize dosage and make other therapeutic decisions. But they are left with products that just list a single dose. I would still appeal for consideration of changing labeling requirements, to a degree, to represent a therapeutic range rather than just one dose. I understand the reason we do not do that. That goes back to the Durham-Humphrey Amendment which is at the heart of a lot of our problems. Industry is required to write labels for over-the-counter use which means one dose.

Dr. Washington: I am George Washington, a practitioner. John, maybe you could answer this. How do the drug companies reimburse the practitioner? I think this would play a part on what you get if you are paid for your time and all this instead of a little bit of drug to use free. Because it is a part of the practice if you are paid for your time just like a consultant is paid for his time or Tom is paid for his and not expect it to be done free just for a little bit of drug to use.

Dr. Paul: I would be glad to answer that, George, and if others from industry would comment on it, we would be happy to have their comments. It is important to have a business agreement with the investigator. Part of that agreement is an agreed upon fee per case. It should be sufficient to reimburse that professional for his or her professional time. We have found that if we give drug to someone, there is no real vested interest either for the investigator or the pharmaceutical company to get the data back. Until that data comes back we really do not have a trial. It is a good question. Does anyone else from the pharmaceutical industry have a comment on that.

Dr. Dawley: I am Dr. Bud Dawley from the Schering Corporation and I think everyone today with clinical trials do a first class study per animal and do compensate the investigator. But if what Dr. Davis tells us is true, that we have doubled the number of veterinarians in this country in the last ten years, the case loads have not increased to that extent. Each individual veterinarian is going to begin looking around for a little more work to do to make a living and that will make him much more informed and objective. I do not think you will have to teach him anything else in school. I think he has to make a living and that is the way he is going to do it. I do not think we will have a problem.

Dr. Paul: Dave Aucoin has been trying to get to the microphone.

Dr. Aucoin: I guess I finally got here. This is a question to Dr. Davis and you John, too. Dr. Davis, you brought up your point of using a phase four trialing system. I am involved in a human clinical pharmacology unit now at Cornell for three years and they do well over \$100,000 a year in clinical trials. It is a super system. The question I have to ask you is do you think that the problem with the system lies in the regulatory agencies which may gum up the works by not allowing the investigator to go from one to two or two to three without the data being complete? My question, and maybe Dr. Paul is that the expense of this system to industry is incredible as known by the cost of developing a new drug in

the human market. It doesn't say if we follow their system it will be the same cost but what I get from the veterinary developers of drugs at the Animal Medical Center; they complain of tens of thousands of dollars and what we are talking with the phase four system is really millions of dollars. I wonder if we can go to a phase four system or invent a new system, perhaps, rather than to spend the money in the regulatory actions necessary to go through that. Maybe you can comment, Dr. Davis and then you, Dr. Paul about the money involved in that sort of system.

Dr. Paul: Lloyd.

Dr. Davis: I am not terribly hung up, Dave, on necessarily having to mimic that classical system which is used for people. It just seems that it does provide a very logical sequence of development of information that has always impressed me scientifically. I think any way that we look at it drug development is going to be expensive. I guess where I may differ a bit is from the general emphasis--you know we are placing most of the emphasis on this meeting on clinical trials which is within that system's phase three. I believe that the really hard rigorous, useful data is acquired prior to that point. If it isn't, I do not think we ought to be out working with a large number of patients because we are asking people to fly by the seat of their pants. The scientific rigor really should lie in what I am now calling phase one and phase two trials. You know, it has not been very long since we had no pharmacokinetic data in the development of new drugs. It just has been within the past 20 years that these concepts have come about. I think if I were doing a scientific study for a sponsor, one of the first things I would want to know are these disposition and toxicity data before I even planned a study at a little more advanced level. The study, which Dan Gingerich discussed this morning, sounded to me like a nice, orderly, scientific, logical approach to learning about a new drug. I do not know if that answers your question, specifically, or not, Dave.

Dr. Paul: I will try to take a crack at it from the other side, Dave, but I will need some clarification. You are suggesting that the phase method of drug development could be extremely costly. Is that it?

Dr. Aucoin: Yes, that is correct.

Dr. Paul: Is that because of the large number of patients that would be involved in phase four? I need clarification on why it would cost so much more.

Dr. Aucoin: Yes, phase three just involves large centers and large numbers of animals. The statisticians here are better at it than I am but if you are going to introduce a drug into a population where there are many parameters, you need a large group of animals to eliminate bias. So what I see now in clinical trials, what we call phase three in human medicine, they would call really phase two. We use a few hundred animals rather than thousands and thousands of animals, depending upon the product, of course, which is expensive. If we go to phase three where we are literally testing a urinary tract anti-infective against ten and twenty thousand animals, that is where I think the money is. Yes, phase four could certainly be money but I would think phase three is where

industry could get a lot of problems. By the way, I am not advocating that system, I like this system. I think we could come up with a new system that would sort of be better than what we have now and not quite as regulatory as what they have in human medicine.

Dr. Paul: I still can not give you a direct answer, Dave. I am not trying to avoid it, I would have to actually see what the figures would be. I know that there are some drugs that have been introduced recently where there have been literally thousands of patients involved in their testing. It has to do with the type of drug and the kind of data that you need, so I cannot give you an absolute answer. Possibly someone else could. My colleague, Dr. Muser, was headed for the microphone a moment ago and if you still want to do that, possibly you have comments, Rainer.

Dr. Muser: Not on this particular subject but also related to money. I think there is another side to the coin. I would like to say something that has been on my mind for quite a while. I believe academia has an obligation to spend time on the evaluation of animal drugs for the benefit of the public, for the benefit of the students going through the schools. How it is being done is a different story. I would like to repeat what has been said before: I do not think we will satisfy the needs of everybody concerned if we concentrate on post-graduate programs. I think the veterinarians who graduate from the veterinary schools have to have a basic idea of how to look at a drug so that veterinarians do not draw conclusions based on what they found in one or two animals.

I would like to say another thing concerning money. We have actually received letters from lay people, not veterinary professionals mind you about drugs used by veterinarians which said "We would like to have results from a study by someone who you did not pay because anybody you pay is biased and does what you want him or her to do." So I think there is another side of the coin, so to speak, of spending money on clinical studies. I do not have any problem with it whatsoever, but I think it is a legitimate concern that someone might feel compromised if we offer money in terms of a professional fee, or whatever. This needs to be considered. Within reason, I think, any company nowadays is prepared to spend money. Thank you.

Dr. Paul: Dr. Mercer has been patiently waiting.

Dr. Mercer: General comment as a follow up to Dr. Powers' comments regarding the training programs for veterinarians. I would like to emphasize a point that the government, federal regulatory agencies, as well as the pharmaceutical industries themselves, are looking for and need a well trained individual to run clinical trials and generate this data. We at the university level are spending, depending upon whose numbers you are looking at, \$18,000 to \$22,000 a year to train a veterinarian. This veterinarian is going into the field at \$18,000 a year. The training costs continue to escalate. I just ask one question. Does government, the drug industries, FDA, EPA, as well as other government agencies, have any basic responsibility for assisting in the costs of the training program?

Dr. Paul: Does anyone care to answer--yes.

Dr. Urbeck: I am Dr. Urbeck and I am a small animal practitioner and I conduct some clinical trials. Kind of in response to what he was saying I would like to say that personally I do not think I am very bright but yet I felt that Dr. Tom Powers spent about fifteen minutes describing me. I consider myself a veterinary clinical pharmacologist when I am running clinical trials. Dr. Lloyd Davis said we need knowledge, skills and special interests. I hope that with my running a clinical trial for a company that I do have that. There is one thing about this idea of knowledge and Charlie touched on it.

Knowledge comes with people that are smart and we can have a lot of knowledge but one of the things we can not have that we need to have, and that only comes with experience and a little bit of age, and that is wisdom. We need that, too, when we are running these clinical trials. I find myself a little bit distressed when I run clinical trials with the low amount of esteem that the federal regulatory procedure places on my clinical judgment. As an illustration to this might be the issue of controls. To me when an animal is sick, if it gets better, it has served as a control and the medicine that made it better has helped in my clinical judgment of all the factors that Tom was talking about in making me a veterinary clinical pharmacologist in saying that this particular animal responded to the particular medicine I was giving to the animal. Yet that clinical judgment in a single animal control is given absolutely no value in these clinical trials from the standpoint of my entire investigation.

Dr. Paul: Dr. Jenkins wanted the floor, I believe.

Dr. Jenkins: There are two unrelated comments that I would like to make. First, we are in an era with a variable explosion of knowledge in pharmacology. There are now almost two populations of veterinarians in a sense. Some of the older practitioners, and I count among those in one way, just do not have the pharmacological basis that exists today. I think we do a great deal more at the professional student level now and recent graduates have a more solid foundation. However, some of the older practitioners, and this is where I support you, enjoy wisdom of experience which some of the younger practitioners perhaps do not and they in turn need the additional training and exposure. I think this is where continuing education and other similar programs become very important. I have discovered something not to be true that I was often told at continuing education meetings, namely, that practitioners just want to learn something that they can use the next day in their practice. This is truly not the case. I find them to be hungry for basic knowledge of pharmacology. I would support additional training both at Tom and Lloyd's suggested levels. We dabble in this ourselves as well as provide programs at professional continuation education meetings.

The other point I would like to make is simply because I am a member of the Center of Veterinary Medicine's Advisory Committee and we have not enjoyed much credit yet this morning. I would like to note that in its early days for the Committee, gestation and parturition are over but it

is still a very, very young body that is only just finding its feet. I would in no way discount a very active, positive and contributory role for this committee. I would expect that role to be played in the future. Thank you.

Dr. Harvey: I would like to respond to the challenge posed to industry; it seems to me there are enough places under the sun for all that we have heard this morning. There is no way we can replace the experienced judgment from clinical practice. That will not occur at an institute of higher learning in my opinion. But we need both kinds. We need the centers of excellence that Dr. T. Powers is talking about. Somebody has got to make some decisions early on. We talked earlier this morning about perhaps tightly controlled clinical trials. These kinds of places that have these residency programs may be the places of choice for that before broadening it out to the number of practitioners involved. As an aside, on behalf of Monsanto, let me tell you that we are strongly urging and supporting, not only with the psychological pushes but with bucks, a major grant program of training and research with Washington University in human medicine. I believe industry has a responsibility to help, in fact, fund these chairs and make those centers the best they can.

Dr. Paul: Dr. McDowell.

Dr. McDowell: Dr. Bob McDowell with the Food and Drug Administration. I think we in FDA are being chastised somewhat. Probably a lot of it is earned by ourselves and a lot of it is not. I would like to cite a case where John Paul would be able to back up this word and that is on a case of fenbendazol, the most recent approval involved migrating larvae. Previously Bob Griffith said "the agency would offer a waiver of controls." Well, in the case of fenbendazol for migrating larvae, we not only waived the controls but we waived the clinical trial. I know when I prepondered this in the Center that we could not tell whether that horse, it would be impossible to do clinical trials for the migrating larvae. And I can recall a meeting where John Paul just about lost his teeth when we proposed that it also be an over the counter drug because the veterinarian and the horse owner would probably be no better position to determine the inside state of the mesenteric artery with respect to the migrating larvae. So there is flexibility in the agency and I think that we should be recognized that we will be willing to work with you and create a better circumstance for drug approvals.

Dr. Paul: OK, Dr. McDowell, I will support you. There were, of course, controlled efficacy studies in a laboratory setting. You did waive the requirement to do clinical studies, either controlled or not, and I would like to recognize you for that enlightened measure that you took.

Dr. Patterson: Let me answer this as long as you are all going out on this waiver business, I also want to point out that Adaquan came to the market with a waiver, hyaluronic acid came to the market with a waiver so when you challenge the agency as not being flexible, you are not being quite fair. I can name a few others, but I think that serves the latest two. We do have flexibility and you know that, John.

Dr. Gingerich: I would like to make a couple comments based on the two papers this morning. One, Lloyd, regarding your suggestion of conducting phase I, II, III, and IV studies, I maintain that we are already doing phase I, II, and III studies. At least at Bristol we are phasing and I believe several other companies are as well. The only difference is we are not calling them phase I, II and III. We are simply doing them but not calling them phases. I would be very cautious about changing the terminology. Whereas I think you hit the nail on the head, if we begin to use the terms phase I, II and III, we are inviting more regulatory activity. And whenever I get a chance to vote against more regulatory activity, I always vote against it.

The other comment is regarding the half million clinical cases that go through the colleges of veterinary medicine, we recognize that as a very valuable resource. But frankly, it has not been a resource that we have ever figured out how to tap. I do not think it is because we do not believe it is a resource, I think it has more to do with the academic institution not really coming to grips with the regulations. So when we come and ask you to consider a protocol that is too simple or too boring or any of the things you have been talking about, that is because that is the regulatory climate in which we must operate. That is regulatory reality. If you wish to participate, you must do so by coming to grips with the regulatory reality that we face.

On another matter, I would like to ask someone from FDA, and I do not care who, but someone made the comment about the clinical pharmacology unit where the clinical pharmacologist examines the case, looks at the drugs, etc. and then decides what dosage and route of administration should be used. That is not supposed to be something he or she can decide under current regulations. The approved dosage and route are already on the package insert. So I would like to have an FDA person comment on the acceptability of a clinical pharmacologist making such a judgment.

Dr. Paul: Anyone from the FDA who would like to respond to his question?

Dr. T. Powers: You see his question is going off label, Marvin.

Dr. Norcross: While I consider the answer to this question, let me ask a question and make a comment on some of the other comments that we have enjoyed this morning. First of all, as far as pharmacologists, Tom, that comes back to your area. There has been and there still exists a tremendous shortage of trained pharmacologists in the United States and the world today. If we want good research and we need good research to be responsible to the Food, Drug and Cosmetic Act, then we must have well-trained people to carry out these studies. Some of them, even are boring. I think folks that have been involved in research know that collection and documentation of data, seeking the truth, is not always an exciting area. So, we have a shortage of trained pharmacologists. Industry responded by saying yes, we recognize an area of responsibility to train more pharmacologists and I think we in the Center for Veterinary Medicine agree with that 100%. We offer long training studies; programs where we send people for training and they return well-trained in this area. I would further submit that the research studies that we do, for

example, in the consortium program contribute to good science in this area. There is a shortage of pharmacologists. We recognize our responsibility and with our limited resources are doing the best we can to alleviate that shortage.

Now, Lloyd, you brought up a very interesting point in your discussion on phasing. Dr. Gingerich addressed it, and I agree with you. We are phasing our studies. I would ask a question of you and John and members of industry who are not submitting these studies to the Center of Veterinary Medicine in a phased fashion. Is this something of benefit to industry, and if so, I would like comments on that.

Now the point you brought up, Dr. Gingerich, regarding the question can clinical pharmacologists then decide the route of administration and the dosage in a particular case. Then you mentioned the extra label policy. The answer to the question is "Yes." Under the extra label policy, he can do that. I think the policy has been discussed adequately in the past year or so and this can be done within the guidance provided by the extra label use policy.

Dr. Paul: OK, Marvin, I will respond to your question about phasing and submission in phase. As I recall, that was one of the recommendations of our Task Force from the Third Symposium of the AAVPT that was held at Ohio State. Is that right, Tom?

Dr. T. Powers: That is correct. We purposely did not use the word "phasing." Instead we requested a segmental review in process an attempt to stay away from what is described as the phasing of the human drug review process.

Dr. Paul: Yes, that is as I remember since I was part of that. Since I am from industry I would like to give other people from industry an opportunity to respond to Dr. Norcross's question about whether it be segmental review or phasing of studies in the submission to the FDA.

Dr. Davis: I would like to comment on Dan's comments. I do not think there is anything sanctity about the phasing. The point that I am particularly interested in, though, is that when we are developing drugs for the animal health market and since we are veterinarians, that our function is clinical. I am seeking the broadening of what is regarded as clinical investigation. I think generally, it is narrowly viewed as being the clinical trial. All the studies being done in the target species truly are clinical from a veterinary point of view.

Dr. Gingerich: I would like to pick up on that point and give one warning. That is if you begin to call all those studies clinical trials, then you have regulatory implications that we do not now have. So I would be reluctant to do that also. We now know how to deal with the regulations we have and the guidelines we have. Let us not be too free with the change of terminology on things like clinical trials. I agree with your concept but I am reluctant to change the terminology.