

April 19, 1985

Section III - 10:30-11:00 Open Discussion

**Dr. Jenkins:** "Clinical Studies: Management and Evaluation of Performance" is open for discussion.

**Dr. McDowell:** I do not think I have ever put in so many appearances before and after discussing yesterday, I have some comments I would like to make and eventually get to some of the discussion this morning. Yesterday, Tom Keefe said he can not alter a clinical report. But that would not preclude industry having an addendum sheet attached to their clinical report and if the clinical pathology is not addressed or if there is not an adequate approach to target organ toxicity, I think this could be part of the report and attached to the clinical responses.

This morning I noticed another thing. We had a discussion as to what an adverse reaction is. I said and I have heard this raised around FDA that if you give levamasole to a dog and you expect vomiting and everything else that everyone else have heard about levamasole, one person said, "Well, this is reported, we know that this is not an adverse reaction because it was already reported and so we expect it." And the other approach is, "Heck, this is not something you would want the drug to do. It is not the intent of the drug to produce that reaction. It is used as an anthelmintic. This is not the usual reaction that you want from an anthelmintic." So there should be some discussion of what an adverse reaction is and we may, in fact, be benefited by having an adverse check list because I think adverse reactions are not adequately handled and it is probably because there is a burden. It might be too much of a burden in its present format, or lack of format, for handling adverse reactions.

And finally, I will address the issue to Rich Carnevale, here. When I heard him saying finally here is the clinical testing which he was proposing here in the end would primarily be directed toward efficacy. I think that there is inadequate means addressed in the present protocols for safety and I think that this should be beefed up. And if anybody, including Rich, or anyone else wants to address it, I will be happy to listen.

**Dr. Jenkins:** Thank you very much, in fact, all three of your questions are targeted at that very point. I wonder if the panel would like to comment. Can we start with Bill and just move across, if you like.

**Dr. Kay:** Rich, why don't you start with that. I missed the question.

**Dr. McDowell:** Well, one of the questions is what is an adverse reaction, whether it is adverse to the animal or if previously reported, it is no longer an adverse reaction? I think that this has to be defined. The second was an addendum report to the clinical evaluation, if it has not addressed safety issues or there is something in the clinical path which may be indicative of a safety issue. I think it should be the responsibility of the drug sponsors to address these issues. And finally, whether we should be heading towards efficacy in the clinical response and not really addressing safety as much as we might want to.

**Dr. Carnevale:** Well, Bob, I will comment on that last question about safety. I think we have fairly rigorous safety requirements in our target animal safety guidelines that address safety fairly well, at least in the laboratory sense. I am not sure what you are getting at with regard to safety in the clinic. I think that has always been a part of clinical field studies. What more rigor would you propose we apply to safety in the clinical field studies.

**Dr. McDowell:** What I had in mind was the target organ response and I see that this is not really being done. At least in the work I have been looking at for the last month. It is overlooked completely.

**Dr. Carnevale:** What do you mean by target organ response?

**Dr. McDowell:** Nephrotoxicity, where you have the inability of the animal to concentrate urine, where you have albuminuria and things like this coming through and it is not being addressed. So these are areas that indicate a problem with a drug and the animal's response and I think, at least in the present format, it is not being adequately addressed.

**Dr. Carnevale:** How do you propose we address it?

**Dr. McDowell:** This, I say, if they do not expect the clinician to do it, I think it is the responsibility of the drug company to explain the problems. Like if you have albuminuria in an animal before you. It means the glomerular membrane has increased porosity, it is leaking, because albumin should not be in the urine. Or things of this nature. There is a lot that appears there and that we are not really getting the response from industry on.

**Dr. Jenkins:** I think it is only fairly, then, to tell our industry representative to comment on adverse reactions. Yes, Jim, please.

**Dr. Carnevale:** All the case reports that we design have a place for the investigator to record any adverse reactions. Secondly, if we are working with a drug like an aminoglycoside that is nephrotoxic, we do renal function tests, before, during and after drug administration. I think we are fulfilling any of our obligations in terms of our reporting adverse reactions.

**Dr. Jenkins:** Bill, if you would respond.

**Dr. Kay:** I think the issue of an adverse reaction is either untoward, unexpected or unwanted. I think there are varying types of adverse reactions. Those that ought to be recorded, if something, and we can take levamisole for a minute, the fact that some animals vomit and that it is known that some animals vomit does not mean that vomiting should not be reported because the amount of vomiting, the persistence of vomiting, the frequency of vomiting is as important as knowing that from time to time an animal vomits. Let us talk about salivation, which might be considered to be a very minimal side effect or adverse reaction. We have been involved with the FDA's adverse experience program for many years. If, after reporting 200 cases of a particular product causing salivation, it is

probably legitimate to say enough already, however, only when someone has made the determination that salivation is indeed persistent, perhaps it is consistent, perhaps it is very, very frequent, until there is a broader scope of knowing how adverse "adverse" is, it is probably important to report them, albeit that they might be in some cases, reasonably well known. Most adverse reactions are not as well known as they will be in the future. We will know more about whatever reaction we report if we continue to report them.

Dr. Jenkins: Thank you Bill.

Dr. Swenson: I appreciate all your comments, Rich, as the sponsor of the drug, clindamycin, I concur with everything that Tom Keefe and Dan Gingerich mentioned yesterday. I am very sorry you did not continue to share with us your thoughts because I think it would have been very helpful if you had spent another 10 min up there, it would probably have been more beneficial than this forum or format that we are in right now. I would like to make one comment and that is the last dose determination symposium, you and I sat on a task force and we heard a member of CVM mention that there was a potential for a change and shift in attitudes about label claims with antibiotics as it regards to "diseases caused by." In other words, in going back to the old labels that we used to see 10 yrs ago, diseases caused by organisms sensitive to antibiotic X such as i.e. Would you comment on that because I was very encouraged in 1983 and I have not seen any changes in attitudes yet.

Dr. Jenkins: Clearly your question, Rich.

Dr. Carnevale: Yes, I remember that discussion in 1983. Unfortunately, I do not think much has changed since then. I would like Bob Griffith to respond to this question. I still believe our policy has been to operate on that 20 case per organism rule and that is what I would like us to look into. Now, if we have not done anything since 1983, maybe it is time to do so now. Bob, would you want to comment on current policy in your division?

Dr. Griffith: As a rule of thumb we have ordinarily considered a minimum of 40 cases necessary to constitute a viable clinical study. That is, for each indication, 20 cases per organism with the test drug and 20 cases with the control. If there are two organisms involved for the same indication, it would be 10:10, 10:10. This is basically an arbitrary standard, but we felt that it was a reasonable starting point. It's not written in stone. We have been flexible in applying this criterion. We have approved several products that did not specifically meet the 20:20 standard. Although utilized with flexibility, we recognize that the standard has been the source of some concern. We're willing to consider any reasonable alternative to verify the identity and clinical drug susceptibility of pathogenic organisms associated with infectious diseases. Perhaps this is a very appropriate issue for consideration by the Advisory Committee.

Dr. Carnevale: And let me add in all fairness to the folks that devised that policy, that we really did that at some urging from the industry.

There was much concern that we were not telling the industry what we wanted. For example, "How many cases do you want? - What is a valid claim?" So we set this down as guidance and when you look at it, 20 and 20 seems like small numbers, right? But when you get into the clinic, it is hard to do. So it was an attempt to try to set down some reasonable standards. As Bob said, I do not think it is written in stone. I would like to see a change in that policy because it has caused us some difficulty. I do not like the single organism labels anymore than anyone else.

But then again, one more comment. The reviewers need to base their decisions on some basic organism efficacy, some standard, and that has been in the clinical study. Now, if it should not be in the clinical study, then this group should advise us how it should be done. How do we label these products for organisms when we do not have adequate clinical data on each and every one of them.

Dr. Jenkins: Tom Keefe is going to do just that.

Dr. Keefe: What I would like to suggest may be a little more flexibility, Rich. Twenty organisms is not unreasonable if it is per organ system, for example, skin/soft tissue. But when it is 20 organisms for abscesses, 20 for abrasions, etc., it is a little overdoing it. It is your requirement of 20 cases per subdiagnosis that is killing us as far as getting enough cases. So if your requirement were for 20 organisms from skin/soft tissue, from respiratory, or from a system rather than subdiagnosis, I think it would be a lot more helpful.

Dr. Griffith: We have also granted a claim for a given organism based on a model study if you had clinical data on other organisms.

Dr. Jenkins: I think we will take one more question and then close it.

Dr. Dawley: This is just a plea, let us for goodness sake, let us make sure the Task Force addresses this this afternoon. I do not know A, B or all three of you.

Dr. Jenkins: That is not a question, that is a plea, so we will take another one.

Dr. Jenkins: You have been a very good audience this morning and shown great fortitude through long sessions so I think it is time to close it but before I find time to thank our three panelist then is to remind us 1) about paying your account now, if convenient, 2) if you have an interest in the Hawaiian Islands to see Ron Chatfield and with that then, to Bill Kay, James Rourke and Rich Carnevale, I would like to express our gratitude in the usual way. Thank you very much.