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FOOD AND DRUG ADMINISTRATION  
CENTER FOR VETERINARY MEDICINE

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C O N T E N T S

DISCUSSION OF QUESTION 4	
CVM Presentation:	
Dr. Patricia Leinbach	4
DISCUSSION OF QUESTION 5	
CVM Presentation:	
Dr. William Marnane	34
Final Review and Recommendations	58
Discussion of Additional Issues Raised in the May, 1997 VMAC Meeting	62

P R O C E E D I N G S

MR. GUIDOS: This morning we are going to start discussing question no. 4. Dr. Patricia Leinbach from CVM is going to give the agency's presentation.

**DISCUSSION OF QUESTION 4**

**CVM Presentation**

DR. LEINBACH: Good morning.

[Slide.]

I am going to very briefly summarize CVM's position on this question no. 4 which is, "can sterility validation be reduced without increasing the risk of microbiological contamination?"

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The agency has already substantially reduced the validation data for aseptically processed products. I put aseptically processed products here because that is the predominant procedure that is used in sterilizing veterinary drugs. It also applies to other processes, which would be terminal processes, but I am not going to concentrate on that because those processes are not used that much by the veterinary industry.

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We believe that we currently rely on minimum data for these aseptically processed products. However, the

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agency and CVM are amenable to consider further means to reduce the amount of validation information when it is possible.

[Slide]

We encourage discussion with us and with the animal industry on ways to reduce validation requirements without increasing the risk of microbial contamination.

[Slide]

As we discussed yesterday, we are currently involved in developing guidance that would lessen supplemental filing requirements for veterinary sterile products that are already approved, and I would just like to elaborate on this a little bit. What we are trying to do is to categorize post-approval changes into high risk, medium risk and low risk categories. For instance, a low risk change could be put into effect immediately and possibly filed in something like an annual report or a biannual report.

An immediate risk change could be put into effect with what we call 30-day CVE changes being effected. What that means is that the firm would submit it but they would not implement it for 30 days after we received it. If they don't hear anything from us in 30 days, they just implement it. A high risk would still require pre-approval before it

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could be implemented.

I want to point out that what we are doing here with this is that we are lessening the regulatory filing requirements. The amount of data that would be necessary to support these changes would not be changed. That would still be required to be on file at the firm for the investigator or for the supplement when it is filed. But we are trying to help get these changes into effect a little sooner.

[Slide]

Just briefly I want to comment on a couple of position statements that were in the manual. AHI's position is that the current SAL of  $10^{-3}$  is acceptable. They encourage flexibility on how this SAL is achieved, and the sponsor should be able to utilize a variety of approaches. CVM agrees with that. In fact, we do practice that. We allow aseptic processing, which is an SAL of  $10^{-3}$ , and when sponsors have approached us with proposals for different means of accomplishing certain processes, we have considered them and quite often we have accepted them or accepted a slight modification. But most of the time these are privileged communications between us and the sponsor and they don't become FDA policy because they are confidential.

[Slide]

The AVMA position is that a system based on eliminating endotoxins in the most sophisticated technology available is detrimental to drug availability, and we certainly agree with this. I guess sometime along about 1991, the USP adopted the LAL method as being the best approach to determining bacterial endotoxins in sterile products. Shortly after that the FDA followed suit. We also accepted the LAL method. This particular method is available in kit. It is not that sophisticated; it doesn't require very sophisticated instrumentation.

The second part of the AVMA position is that the benefits are ignored if endotoxins and other contaminants must be totally eliminated. We agree with that position too.

I would just like to say a few words about this endotoxin-free statement. That came about with the use of the rabbit pyrogen test when you would test the rabbit and if it didn't give a response it was considered to be pyrogen-free. But the fact is that rabbits are not that sensitive, and individually there is a lot of variation in the response that you might get. The LAL, on the other hand, is very sensitive. It is very specific and it is quantitative. So, now what we are doing is, based on the amount of drug product that is actually given to the

smallest animal in the class that it is labeled for, we can calculate a limit for LAL so that CVM actually does not have a requirement of zero endotoxins. All the products are approved with a safe limit of endotoxins. That concludes my remarks.

DR. LEIN: Thank you. Questions from the industry?

MR. STRIBLING: Questions or comments?

DR. LEIN: Questions or comments, either.

MR. STRIBLING: If I may make three brief comments, after beginning by thanking Dr. Leinbach, endorsing what she has just said, and insofar as the Alliance is concerned, certainly the opening that we have asked for is that the Center be willing to look at the requirements and determine whether they are necessary to be continued or not, and from what Dr. Leinbach said and what is in the papers, the Center is willing to do that, and that is fine. We look forward to working with them on that.

I infer from what has been said that if the terminal sterilization regulation, proposed regulation, ever rears its ugly head again, and sometimes things lie dormant and buried in FDA and suddenly resurrect -- I hope from what I have heard that unless there are data to suggest the contrary between now and that time, the Center for

Veterinary Medicine and the Division of Drug Manufacturing Quality in the Center would continue to oppose the inclusion of animal drugs in that regulation.

Three quick comments. Some of my members have asked me to read the last sentence on the bottom of page one, and just make sure that this is correct because they view this very favorably: For processes that require recurrent use of the same equipment, three validation runs are required to document repeatability of new processes. Thereafter, only one revalidation run is required annually to document that each process still produces the desired microbiology quality. Formerly we were required one run every six months for each sterilization process.

The last sentence -- there is no doubt about the correctness of that. Does this mean that if an investigator comes in, or a company, and finds if only one run has been made and there have been no other changes that would require additional runs, that that would be sufficient for the year?

DR. LEINBACH: Yes, that is true, but I would like to just give a little explanation on that. That is for each process, and for processes where you are using the bracketing approach, where you are doing the smallest and the largest, you need to do one of each, each year, and the way we have asked for that to be done is to do it on a

six-month rotational basis. So, at least every six months you are doing something, although it is just one per year of each.

MR. STRIBLING: Thank you for that clarification. I am glad I asked the question because I am not sure that is what my members would have understood with that statement.

DR. LEINBACH: It is one for each process.

MR. STRIBLING: Thank you.

MR. GUIDOS: I just want to state for the record that you are referring to CVM's discussion paper.

MR. STRIBLING: Discussion paper, yes, and I didn't want our people misled because sometimes there is a breakdown in communication and it has been cleared now.

The second comment is simply to refer and reference the letter that we submitted from Dr. Muir, the gist of which was, as you read it, that everyone agrees that endotoxins are bad. No one wants microbiological contamination. We agree to that. We stipulate to that.

The issue is what happens in a drug manufacturing situation where a company has validated processes and procedures and is operating under GMP? And on that, I am afraid there has been very little data, if any, submitted here, and we agree that in order to deal with questions such as this question, it needs to be looked at in terms of the

actual situation with data.

That brings me to the third point, and Dr. Leinbach alluded to it and I have written about it, and that is the difficulty that we have because there is privileged communication. The industry sits here saying, "hey, wait a minute, we all are talking about problems with endotoxins and pyrogens, and as we look at what has happened over the last twenty years, we don't see a problem." And the response we get is, "well, there was one terrible tragedy when animals died." But I think that is the situation referred to in the preface of the compounding guideline that talks about a situation where a sterile powder was taken and compounded into an injectable and some animals died. And, I don't think the misuse of a product really has any relevance to what requirements should be imposed on injectables as they are made.

But, secondly, we are told -- and I have no reason to deny it; I am certain that it is true -- that there is information in some jackets that was developed in the pre-approval process that indicates that the level of requirements that the Center is imposing is really necessary because without them there could be some very serious problems. But, as Dr. Leinbach says, and I affirm, because the information in the jackets is privileged and is

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confidential the Center isn't able to share that with us. And I understand that. But it does leave us in a difficult situation of being told, "well, there are data that you can't know about that lead us to impose these requirements that you think are onerous." That is the government's job. I am not disputing that either. But I do wish that somehow we could find a way to explore the data because examining data makes a difference; cross-examining data makes a difference. We can just look at the O.J. trial or any other trial to see the difference that cross-examination can make. And, when we are just told, "hey, there are problems," and we don't know the situation it is very difficult to know the relevance of what happened to the general requirement.

Maybe a possibility would be, since you all are special government employees, for you all to be able to have access to this. Maybe it would be possible for the Center to release not detailed information but summaries. I don't know. I just express a frustration that I think the Center feels because we keep screaming and they say, "but we've got data and we can't show it to you, but there's a reason for what we're doing." We certainly feel frustrated because we are getting requirements imposed that we look at and say, "what's this, and why do we need it?" So any help you can give on that, in your capacity as special government

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employees, we would appreciate. Thank you, sir.

DR. LEIN: Thank you. AVMA, any statement?

AVMA REPRESENTATIVE: I think our position is pretty well clarified.

DR. LEIN: Anyone from the floor? Yes?

MR. WOOD: I am Richard Wood, from Food Animal Concerns Trust. From the perspective of a group with consumer interests such as ours, as we reviewed the materials from the May meeting and looked also at the background materials for this meeting, we question or are concerned about not seeing any hard data or factual information that would support the issue of sterilization validation. For us, not being an industry group and not fully understanding the processes and the issue at hand, that kind of data and information is very important for a group such as ourselves to be able to determine whether or not this is a valid step to be taken, and what kinds of helpful perspectives we might bring to the question.

Apparently, as the previous speaker indicated, there are problems in providing that kind of data and information, but we would hope that at least VMAC would have that data and information before it as it makes any kind of recommendation. Thank you.

DR. LEIN: Thank you. Others?

DR. GLOYD: Just one comment. Going back to what has just been said and referring to Dr. Muir's letter, I think it is actually under question 3 in the book, but I hope you have all read that because I think he has some pretty significant information there.

DR. LEIN: Statements or questions from the committee? Yes, Dr. Wolf?

DR. WOLF: I have a couple of questions for Dr. Leinbach. On the 30-day CVE, do you foresee any problems in perhaps a delay at the level of the CVM or some reason that the information just wouldn't get back to the company? They would assume everything is okay, put the new process into action and then subsequently find out, no, they weren't supposed to be doing that.

DR. LEINBACH: No, there won't be any problem like that.

DR. WOLF: Okay. I guess my second question is if you are going to define specific limits for LAL testing, do we really know enough about endotoxin tolerances in the various species to do that effectively?

DR. LEINBACH: Individual tolerances have not been established across the species. What we have done is use the tolerance that was established for the rabbit because it is more sensitive to endotoxin than humans, and that is the

sensitivity that we have used in the calculations.

DR. LEIN: Yes, Dr. Koritz?

DR. KORITZ: For Prof. Leinbach, the current sterility level of  $10^{-3}$ , for clarification, is that a probability of 1/1000 or less of vial or something not being non-sterile?

DR. LEINBACH: Right.

DR. KORITZ: So, I can gather then that for each step in the sequential aseptic process there are probability level statistics associated with each of those processes?

DR. LEINBACH: That is the assurance level that is associated with the documentation of the aseptic filling step. Some of the other steps that you use for components etc. are like terminal sterilization. So they would be  $10^{-6}$  but that is the least of SAL that we have associated with aseptically processed products.

DR. KORITZ: Thank you.

DR. LEIN: Other questions? Yes?

DR. GERKEN: So I am to understand that when you talked about the safe limit of endotoxin determination, that is only on the rabbit, and that is used across species?

DR. LEINBACH: Yes. We don't have individual limits for all the species of animals.

DR. GERKEN: Do you have any limits for any

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species, or do you just arbitrarily use the rabbit for all species?

DR. LEINBACH: We use the rabbit.

DR. LEIN: In a way, what you are talking about though basically is that the product goes out to use on your reports. If there is a real problem we should have a pile of animals starting to show up here.

DR. LEINBACH: Right, right.

DR. LEIN: It eventually gets to the species that it is designated for.

DR. LEINBACH: Right. If there is an error in it, it errs on the conservative side because the rabbit is more sensitive --

DR. LEIN: Right.

DR. LEINBACH: -- than most other species.

DR. GERKEN: I understand that. I just wanted to make sure I understood what you meant.

MS. HUDSON-DURAN: I guess as we get more drugs the USP will have the information but we are allowed to dispense and veterinarians are allowed to use extra-label. So, particularly in my area, if we have a large animal product that weighed 1000 lbs. and we elect to use that on a rhea that weighs 20 lbs., then again somewhere we need to be able to find out that kind of information.

DR. LEINBACH: That could be a problem. If it is a USP product the limit for the endotoxin will be in the USP. So, you can look it up there. If it is not a USP product, you could contact the sponsor and ask them what their specification is. That is the only thing I can think of to suggest.

MS. HUDSON-DURAN: Okay, thank you.

DR. LEIN: The problem is to come up with the data on what it is going to do in the rhea because it is probably not established. So, again, I think it is trial and error, and reporting that would be of interest because that is the only way we will accumulate data.

DR. GERKEN: There have been times in the past when animals have died and the question that arose was, was it due to endotoxin in the preparation and preparations are then sent to either FDA or the company -- and I am not really sure which -- for assays. I don't know the answer to this. Are you confident that the endotoxin assay that is done on returned material is accurate? In other words, you are able to find endotoxin when endotoxin is present in those returned materials so you have positive controls that you know you can determine, even though the preparations may be unusual, like the oil preparations? Those things have been worked out so that if they say there are endotoxins in

there you can find them?

DR. LEINBACH: Right. Whenever we approve a drug the LAL method has to be validated to show that it works for that particular drug preparation, and we have only found one with which the LAL method was incompatible, and it was an oil preparation.

DR. GERKEN: I know that especially with the vitamin E selenium preparation there is always a question about that, and I just wondered about it.

DR. LEINBACH: Right.

DR. GERKEN: Thank you.

DR. LEINBACH: It works for those products.

DR. STERNER: A point of clarification, that is, we are talking a little bit about apples and oranges when we talk about endotoxins versus microbial contaminants and sterility levels. If you start out with a product that has a high microbiological burden and then you sterilize it, assuming it is a gram-negative organism, we have now created Sue Duran's concern over endotoxin and killing the animals. The trouble with returning multiple dose containers, which those in my field deal with all the time, is that after the bottle has been opened under field conditions it is usually contaminated by goodness knows what-all. So, you have no way of knowing, on return, if it is microbial contaminated,

whether that originated in that particular lot unless there are other returns with the same organism, or whether it happened in the field. Knowing the human foibles of end users, it is more likely to have occurred in the field.

DR. GERKEN: I understand that. We are talking about comparing what was a multiple use and a new product, of which someone has another lot, to know whether it was before -- we are talking about different scenarios. I understand that, but I just wanted to know the accuracy of the test.

DR. LEIN: Other questions from the committee? Hearing none, let's at least go committee member-wise as to their response to question 4, which is up on the board: "Can sterility validation be reduced without increasing the risk of microbiological contamination?" I guess we will start with Dr. Kemp this morning.

DR. KEMP: Thanks. I think the agency's response to the request for modification of requirements is probably appropriate and it is good, and I would suggest continuing to reevaluate these processes as they come up.

But I have some real questions about whether or not your assessment of what the limits should be is going to be something you are going to be able to work with and have any idea of what is going to happen in the real world, when

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you base it on a rabbit and you are concerned about the rabbit's sensitivity, and have something approved on the label that we can use any way we want to. So, you take a small animal and you calculate something we can use on a horse or a cow -- I mean, it is a shot in the dark, at best. We are going to be going on trial and error down the line. Reiterating Sue's pet idea, we need the information available to us. If you have different standards out there we need to have some way to get a hold of them.

The other concern I have from listening to Mr. Stribling's comment about privileged communication, I wonder if there are public health concerns that are associated with this question about privileged information that would not make this information be forced into the public sector, either from Freedom of Information requests or make it available somehow. I think it is a real concern. Dealing with FDA as much as I have, I have a lot of faith in the fact that the positions you have taken are based on reality, and they probably have widespread implications and should be applied across the board. But I would be in the same position they are if I had a company and I was looking at millions of dollars as an investment. I would like to have some justification for it.

MR. STRIBLING: May I add something, Dr. Lein? I

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want to thank Dr. Kemp but I have to say I don't think my client companies would really want to have that data made public. So, we are our own worst enemies on that one, but thank you.

DR. COOPER: In addressing question 4, I have listened to quite a bit of the conversation that has taken place this morning but I missed the meeting in May. When we look at question number 4, I guess a realistic answer is that we don't have enough known information to really make a judgmental decision. It seems as if  $10^{-3}$  is acceptable in terms of the standard.

CVM has been open in terms of expressing a willingness to look at other standards that may be used based on appropriate data, and as long as that opportunity exists I think it gives us an opportunity to have some assurance of safety as it relates to microbiological contamination. I think it probably gives us an opportunity to move.

I was glad to see Mr. Stribling respond to the earlier question. I think if you insist that some of the information that is in the closed jackets is released, there would probably be more anger with CVM for sharing that information than not. So, I think as we look at this, perhaps the only way that we might reach some consensus is

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to have some instructional guidance that may go out to the CVM staff as well as industry as much as possible, based on what is known. I think as long as a product's safety and the health and safety of animals and the consumer is the most important priority, we will probably be okay.

But based on what I have heard, there is always the probability that something more definitive would be designed in future years, and I think that with that probability we can hope that we will be a little more sophisticated in terms of how we look at this particular standard.

DR. LEIN: Dr. Gerken?

DR. GERKEN: I too don't really think that I can answer question number 4 without having data, and it is the same thing, we can't have the data. So, we have to take a lot of this at face value.

I do think that there should be a difference in the standard between animal drugs and human drugs and I would support, because of the way they are used and the kind of species that we use them in, a difference there in what the guidelines are. But I am not sure that I can answer that sterility validation should be reduced. I don't see evidence, as Dr. Lein indicated, of the bodies lined up. So, you know, we must be doing all right. But I don't know

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that that makes me feel real warm and fuzzy either because I don't know that. That may be out of ignorance rather than anything else.

DR. RAVIS: Even though we don't know a lot about endotoxins, I think CVM's direction with that is fine in terms of their approach. One thing in terms of their process validation is, again, in light of not seeing a lot of recalls of veterinary products because of endotoxin, that perhaps they could be relaxed. But after relaxing the regulation on validation, they probably should be watched carefully for the next two or three years to see if there is an increase of recalls.

MS. HUDSON-DURAN: Well, I like a quality product and I think  $10^{-3}$  seems to be adequate. The problem that I have is that we are using a lot of products extra-label and many times we do have animals that die. Particularly if we are using an antimicrobial extra-label, that animal may die and we assume that we have chosen the wrong antibiotic. So, I think we really need to be assessing some of these products.

The other concern I have is particularly with the calves. At the last meeting we talked about the calves. They are the most sensitive to endotoxin. So, my opinion is, regardless of how somebody handles a product that we

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need to get the best product we can so that will, in my opinion, decrease the problem because even if they are contaminated immediately they don't have time for the bacteria to cook and die and get further contaminated.

So, I don't think we need to have stricter regulations but I think that the ones here seem to be adequate.

DR. BARKER: I would answer question 4 yes. We are talking about processes and the ability to validate microbiological contamination. Some of the validation requirements are a little strict and redundant, and for some processes, especially some of the older processes that have been shown time and time again to accomplish their ends, some of the validation requirement could probably be reduced.

CVM is already in the process of conducting what we are being requested to address in reducing some of these requirements, and I think that is a reasonable thing. In some cases the ends are justified by the means. In many cases there are new technologies that come along that give better means but still produce the same ends. I think that is the case in a lot of the sterility processes that are done.

This, by no means, would possibly lead to poor

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products being put on the market. The material should continue to be as good as it should be. There is information that is generated, I assume, with the use of CGMP material produced actually through the toxicology, and residue, and other studies in target animals. In many cases larger doses of the drug are administered than would normally be administered in the field. If there were obvious pyrogen problems or microbiological contamination at that point in the species intended for its use, that would probably be noted and correction would be made.

So, again, without reducing the mandate of the FDA to produce safe, efficacious and quality products, we can begin to reduce and back off a bit on requirements for sterility validation.

DR. STERNER: Yes, it seems to me, with the assurances that Dr. Leinbach has given, reasonable that the process can, in fact, be done. It is really hard for me to make an intelligent conclusion without incidence data. Nobody has come forth to say this is a problem that occurs one in a million, one in a hundred million lots. I just have no clue. Is this something you deal with on a daily basis, or is this something that we will hear a report on once every five years or so? Without that incidence data, the level of concern would change significantly for me.

Again, are we tilting at windmills here or are we making a real difference in assuring both the end users of animal pharmaceuticals, as well as consumers of food products that originate from animals treated with these products, that we have quantifiably improved the food products that originate from animal origin? So, without that I think we are giving a poorly qualified yes to question 4.

DR. FRANCIS-FLOYD: I would concur with my colleagues. I do support the concept expressed in question 4. I don't think they have a lot of data to suggest whether or not there is a problem. So, if there is not a problem and if we can make animal drugs more available and more affordable for some of the manufacturers to produce, then I would support that.

DR. CLELAND: Well, I agree with the previous speakers. As scientists and veterinarians, we all want data and, unfortunately, this data seems to be lacking and there doesn't seem to be a way that we can obtain it. So, in that regard we are going to have to let the people who have the data make the informed decisions because I don't think we can make an informed decision.

I do appreciate CVM's willingness to consider reduction and some of the things that Dr. Leinbach mentioned

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in her talk this morning, and I think that is a good, positive step. But for me to make any kind of informed decision, I don't feel I can do it.

DR. FLETCHER: I think the answer is maybe. Again, I would emphasize the fact that we don't have facts. There are a couple of issues here. One issue is the limits,  $10^{-3}$ , and then what should be the limit for endotoxin? That is a big question. Maybe  $10^{-3}$  for bacteria is okay. I mean, that is a practical limit that is working. So, I don't see any big push presented to us to change that with data as to why that should be changed.

Then you have the issue of what kind of manufacturing practices we are assured of at that level. It seems to me that CVM is expressing a willingness to discuss that. So, in that sense it might be possible to reduce validation without increasing the risk of having greater than  $10^{-3}$ .

The endotoxin question is another question, and in absence of data for target species, again, we come back to the de facto standard and say, "okay, why change that?" I think until somebody can made an argument that that is not the right level, then that is probably going to be the limit. The same issue then, to my mind, would be in place in looking at the manufacturing practices, can you have a

practice that does not exceed that limit? If you come up with an efficient way of doing it, that is more efficient than what you are doing now, will the agency look at that and say, "yes, we'll approve that." In that case, the answer would be yes. But still there has to be enough validation to meet the limits that have currently been set. In the absence of factual data to change those limits, then I think that is where we are.

DR. KOONG: Excuse me, I must apologize. I don't feel like I have the technical background or experience to answer this question. In cases like this I hear from my colleagues and experts and make a judgment but they haven't helped me much. So, I have no answer to this.

DR. KORITZ: I think 1/1000 safe level on bacterial contamination is appropriate. Of course, whatever processes you would use would be subject to that level of statistical probability.

As far as the endotoxin concern, if, indeed, the calf is the most sensitive of the common veterinary species, then I would encourage FDA or some other group to conduct a dose titration study with endotoxin in calves to see if we have a potential problem out there or not, i.e. the calf versus the rabbit as far as relative sensitivity to these things.

DR. WOLF: We don't have the information we need to make an adequate judgment on this, but the CVM and FDA does. I think, like a baseball team, you want to let your players play their best positions. So, I believe that we ought to give them maximum flexibility in evaluating the validation processes, accepting new data from companies which show that they can meet or exceed the current standards because I think they are dedicated to their mission to provide us with quality products.

DR. POUST: The question that has been asked I guess is strictly from a Good Manufacturing Practices point of view. I would encourage the dialogue that has been established between the Center and the industry. It sounds like people are looking for ways to actually reduce this sort of testing.

I am not sure that anybody can make a sweeping recommendation to address this. I believe that these processes are sufficiently unique that they need to be handled on a case by case basis, with specific products, specific processes and individual pharmaceutical companies.

The issue of confidentiality is an interesting one, and I don't know if Mr. Stribling's clients would allow release of information without attaching their name to it. I presented some confidential information yesterday and

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tried to censor that and, hopefully, nobody is leaving here knowing what drug I was talking about or what company I was talking about. If you do, that means I was careless in my censoring.

So, there are ways I believe to get confidential information out there. What we are really interested in is the science and the data here, not whose data it is or what drug is involved. Maybe industry needs to look a little bit harder at that issue, especially if industry would tend to benefit from the release of this information.

The larger question that seems to have been asked here is that apparently there are no good specifications for knowing what levels of endotoxin various species of animals can tolerate. It looks like there is a magic number for humans. If you take those numbers that I mentioned yesterday, and others that you will find in the USP, and normalize them all to dose you will probably come up with the same number. I don't know what it is; I didn't do the calculation.

Some of us were talking about this at lunch yesterday. This sounds like a fertile area for some research in an academic environment and, of course, as all good academics will do, somebody asked who is going to pay for all this. Sure, academics are interested in doing the

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work and publishing the data, and this is an issue where we probably should follow the science or grade the science if it is there. So, I am going to suggest that perhaps the Center finds the money in their budget to sponsor this research; that it be done; that it elicits proposals from academia and that academicians try to win some contracts and do the research and publish the data.

DR. GLOYD: Is this a commercial?

DR. POUST: Not for me. I don't do that kind of work.

DR. LEIN: It sounds like the committee at least is saying that question number 4 should be looked at. They really don't have problems with what is happening today in what Dr. Leinbach presented, at least in their looking at this sterility problem and the levels they have set.

Again, I think everyone is concerned about needing more data to make this a more definitive answer than what we have. I guess all of us would feel that if this could be shared somehow anonymously, that would be a good way to do it.

On the other side, I would like to say that certainly I think having the LAL test today, which we have utilized in the laboratory too, is good because scientifically you have something that you can measure

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endotoxins with, but having a biological test with it, the rabbit which probably ought to stay there because at least we know that that was used prior and gave us a feeling of security because in other species we were not seeing a problem. So, having both of those tests I think is important, and then trying to correlate those two.

The data that should be coming back to you if products are having a problem -- I think if there was a big problem, and I can almost say this at least from a diagnostic lab standpoint, we would begin to know about that. We know about every other product that causes a problem. Again, it is in the number of reactions and tests that would come back to us and dead animals, and I don't think we are seeing that. Usually that doesn't remain a secret in veterinary medicine. We know pretty quickly what company is involved. And this is not going through CVM; it is not going through the parent company. It is really coming through the veterinarians and through the producers. So, I would suspect this is not a big problem or we would have had indications of this problem.

We know when there have been problems, and I think we heard today that basically that has sometimes been in compounding. So, it frequently has not been the manufacturer but what we have done with the product and how

we have used it. I think we all feel that using it extra-label is certainly a concern, and one that we need more data with. As we get into species today, that are, well, quite exotic compared to what we may have been working with before, we could have reactions that we would have to look at. I think reporting there, again, is going to be important. But I think that will be done if there is a severe problem.

So, I think we all feel it is a topic that needs to continue to be looked at and, certainly, we don't want to increase the sterilization situation just because, again, it is a method that gives us zero tolerance, if we wanted to go that way, to try to clean that up and increase the price so that we would have less drugs on the market. So, stand where we are today and continue to study this, and if we could see the data some day, in a way that would not threaten the companies, that would be of interest.

DR. GLOYD: Dr. Lien?

DR. LEIN: Yes?

DR. GLOYD: I think a lot of the talk that has been going around the committee teases around the borders of the professional flexible labeling issue. You talk about the release of the data. That is part of that concept which would work up finally into a labeling issue but once a

company has a produce approved that they had some other data in which they were confident they might release that data through an entity such as USP, then that would appear in the literature, and as eventually more information was available, it might eventually appear on the label. You know, you can't talk about these things without them branching off into other areas, but I think that is really the essence of where this release of confidential data may lead us.

DR. LEIN: Yes. Again, that brings us back to supporting FARAD and the USP. Somehow we have to do that, that the data is collected and available.

Any other statements or questions? We were scheduled for a break before the next question and we are about half an hour from that. Why don't we take a break now, say for 15 minutes, and then we will come back to the question, question 5.

[Brief break]

DR. LEIN: The next question is our last question, number 5: "Should a process be developed, that would involve representatives from the animal health industry and its regulators, to review and identify inconsistencies in the application and interpretation of quality standards for animal drug manufacturing and to prioritize the identified

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issues? Or are current mechanisms sufficient to meet the need for communications between FDA, headquarters and field, and industry?" Our presenter this morning for CVM is Dr. William Marnane.

## DISCUSSION OF QUESTION 5

### CVM Presentation

MR. MARNANE: Good morning. This question, I think, is pretty appropriate as the last question. As I have listened during the last two days, I think I have heard pretty much the same comments coming up, those comments being that, certainly, we need more dialogue with the regulated industry; they need more dialogue with us.

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So one of the keys that we see as a center is communication. There is no reason for me to reiterate the question. Dr. Lein read that very nicely.

[Slide]

I would like to move on to this slide. Essentially, when we put together our discussion paper on this particular issue, we looked at it from several points of view. I think that we have convinced ourselves that we have done a pretty good job, in fact, communicating with industry, initiating this process for prioritization of development of guidance documents. I think we have to look

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back at some of our earlier attempts to do this. The animal drug manufacturing guidelines that were provided for the May meeting, those were first given to industry in 1992. In fact, what happened after that is that we did meet several times with industry. We revised those guidelines in 1994.

Likewise, for the development of the sterilization process validation guidance documents that covered both human and veterinary products, there was a series of four domestic workshops that we had. The first two of those workshops were conducted when we, in fact, had only a draft guidance document. The industry had, as we perceived, plenty of opportunity for comment prior to our putting that out as the fairly final guidance document, also I believe in 1994, in November.

So, in many ways, if you look at the proposed good guidance practices document that has been mentioned extensively during our two days here at VMAC, we initiated in many ways the processes that are contained within the GP guidance.

However, in reality, I think what we did come to realize is that even with these efforts, which were predominantly Center-derived efforts, we didn't offer enough opportunity to industry for up-front involvement. So, in August, 1996, at what we call an AAP workshop, an Alternate

Administrative Process workshop, we offered the industry some further opportunity for different mechanisms, informal mechanisms, by which they may interact with us or even interact without us and prioritize the development of guidance documents.

There were three options that were offered, one of which was that they would develop their own guidance which would, in fact, set a benchmark or standard for the animal drug industry to follow, and received really essentially no comment from us regarding what our position was on that benchmark that we had established.

The second opportunity we offered them was that they would develop an informal guidance document and we would provide them also informal comment on the acceptability of the concepts within that.

The third was that they would work closely with us in the development of pretty much a mutual document. Of course, at that time the reason we were offering informal possibilities is because we were concerned about the legality of how closely we could work with industry because of the Federal Advisory Committee Act which does have certain constraints.

Since that time, of course, this is where the opportunity came about with the good practices guidance

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document, which sort of legitimized a more close interaction so that we could have better communication up front with industry.

So, essentially what we are saying here is that we believe that we have done a pretty good job but clearly, from what we heard at the May VMAC meeting and what we have heard here in the last two days, there has to be more communication up front with industry.

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I think that is essentially what comes out when we look at the Animal Health Institute comments and recommendations. What they are saying is that the majority of issues are caused by inconsistencies in interpretation. We have done our best, I think, to put out a guidance which addressed the most significant issues as we have seen those issues, however, even with the written word there are opportunities for misinterpretations. So, clearly, we need to have potentially further informal meetings with industry. We have done the workshop route. I don't know that there is much more to be gained through that mechanism. It is a very large impersonal mechanism.

I think what AHI has suggested is that we resolve some of these inconsistencies and miscommunications and re-prioritize some of the work through a working group. I

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think what they have proposed is that we form an informal working group that will report to the Center director. It would be made up essentially, I believe, of three individuals from the AHI, one individual from the ADA, four individuals from either the Center for Veterinary Medicine or ORA, depending on what the issues are. This is consistent, I think, with some of the communications that we have had with the Animal Health Institute, and we have been invited on a number of occasions to attend round-table sessions with them to discuss such issues as the pre-approval compliance program and problems associated with that. But I think it would be useful, and I do agree with the suggestion made by AHI that, clearly, we do need this more in-depth type of communication, but we need to extend it to other parts of the industry and have also representatives of the ADA present for these types of interactions.

[Slide]

These are the comments and recommendations from the AVMA. Essentially, what they have stated is that identification and remediation of inconsistencies in the application and interpretation of quality standards should be an ongoing activity. Absolutely. I mean, I couldn't agree more because we have these things coming up weekly.

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Many times sponsors do contact us by phone; they come in; we meet; we resolve issues, but I think we need to maybe do this in a broader forum.

Also, the AVMA states that to be effective such reviews must be a cooperative effort among regulators, manufacturers and users. Yes, we also agree with that as well.

So, I think the bottom line here is that I think we all agree that greater communication, prioritization and working together certainly would help us achieve many of the problem areas and resolve these issues. So, I think those are pretty much my comments. Thank you.

DR. LEIN: Thank you. Questions or statements from industry?

MR. STRIBLING: Only one quick statement, and I will speak as an attorney rather than in my Animal Drug Alliance capacity. I have clients before all centers, and I work with all centers, primarily with human drugs and next with veterinary drugs. There is no center at FDA that is more open to meetings, to talking, and I could not ask for anything more than we have gotten, and will continue to get from the Center for Veterinary Medicine.

We have had strong objections from time to time about the way rules have been processed and come out. I

think that is going to be taken care of. The Center's continued endorsement of greater communication is consistent with what it has always done, and we as an alliance and I as an attorney practicing before the Center are very grateful for that.

DR. LEIN: That is good to hear. Comments from the floor? Yes, Mr. Wood?

MR. WOOD: I am Richard Wood, with Food Animal Concerns Trust, and we do recognize, being a group coming from a consumer perspective, the need for this process to be ongoing and to be supported. But the way we would like to answer number 5 is to support the GCGPs, and to have them fully implemented because they would encourage active participation by representatives from the animal health industry to review and identify any inconsistencies in the application and interpretation of quality standards for animal drug manufacturing.

Also, the GGPs should allow the industry an opportunity to help prioritize identified issues by enabling the CVM to solicit or accept early input on the need for new or revised guidance, and also allow the opportunity for other public and consumer groups to also propose draft guidance documents, including those pertaining to quality standards.

We oppose the establishment of a formal working group as proposed by one of the organizations. This step would create a group, in our view anyway, acting outside the procedures created by GGPs. In essence, such a group would nullify the GGPs and provide for decisions to be made in an environment comprised solely of industry and regulators, isolated perhaps by veterinarians who are not affiliated with any of the pharmaceutical companies would be at the table and would not be party to that, as well as consumers and the public.

Establishing the GGP process, careful public participation steps are identified, at least under level I, and these steps should serve to increase consumer confidence and the decisions made by CVM. Thank you.

DR. LEIN: Thank you. Joe?

DR. GLOYD: Mr. Wood's comments lead me to think about the efforts that are being made right now to revise the Good Manufacturing Practices for feed manufacturers who add medications to feed. There is a committee of the American Association of Feed Control, called the Medicated Feeds Committee, that has been working on this for a couple of years, and I have attended those meetings as a liaison.

What they have done is they have put together a document that would unify the Good Manufacturing Practices

requirements that would apply from the major feed companies all the way down to the farmer-feeder who has a mobile mixer. Rather than having two sets of guidelines for licensed and non-licensed, they have tried to reduce it. Along the way, they have provided for notable exceptions that would apply unlicensed farmer-feeder.

This concept I think is a little akin to what is being recommended here by AHI and others but, at the same time, I think that CVM, as Mr. Stribling said, is very open to this whole idea. So, obviously it is going on in another area and I think it is certainly progress, and I suspect that the Good Manufacturing Practices document for medicated feeds will come before CVM for consideration in the fairly near future.

DR. LEIN: Other questions, statements from the audience? Committee, any questions or statements? Yes, Dr. Wolf?

DR. WOLF: I have a couple of questions. The comment about inconsistencies in interpretation, do these most commonly relate to a specific sponsor or situation, or is it more general inconsistencies?

MR. MARNANE: If they are related to specific situations, those are the ones that we identify. That is how we did our prioritization initially. That is what we

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wrote to in terms of early guidance documents in 1992 and 1994. So, I think what we are dealing with now, having I think addressed most of what we would think were the regular inconsistencies being identified, are things that crop up that are unusual predominantly.

The reality of it is that we could probably address most of these inconsistencies if sponsors were simply willing to call us up or come in individually to see us. Frequently, however, what happens with these identified inconsistencies, if you want to call them that, is that they grow in magnitude and we end up having a meeting, like we have had here today, to try to clear the air regarding these. Certainly, I think what we need, as well as the GGP process, is just more communication when these things come up, the willingness by individual sponsors to contact us so we can deal with them because they do not warrant, I think, being elevated individually to the point of developing guidance documents.

DR. WOLF: And one other question, if we had such a working group as was proposed by AHI, and these refer to a more specific situation with one sponsor, would that sponsor be willing to reveal perhaps proprietary details in a meeting that might be pertinent to resolution of the problem?

MR. MARNANE: That is a very interesting question because I have observed many times situations like that, where I know that the specific sponsor is in the room and generally they are usually quite reserved even among themselves. I don't think anyone really wants to speak sometimes to the issue. So, you are right.

DR. LEIN: Other questions? Dr. Poust?

DR. POUST: There are a number of guidance documents in the works basically, I guess, being generated by coming out of CDER, and I am wondering if there is adequate mechanism for CVM and this veterinary pharmaceutical industry to insert themselves into the review and discussion process. I guess I go back to my favorite because I have worked with it for a long time, and that is the stability testing. I know there is a new guidance document coming in that area. I happened to have seen the table of contents put up on a screen in Boston last week. So I know it is coming. I think that was done to give credence to the fact that, yes, it is coming because industry becomes very doubtful of these things.

I guess my question is, is there an adequate mechanism for this industry and CVM to insert themselves into those guidances, or might there be a mechanism by which CVM and the industry would review those guidances and

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perhaps generate their own addenda as necessary and appropriate?

MR. MARNANE: Yes, we do have mechanisms to insert ourselves into some of these processes. One of them has been mentioned. Of course, that is the PAC SAS. Also, we are involved in BACPAC, which is another SUPAC type document that is being developed jointly by CVM and CDER that has to do with bulk active ingredients. Once again, that process should lead to a lessening in filing requirements for certain types of submissions when there are changes post-approval for bulk active ingredient manufacturing processes.

We have, however, taken the tack not to necessarily follow all of the SUPAC process that human drugs is involved in for several reasons, one of which is that it is resource intensive. They have hundreds of chemists over there that have been involved in the development of these processes. SUPAC-IR, which is the first document that came out, took eight years. We don't have that kind of time. So, what we have done is, at least in our opinion, adopted what we call an Alternate Administrative Process program that essentially takes a lot of the concepts of SUPAC and just rolls them administratively into a different process that allows companies to come to us with these things,

identified as minor changes, and those minor changes are equal or equivalent to those things identified in SUPAC as minor changes.

So, I think, yes, we do have mechanisms. They are not identical to those in human drugs, nor do we feel that we have a need to have an identical system because we do have some constraints that do not exist over there.

DR. KORITZ: I have a question for Bill Marnane. There has been a concern stated about the establishment of formal working groups which exclude veterinarians, consumers and the public. I would assume that under the GGPs it is possible to have working groups of experts deal with very technical issues, and then subsequently have a more open process where there would be public input from all concerned groups. I just want verification of that.

DR. BEAULIEU: Yes, that is my understanding. Not every issue of interpretation warrants a level I guidance document that would have to be issued under the GGPs. I think this is going to be an ongoing process to deal with specific issues. Some of them may, in fact, become elevated and recognized as general issues that warrant the issuance of a level I GGP. Of course, that would involve everyone that was concerned at that point.

DR. LEIN: Other questions? Dr. Cooper?

DR. COOPER: The question I have, I guess, is the AHI question where they propose the formation of a committee, the question I have is would this committee be allowed under the Federal Advisory Committee Act?

DR. BEAULIEU: We have been dealing with AHI and other industry groups for years under FACA. I am not prepared to lay out all the requirements, but our attorneys are pretty careful in making sure that we do this in a way that will not violate the Advisory Committee Act or the Administrative Procedures Act. Those acts do impose some constraints on the way we can hold these meetings but we have been able to work with those acts and hold productive meetings in the past. Nothing has changed to limit our ability to do that, that I am aware of.

DR. COOPER: In terms of this proposal, have you looked at it as it relates to FACA? Are you able to give a yes/no answer based on the limitations that FACA imposes on the formation of advisory committees?

DR. BEAULIEU: Yes, whatever working group we come up with, we cannot essentially ask them the same kind of questions that we are asking you unless they are, in fact, empaneled as a legitimate advisory committee. In other words, we can't go to that group, whatever that group might be, and say, "we want you to tell us -- we want you to give

us a recommendation on how we ought to deal with this issue." That would be in violation, as I understand it. But that doesn't stop a dialogue. That doesn't stop us from talking conceptually about what they think the problems are; what they think some solutions to those problems might be. Obviously, we walk a fine line here as we talk, as we dialogue.

DR. COOPER: I raise the question because GGPs apparently provide the dialogue. This is an alternative proposal which, in my opinion, could limit the dialogue that you have with the broader industry and the community that is served. So, I was raising the question to see if this alternative was acceptable under FACA. I guess what you are saying is that you have not reviewed it in that context.

DR. BEAULIEU: I think there has to be this alternative for certain issues. Not every issue can be dealt with under the GGPs which require this public discussion associated with level I guidance documents. Many, many decisions need to be made within the agency that don't reach the level of being addressed by a level I guidance document.

MR. STRIBLING: A couple of things. Number one, as I recall, Dr. Sundlof's charge at the beginning of the meeting yesterday was to be aware of the law insofar as we

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have to get it changed depending on what you all suggest, but for purposes of your thinking go ahead and endorse what you think is right, and if we need to get the law changed we will do so. And, I think that is appropriate here.

Number two, I have told Dick Guyer from the beginning on this particular comment that I personally didn't want to spend any time on it because I think the Federal Advisory Committee Act would make it very difficult to do.

Number three, these guys meet with AHI regularly. They meet with the Animal Drug Alliance regularly. They meet with AVMA regularly and Lord only knows who all. Even though they cannot come and say formally to us, "please give us your advice on this," believe you me, we have and do give them advice on a lot of things. So, I am not sure that we lack any opportunity to do that.

DR. COOPER: I guess, being the devil's advocate, the way the question is raised by AHI, I guess the majority of you are saying that there is adequate opportunity.

MR. STRIBLING: I am saying that.

DR. COOPER: Yes, well, most of you who have commented to this particular point say there is adequate opportunity, but to have this as another proposal would lead me to believe, at least from the AHI perspective, that there

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is not the open dialogue that they would consider acceptable. Would someone from AHI like to respond to that?

MR. STANK: I believe I have the gist of your question. Your microphone was not on and it is difficult to hear in the back. I think you were suggesting that there is not a dialogue going on now with the AHI.

DR. COOPER: My question was, in looking at the general statements that have been made about GPPs, the AHI proposal seems to suggest that there may not be adequate open dialogue to discuss issues that are important. So, I am interested in why you propose this alternative as a response to this question.

MR. STANK: Well, the GGP process is new and, although we participated in reviewing, as Bill has pointed out, Good Manufacturing Practices in the past and we have had an opportunity to participate with CVM, that is not the question at all. We feel we have a good relationship with the CVM in being able to address issues.

I think what we are attempting to do here, if I understand this correctly, is include the Animal Drug Alliance in these discussions in a more formal way. You will note that they are provided for in the membership. We do have ongoing discussions with the Agency on specific Good Manufacturing Practices. That is a continuing process. We

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have a number of issues on the table right now that we are discussing, which is in the notes that Bill presented in the documents on the table.

It is something that I think is necessary because issues continue to come up, new issues. There are some problems out there that we think need to be resolved and we are working towards those -- stability guidelines, a good comment over here. We have our own set of CVM stability guidelines that we are working on that reflect the VICH process, for example, which is different than the ICH process for human drugs. So, there are some differences here. They also include the premixes and feeds, for example. So, there are differences that we have to address on the animal side that are not addressed on the human side.

So, those discussions are ongoing. We are working with the agency right now to develop a set of CVM guidelines that will apply these new VICH conditions.

DR. LEIN: Thank you. There is another industry statement.

MR. INCORVIA: The idea behind the working group is not meant to circumvent the GGP process. It is more meant to be a dialogue and open discussion of issues that affect the industry so that we can identify the inconsistencies that have been talked about. Sometimes it

is within the Center. Sometimes it is between the Center and the field. Sometimes it is just between the field. There is a lot of discussion that goes on in individual conversations about what is being meant. The idea is that if there were a group we could discuss them openly so that we could have a consistent interpretation across the industry and, if need be, then it could lead to something in the GGP process if there is some inconsistency that we feel needs to be addressed. Sometimes it may be just a misunderstanding that can be addressed in this group. So it is not meant to circumvent the GGP process. It was just an additional dialogue, and it did include the ADA.

DR. KOONG: I would like to respond to Dr. Cooper's question, basically, if you form a working group, is that against the law?

DR. COOPER: That is the question I asked.

DR. KOONG: That was the question.

DR. COOPER: Right.

DR. KOONG: You know, the law was created for advisory committees. Those are statutory, like this one. But the working groups -- you know, you all can hire consultants, for that matter, but let me remind you personally, Dr. Cooper, you are one such working group which is not censured by law. That is the GPRA working group.

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Your agency just formed it a couple of weeks ago. That is an example of people working together in the spirit of the law.

DR. COOPER: But we can talk about GPRA, in fact, we have an exemption -- I work for the U.S. Department of Agriculture and we are respondents to the Government Performance and Results Act. We have an exemption under FACA which allows us to have broad interactions with the university partners that we work with. So, that does not carry the same merit as the question I am raising here. So, our agency has a special exemption that allows us to have these groups formed as we garner support for our research and education activities in USDA.

DR. FLETCHER: Is it not true that there would be some issues that are not addressed by GGPs because that is more designed to be prospective? There may be existing issues for which the agency would want some dialogue like this. Is that correct?

DR. BEAULIEU: Absolutely.

DR. LEIN: Further question or statement? No?

MR. MARNANE: I was just going to bring up -- and I think Jess has mentioned this previously, I mean, some of the inconsistencies we clearly need to talk about that we cannot make everybody truly understand. What our intent is,

is some of what, in fact, appears in our reviews. I mean, that is some of the dialogue that I think would be useful, and that is where a small group of representatives -- because I have even heard Jess say today, with clarification from Dr. Leinbach, that that clarification was extremely useful. That is the type of clarification we could have I think within a small group, that could be filtered back to members of the trade groups that would, in fact, alleviate some of the misperceptions as to what our expectations are.

DR. LEIN: But if Jess wanted that information he could also call the agency for that information? That would be no problem? Right?

DR. BEAULIEU: True.

DR. GERKEN: I wanted to know is there any objection to having a Food Animal Concerns Trust representative on this "working group?"

MR. GUIDOS: I don't know that that gets to the issue. It is not just a matter of having this group or that group. I think it is a matter of allowing the public at large and other interested parties to participate. I don't think you can get around FACA by choosing one consumer group to represent all concerned groups.

DR. GERKEN: I understand, but they raised the issue and I just wanted to know whether they are opposed to

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having outside representatives, other than the two that were identified here.

MR. STRIBLING: Dr. Gerken, I am trying very hard to be supportive of AHI just in the spirit of friendliness, but, quite frankly, that isn't something that we feel any need for simply because we have good communication. We will take anything we can get. Anything more would help. Certainly, even with AHI -- I meet with the AHI staff from time to time so that we keep in touch. So, I don't want to shoot down what you are saying but this is not a proposal coming from the Alliance.

MR. STANK: I would like to respond to that. If that is the situation, then AHI would withdraw the proposal for recommendation of a committee. I think we too agree that the current process works just fine.

MR. STRIBLING: But we do thank the AHI for suggesting something that would include us along with them.

DR. LEIN: It sounds like a happy family!

[Laughter]

Any other questions? Any from the audience? Statements? If not, let's come back to the committee's decision on this. We will start in the center here. Dr. Koritz, could you start please?

DR. KORITZ: Well, it sounds like things are

functioning by some means that is not completely understood by the committee --

[Laughter]

-- and that there are, indeed, mechanisms by which groups of technical experts can discuss technical issues; that there are processes by which a greater and wider involvement of consumer groups and concerned veterinarians can look at those decisions for the impact on animal health; that there are, certainly, strictures provided by the FACA that need to be taken into consideration. So, I am content with allowing things to proceed as they currently are.

DR. WOLF: It seems to me that the CVM FDA is working very well, cooperatively with the industry, with the public. The GGPs allow for significant public, industry, sponsor and user input as is necessary and that adding another layer of review won't add significantly to the process, other than delay and expense.

DR. POUST: It sounds like that there is some agreement that there are inconsistencies which don't lend themselves to the GGP process. These are specific issues that may ultimately become part of a larger GGP document but, on the other hand, it sounds like some of these inconsistencies, or perhaps all of these inconsistencies can be resolved as long as the various parties are willing to

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talk to one another, and it sounds like they are, without the formation of some sort of a special committee. So, I guess the answer to the first question under number 5 is no and the answer to the second question is yes. At least, that is what I think I am hearing.

DR. KOONG: I just ditto what Dr. Poust just said.

DR. FLETCHER: No and yes.

DR. CLELAND: When I read this question, and one of the reasons I asked the question yesterday about GGPs and if they have taken effect is that I really think we need to give a little time to see what the GGPs are actually going to do, what they will cover and won't. I think it sounds like right now the other things are already taken care of. So, I concur.

DR. GERKEN: It sounds like you are making an effort to fix it, so let's not mess with it until we see if it's broken again.

DR. COOPER: I think with the answer to my question, with the withdrawal of the alternative committee, I can say no and yes to the question.

DR. KEMP: As it was so eloquently stated by Dr. Fletcher, no and yes.

[Laughter]

DR. RAVIS: No and yes.

MS. HUDSON-DURAN: I am going to add a little twist because, assuming all the people at the table won the lottery today and they didn't have to work anymore -- things change when people change so, again, if it is working fine now, that is good but if we have a change of administration it might not be the situation. So, at that time, have some kind of note that if there need be in the future, committees made of unbiased that it could be arranged because, you know, everything is temporary.

DR. BARKER: Does Janet Reno know about all this communication that is going on?

[Laughter]

There is a point where you start to dialogue yourself to death and the line between the regulated and the regulators starts to get blurred. So, no and yes.

DR. STERNER: Question number 1 no, because at this time it appears to be a redundancy, and question number 2 yes.

DR. FRANCIS-FLOYD: I think CVM should be commended for what they have already accomplished in this area and they should continue their efforts. So, no and yes.

DR. LEIN: It sounds easy. It sounds like no and yes is the big run on this. Again, I feel that certainly

this has been a good step forward and something that the committee appears to be very much in favor of, and this happy family idea is a good one if we can continue with that. So, I think we all concur on the no and yes.

**Final Review and Reconsideration of Recommendations**

DR. LEIN: We are opening the discussion now to review the five questions. If there is any change or further thought that people have had since yesterday and today, I would open the floor to comments, and then I will come back to the committee for any comments they may have. Seeing none from the audience at this point, any comments or statements from the committee? Yes?

MS. HUDSON-DURAN: Well, since I am leaving I would like to say one thing. Since I am into labels, I would really like to make a recommendation, which was suggested yesterday, that we have some labeling, some improvement in labeling that basically tells the consumer what products we have available. I mean, if we can go in the grocery store and know, as a lay person, what we are buying in the food, certainly if we are making decisions about veterinary products we should know what is in the product, and if it is not on the label at least have -- and our veterinary pharmacy group may very well take that on as a project, to have some kind of "orange book" or at least

somewhere where we can technically look at bioequivalency sheets to help make some of those type of decisions.

DR. LEIN: I believe that is a great idea. I would be concerned about getting too much on the label because I know much is read off the label becomes too complicated. So, having a secondary reference system I think is a real way to go, and we want to encourage veterinarians and producers, if it is over-the-counter drugs, to read the labels. Sometimes too lengthy of a label doesn't entice people to make that move.

Other statements or concerns? Yes, Dr. Barker?

DR. BARKER: Well, I think in all five questions we have usually mentioned the same thing, that this committee in no way expects to see any lowering of the standards or any reinterpretation of what is required by CGMPs in the manufacture of drugs. FDA will communicate more; will be more flexible in its interpretation of methods and processing in attaining some of this is implied in the statements that have been made by the committee. But we still expect that safety, quality and efficacy will be the highest points in your considerations.

DR. LEIN: Thank you. Well, I think we all feel that this has been quite beneficial and, again, I would just like to say that at least following through on good

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scientific background and data, at least harkening to what Dr. Barker just said, is very important and we do need the safety there but we don't need progression to new methods that are just raising the bar basically and creating more expenses if we can do it with what we have today and we have the safety and assurance of the compounds that we are dealing with. So, we are happy that CVM is certainly taking into its decision-making that the field doesn't have to be level across the animal and human drug situation; that there can be differences and still have the safety issues and the concerns taken care of adequately.

At this time, I think, Jess, you had a statement that you wanted to make.

MR. STRIBLING: I just wanted to say thank you. The Animal Drug Alliance has been working for five years to have this question begun to be discussed in an open forum. We are committed to safety, to effectiveness, to quality products. We agree with Dr. Barker that we would not want products not to be safe, effective or quality, but the whole issue of looking at whether every new requirement, or even maybe some older requirements, make a real necessary contribution to that is what we have been talking about. We have succeeded after a long haul in trying to get this publicly raised. For that, we are very grateful to the

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Center for Veterinary Medicine, for whoever in the Center made the decision that VMAC was the appropriate place for this to begin to be discussed; for the determination and commitment that obviously Dr. Sundlof had to making sure that this would be a very open process and that industry and the profession and other interested groups would be able to be involved; for the extraordinary work that Dick Guyer did and the assistance and effort of Bob Guidos and Sharon Thompson working with him. This has been an extraordinarily well prepared, well organized advisory committee meeting thanks to innumerable hours of those arranging it, and the members of the Division of Chemistry and the field and other parts of FDA too, and we are very, very grateful for that.

I have attended advisory committees with clients before advisory committees on medical devices, many advisory committees on human drugs, even some meetings of VMAC at times past, but I have never seen an advisory committee go till 7:30 the way you did last night. I have never seen an advisory committee stay awake past three o'clock. You all have been awake the whole time last time, all the time this time.

My discussion on advisory committees when people ask me to talk about it is normally, "well, they read the materials on the plane getting here." It is obvious to me

that you all have spent a lot of time studying, reading great volumes of material, thinking about things, asking very pertinent questions, giving very careful thought, and really we thank you so very much. You are special government employees and you have really performed with distinction and we are grateful to you.

DR. LEIN: Thank you for those comments. Yes?

DR. GLOYD: Along the lines that Jess has spoken, I want to thank whoever decided to let me have an input. But the other thing I want to do is I think I want to thank Dick Guyer and whoever else helped him with the synopsis of the previous meeting, the May 13 meeting. That information that is in your books is, I thought, a real piece of work, presented in an absolutely objective fashion and excellent summarization of what everybody said, at least the salient points, and I sure want to say thank you to him and all the folks that must have been involved in that summary. I think that was an outstanding piece of work.

**Discussion of Additional Issues Raised in  
the May, 1997 VMAC Meeting**

DR. LEIN: Thank you. Other comments about the meeting? Hearing none, we will not take a break; we will move forward. We do have a one o'clock item that we need to open the floor for. I know of two things that need to be

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brought up. One of those goes back to the subject of clinical ineffectiveness. Another was some material that Dr. Koong had gone forward with and got a little survey done himself off some data that was presented by one of the presenters at the last VMAC meeting. I want him to discuss that and give his findings basically. It is sort of interesting.

DR. KOONG: Thank you, Mr. Chairman. I wasn't prepared to do this. I did conduct the survey but I was not prepared to make a presentation. So, I had my overheads made about an hour ago during the break. So, I will have to apologize for the quality.

Last May we met here, and I am specifically referring to a survey result presented by Dr. Joe Bertone.

[Slide]

This is the slide presented by Dr. Bertone. He used a list server survey for trying to get an idea of thoughts relative to drug quality. Again, I just wanted to remind you that the population polled was -- I don't understand that acronym so you can read that.

DR. WOLF: Do you want me to tell you?

DR. KOONG: I am not interested --

[Laughter]

-- my apologies, Dr. Wolf.

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DR. LEIN: So much for science, Dr. Wolf!

[Slide]

DR. KOONG: Again, the statistics refer to the members, an idea of them on the list server, and the 53 respondents. I will share the results with you in a comparative way. I have to admit I had motivation for doing this because the population that Dr. Bertone surveyed, to me, was -- I think they are professional professors at universities --

DR. WOLF: No --

DR. KOONG: No?

DR. WOLF: They were all specialists, Board certified specialists in practice.

DR. KOONG: Okay. My bias obviously was that I thought the practitioners in the field must have a different view, and that was my bias. I was totally convinced. I wanted to do a survey to prove that. I keep using the term that I did this survey. Actually, I did not. If I did the survey and sent it out to the veterinarians, they wouldn't know who I was and probably the response would be very, very low. So, what I did, I asked the extension veterinarian on our campus, a well-respected individual, and he sent these questionnaires out and got a good response.

[Slide]

So, let me just give you the rough statistics here. Basically, there are approximately 400 veterinarian practitioners in the State of Oregon. We sent 60 questionnaires out randomly from their booklets, and stratified based under these categories, small animal practitioners only, mixed, large and horses only. We sent out 60; we have 41 response. So, that is a 70% rate. So, that was fairly nice.

[Slide]

Now let me share with you the questions and the result of the comparison. Question 1, do you expect that the quality of drug formulation approved for veterinary use is similar to formulation approved for use in human beings? That is how I will present my data. By the way, those exact questions were the 6 questions went to the practitioners in Oregon: 50, yes; 2, no; 1, maybe from the previous report. The OVMA results, 39, 1 and 1.

[Slide]

The next one, the second question -- by the way, I did have Dr. Bertone's permission to use his questions to send out the survey. Question 2, do you believe the quality standards and controls considered essential for human drugs which are now, and have been, applied to veterinary drugs should continue to be applied to veterinary drugs?

Again very similar results on the second question. You can make your own judgment. Obviously, you can tell I didn't do any statistical analysis on this.

[Slide]

Question number 3, is there a reason to believe that quality controls for veterinary drugs should be less than those considered essential in manufacture of drugs for human use?

There is a slight difference I think between the two surveys, or some difference, however you want to say that. Actually, if somebody has a calculator you can work out a chi square very easily on these data: 3, yes; 49, no; 1, maybe from the previous survey. By OVMA results it is 12, yes; 20, no; and 4, maybe.

[Slide]

Question number four, do you agree or disagree with the following statement, animal drugs do not need the same quality of production as drugs for use in people? Again very, very parallel answers on both surveys.

[Slide]

Question number 5, is there a scientific base which supports that animals are more tolerant of bacteria and endotoxins than are people? Almost identical results.

[Slide]

The last question, controlling the quality of bacterial contaminants in veterinary drug products in veterinary drug production -- the control measures that are taken are similar to the control measures for drugs used in human beings. The control measures are considered essential in production of drugs for people. Do you believe that it is justified to reduce the quality of veterinary formulation below the standard of drugs for human use to reduce the cost of drug production? A fairly close answer.

That is all I have here, Mr. Chairman.

DR. LEIN: Thank you, Dr. Koong. Any questions for Dr. Koong? Certainly, that data speaks for itself. Hearing none, I want to thank you for sharing that with us because it is interesting.

DR. KOONG: I went out to get the data to prove that my perception was wrong.

[Laughter]

DR. LEIN: That is the great thing about science.

MR. STRIBLING: Dr. Lien, in the same way as Dr. Koong commented, I commented to Dr. Gloyd as this was going on, you know, I'll bet that if this questionnaire, Dr. Bertone's questionnaire, had been given to this panel at the beginning of the last meeting, you all would have come out exactly the same way as this stats. and, yet, after how many

hours -- I don't know -- of going through hearings and reading material and listening and thinking, the way you answered the questions to the Center for Veterinary Medicine suggests that you would have answered some of these questions very differently, making some refinements in some of the words that were used. Yes, we never can tell what is going to happen.

DR. LEIN: Yes, Joe?

DR. GLOYD: I can't help but refer back to the letter from Bill Muir who quotes, any group of veterinarians would have responded similarly, obviously without knowledge of what the manufacturing processes are. I think he also says that that is interesting but irrelevant.

DR. KOONG: I forgot to mention that I do want to thank Jackie Page. At the last minute she helped me put this on overheads. Thank you, Jackie.

DR. WOLF: I guess I would like to maybe disabuse Mr. Stribling of his speculation that we might have voted much differently than that survey at the end of the last meeting. I don't think anything that anyone has said here today has suggested that we reduce the quality of the drugs that are manufactured for animals.

MR. STRIBLING: Oh, I agree with that one hundred percent nor, as I have said umpteen times in these meetings,

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are we suggesting a reduction in quality. Nobody wants that at all, or would or should permit it. The only question that has been discussed is what is necessary to have quality. I agree with you completely, Dr. Wolf, and I agree with Dr. Barker on that. Clearly, that is what we want.

DR. LEIN: Any other statements or questions?

Yes?

MR. GARZA: Just one final comment on the GMP issue. One of the questions was is there any data or information to suspect that there is a problem in endotoxin or any other aspect of drug quality. I think something for your consideration should be that perhaps the absence of such evidence complies with the GMPs.

DR. LEIN: Yes, I agree with you. Without them we probably would have some data that you could share with us. Any other statements?

Hearing none, at least the advisory committee and probably a few other members have received the document on clinical effectiveness. These were statements that this committee came up with, what those terms we thought at the last meeting may be. It was decided by this committee that we would pass this on to AVMA, to their Committee on Biologics and Therapeutic Agents, and the Drug Advisory Committee.

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This was taking a veterinary concern and moving it to a group that deals with these subjects and, basically, the Drug Advisory Committee is an interesting committee because it is represented by the veterinary specialities, and it is represented in a way that I think is important for looking at this because it is selected by the specialities and not by AVMA. So, the people sitting on that really represent, I think very fairly, the specialities and are the leaders of that group in many ways. Of course, COBTA is selected through at least AVMA, and they work together, basically, the advisory committee working very closely with COBTA.

So, they really had two meetings on this basically, and I am on that committee, and have come back with the statement that is here. We probably should have had an overhead made but didn't. Really, the terminology has remained the same. This was approved by the committee and sent back for this meeting for this group again to deliberate and see if they approve this. We will look at this now.

Let me read it. "How should the term 'clinically ineffective' be defined for the purpose of the Animal Medicinal Drug Clarification Act?"

That was answered this way -- it is some

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wordsmithing that was done by COBTA and DAC. "The term 'clinically ineffective' means that in the experience of the attending veterinarian, an animal or group of animals has not or will not respond to the drug of choice in the normal, expected form and time."

Let's contemplate what that says, and I will open it to discussion of the committee at this point or any of the audience if they want to raise a question with that. Yes?

DR. FLETCHER: I have a question on that. What does "will not" mean?

DR. LEIN: Well, I think what DAC and COBTA was saying there is that we have today, on some of our drugs that have been out for a while, at least levels today that effectively will not cover a situation. That means when you look at penicillin that was used in a situation, they would like to use a higher dose.

DR. FLETCHER: So that is, in a way, based on past experience.

DR. LEIN: Exactly.

DR. FLETCHER: Yes.

DR. GLOYD: May I clarify that a little bit? I think that that is really the practitioner's judgment. If he is on feedlot X and goes on to feedlot Y, and he already

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knows that last week feedlot X did not respond to drug Q, then he is not likely to use that drug again for that disease out there.

DR. LEIN: Was there another hand up? Dr. Kemp?

DR. KEMP: I was going to ask if you would tell me what this means because I look at this as extremely unclear. They have the term in there "experience" and I wonder if that goes back to what was in the earlier compliance policy guide where you actually had to go in and treat a group of animals and show inefficacy before we went to an off-label drug lot. That is pretty vague. "Drug of choice" -- well, how do you define drug of choice? Are you talking about an approved drug there or are you talking about the drug you really should use which, in my mind, would be the drug of choice. And, I am not sure what they mean when they say "normal or expected form." I just need some clarification on what they are actually saying.

DR. LEIN: I think the clarification is to stay vague because if you move to a checklist, as the veterinarian out in the field, it does not give him the ability to really utilize his skills in treating animals. We feel that the education that he has and working with the oath, basically, for suffering and pain, he has to make that decision and he has to know what is legally right or wrong.

DR. KEMP: I agree with the use of clinical judgment. The way it is worded, it is confusing.

DR. STERNER: Is it possible to get the wording that we submitted last time for review? I think I was more comfortable with the words we had than what I read here.

DR. LEIN: Do we have that with us? I think what was changed in here was the "has not or will not."

DR. STERNER: Right, and that is the problem. It seems to me that we used words like "or is not likely."

DR. LEIN: Yes.

DR. STERNER: We were more careful in our use of words.

DR. LEIN: Yes. Do we have the May meeting material with us? It should be in the minutes but maybe we don't have it here.

DR. STERNER: I just think it would be of use in our deliberations here.

DR. LEIN: We are looking through some minutes quickly here.

DR. WOLF: Keith, for me, it seems sufficiently weasely to cover most expected situations.

DR. LEIN: We do have it, and maybe we could have a copy made it so we could study it and wordsmith it more. The term "clinically ineffective" means that in the

experience of the treating veterinarian a patient is not responding to the drug of choice in the normal expected form and time, and may indicate a rediagnosis of the condition and a change in drug therapy.

DR. STERNER: This one sounds better to me, but I prefer "and is not likely to" and would suggest that change -- "is not likely to respond to the drug of choice in the normal expected form and time."

DR. LEIN: So staying as is but just "or is not likely." Yes, Dr. Cleland?

DR. CLELAND: I also have a concern or share a concern with the wording "drug of choice" and the "normal expected form and time." Clinically ineffective -- I don't know why we need to say "drug of choice." It has not or is not likely to respond to the drug. I mean, obviously the veterinarian has made a choice of the drug but it is not necessarily the drug of choice. My drug of choice may not be the same as yours. So, I would eliminate the words "of choice." I would also eliminate "normal expected form and time" and I would probably suggest putting in, "in the expected way" and that covers everything. If you say "form and time," then what other things might crop up? I mean, does everything fit into form and time? It is just the normal, expected way. So, I would suggest making it more

general.

DR. WOLF: Do we have to have "drug of choice" in there because there are approved products for certain labeled indications? This would allow more product selection. In other words, it enables people to preselect a drug which may not have that labeled indication. Say, for a feedlot situation, tetracycline is labeled for the treatment of bovine respiratory disease and maybe cefti isn't but you would rather use cefti. So the drug of choice might be tetracycline because it is labeled for that indication but you know from your experience that it is not going to work there.

DR. STERNER: I know that it is not likely to.

DR. KEMP: If a drug is not likely to produce the desired effect, how can it be a drug of choice?

DR. STERNER: Because it is labeled as such.

DR. KEMP: Well, I think you are mixing approval process with optimal drug therapy, and that is not always consistent because, obviously, if it was we wouldn't have to have AMDUCA.

DR. LEIN: We do go away from approved drugs if we are not getting a desired effect.

DR. FLETCHER: I think you could make an argument that if we just leave it "drug," and whatever drug the

veterinarian might be using could be clinically ineffective and result in the necessity to move to another choice. That way the statement wouldn't be specifically aimed at the approved drug but any drug.

DR. LEIN: Other statements?

DR. CLELAND: I understand what Dr. Wolf is saying, but I guess my concern is if you choose a drug, whether you are using an approved drug or an extra-label use of that drug, if you determine that that drug is clinically ineffective, it is the drug that is clinically ineffective it is not whether that approved drug or unapproved drug is ineffective, and what we are trying to define here is clinically ineffective and I know it refers to the purposes of AMDUCA.

DR. WOLF: That is right, and that is why I thought perhaps we had to use an approved drug. We are asked to use an approved drug if there is one available.

DR. KORITZ: In my way of thinking, since this is under AMDUCA and addressing the phraseology "clinically ineffective" is in AMDUCA, you have to indicate that the veterinarian has gone through the thought process of looking at an approved drug which may have that label indication and has concluded that it may not be clinically effective. That thought process has been gone through before decisions are

made to use other drugs.

DR. LEIN: Certainly, it would be nice to stimulate that thought process. Yes?

DR. KEMP: Along those lines, would it not be better to use the term "professional judgment" rather than "experience" because there are other sources of information, other than experience. If you go to the literature, that is not experience but does impact your professional judgment.

DR. STERNER: Could we wordsmith that to be judgment and experience?

DR. WOLF: Professional judgment and experience?

DR. STERNER: And/or experience?

DR. KORITZ: Are we starting to arrive at a consensus on how to phrase the "drug of choice?" Is that to be rephrased?

DR. LEIN: I have heard approved drug and take out "of choice."

DR. FRANCIS-FLOYD: I would suggest if you decide to use "approved drug," maybe we should say "an approved drug" instead of "the approved drug" because in so many cases there isn't one available.

DR. LEIN: It could be approved drugs too, drug(s) because there is more than one for several conditions.

DR. STERNER: You would be implying by this that

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you would be using multiple drug therapy?

DR. LEIN: I see what you mean. So "and" would be better? Yes?

DR. KEMP: A legal question, would this definition be used in other regulations, or is it strictly in application to this part of AMDUCA?

DR. STERNER: They have a way of expanding to whatever space exists.

DR. KEMP: What I am curious about is that it does not only apply to this section of AMDUCA. Do we want to use the word "approved" in here at all, or make it a wider definition about clinically ineffective that has wider ramifications?

DR. LEIN: That is probably why we only had drug in there before, "drug of choice."

DR. KEMP: For Dr. Floyd, in treating what she treats there are no approved drugs.

DR. FLETCHER: That is my opinion. I would leave "approved" out and just say "drug." This may be debatable but I think professional judgment incorporates experience as well.

DR. STERNER: That is part or professional judgment, I believe.

DR. FLETCHER: Yes.

DR. LEIN: Bob brings us back to AMDUCA again. Within AMDUCA we are really also talking about extra-label use of drugs, and when you have no approved drug for a species you are sort of cutting them out when you say only approved drugs. That is what we are after. I think that reflects back to professional judgment and experience, which means that professionally we should be going to the approved drug if there is one.

Shall we work through this word by word at this point? What I have done at this point is "the term 'clinically ineffective' means that" -- and at this point we put in "professional judgment and/or experience." Anyone object to that, on the committee?

DR. GERKEN: Why don't we just leave it "professional judgment?" I think that includes all of it.

DR. LEIN: So, we are going to go to "professional judgment" only. Does everyone agree with that?

[Several committee members respond affirmatively]

DR. LEIN: Okay, "of the attending veterinarian, an animal or group of animals has not" and we are taking out "has not or is not likely" to respond. So, we are taking out "will not." Is everyone happy with "is not likely to?" We are taking out "of choice." Is everyone happy with that? -- "in the normal expected way" instead of "form and time."

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DR. STERNER: Normal expected manner.

DR. LEIN: "In the normal expected manner." Do we want to take out "normal?"

DR. CLELAND: Just "expected."

DR. LEIN: Let me try to read this and see if it makes sense now: "The term 'clinically ineffective' means that in the professional judgment of the attending veterinarian, an animal or group of animals has not or is not likely to respond to the drug in the expected manner. "

Could I hear a motion to that effect from the committee?

DR. KOONG: I so move.

DR. KORITZ: Do we want to have "expected" in there because an adverse effect could be expected? How about "desired" or "optimal?" I know you didn't like "optimal" because it is one of those nasty weasel words and it would have to be defined again, but we want a positive outcome here.

DR. LEIN: "Desired" sounds good; "optimal" might be difficult or might be hard to rate. Shall I read it one more time?

DR. STERNER: Please.

DR. LEIN: "The term 'clinically ineffective' means that in the professional judgment of the attending

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veterinarian, an animal or a group of animals has not or is not likely to respond to the drug in the desired manner."

Okay, we have moved and seconded. Dr. Koong moved and Dr. Koritz seconded it. All in favor, say aye.

[Chorus of ayes]

Opposed?

[No response]

It looks like this committee has approved at least the first part of this.

MS. HUDSON-DURAN: Mr. Chairman, I would like to have a couple of names of people we can use as a reference when we start getting calls when this comes out, as to what this really means.

DR. LEIN: You can call me, and I am never reachable --

[Laughter]

MS. HUDSON-DURAN: I am not being critical, I am just very serious because someone just asked you a question. We did this six months ago and he already had a question about clarifications.

DR. LEIN: I think what we are looking at here is something that will cover veterinary medicine in its broadness basically, and put the need to make these decisions back to the profession itself. Now, within the

profession, within each species group, they may want to come up with, or AVMA may want some day to come up with at least desired recommendations for what you use to meet this. All of us would like to see, if it was an infectious disease, that they are going to try and isolate an organism and, where it can be effective, to look at the sensitivity testing. But I know, and if you have ever practiced before, you don't have that data the day you go out to treat the animals, and you don't have it the day when animals start to die and you think, "boy, I've got to change something here." You can't wait. So, if we put a checklist in we are going to miss something and we are also going to hamstring the veterinarian. If we tell him exactly how to do this, that is going to happen.

The other thing we would like to promote eventually, and more of us are seeing this in quality assurance packages and other things, is that sometime we would like to have SOPs on what we should be doing with different disease situations. But that should be for that particular group of animals or that farm because what you write for one farm is not going to fit the next farm or the next operation. It is really going to be at a very local level.

DR. STERNER: We are back to five representatives

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from CVM. I would be interested in hearing from any of them if they have any comments with regard to the wordsmithing that we have done and our definition with regard to point one in terms of "clinically ineffective" under AMDUCA.

DR. BEAULIEU: Personally, I agree with all the changes that the committee just made to the version that came out. I wasn't at the last meeting; I didn't hear the context in which all this discussion took place, so I don't know whether this version would satisfy everyone but I thought it is satisfactory.

MR. GARZA: The comment is not directly related to that but indirectly, at what point would you consider the use "ineffective" if you are using off-label? At what point would you consider it an issue that the manufacturer should be notified of because ineffectiveness may not necessarily be because it was not a pharmaceutical designated or approved for that use? Ineffective could be anything from super subpotency or endotoxin, sterility issues. So, when you are using it off-label, as an investigator at what point do I consider that ineffectiveness due to experimentation by the practitioner or ineffectiveness because of a manufacturing issue? That is an indirect question but from my perspective it is relevant.

DR. LEIN: That is a difficult one because if you

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are using it off-label to begin with, that could be somewhat experimentation from the standpoint of at least a sub or minor species that you may not have a lot of familiarity with. Usually in that you are trying to go to specialists to get treatment advice. I know that happens because at universities specialty people, especially in minor species, are used very heavily by the practitioners as to what are we going to do with this. Obviously, they try to get a diagnosis. That has to be a clinical impression first. Animals become sick usually before you have good clinical laboratory data to back that. So you are going to use professional judgment as to how you are going to start that treatment because it may take some hours or days before that comes back to you. So, you are working off the professional part of it. That is why we wanted to leave that vague.

Then you will go to what has been utilized before. Or, if you are quite new to this as far as a new species group that you are starting to treat, it surely is experimental and you are going from judgment then of what has worked on a species like that with these conditions. I mean, that is the only way you can do it basically.

I think once you get data pools that are at least increased in number, then you can start to be more scientific on what you are going to utilize on that. I

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think we are leaving it to that judgment of the veterinarian that he is going to seek that material. That is why, again, universities, FARAD, USP, any of these where we have written material would become very important in that judgment. So that is, again, bringing it back to the veterinarian to understand that. We are leaving that vague because it is impossible to write up a scenario for each condition that is going to be there.

MR. GARZA: When I inspect the facilities I look at the complaint files, and some are quite vague with everything from a cocktail under very crude conditions to numerous other conditions, and ineffectiveness could be due to various other conditions the animal has, as well as subpotency. So, at what point do you need to officially notify someone so that the investigator on site can make an evaluation to see whether it is, in fact, an issue of a subpotency versus ineffectiveness because of any other conditions the animal has, or some sort of cocktail where you could never know what the contributing cause was?

DR. LEIN: I think that is the experience of the veterinarian. Basically, he has to have treated enough of the species basically to understand that this drug usually works, hasn't now, and what is that change? Is it subpotency or are we killing animals with the drug? I think

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that would have to be his experience and, basically, some of the clinical tests after the fact, if the animal lives long enough, may give him the desired approach to whether this is a drug reaction or ineffectiveness or subclinical or, you know, do we have a resistance problem if it is an antimicrobial or something of that nature. Hopefully, that would come out.

DR. STERNER: As a food animal practitioner, I would hope that before it got to the point of going off-label I would have met all the criteria of AMDUCA in the first place, particularly because of the financial responsibilities that I would be incurring by free-lancing. I am going to be particularly careful because I am conscious of the burden that society places on me or the responsibility that it places on me, before I use that. I think that documentation in terms of what has been clinically ineffective in very similar circumstances, similar geography, similar husbandry practices are all going to play a role, and I am going to look at the label on this drug and have some probability or have generally some idea of the organism that I am dealing with, and look at that labeling on that product with the expectation that it would have some range of efficacy for the condition that I am attempting to treat. Before I went into a mass medication

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situation, clearly I would want, as you said, to experiment on a few before a large number were medicated.

DR. LEIN: The other thing you have is a litigious world that sort of is sitting there too, and that certainly is here today, and what we are going to choose as treatment sits behind all of us.

DR. GERKEN: Well, I would hope that the point of view that you are looking at, whether it is a manufacturing issue or not, would be on the basis of that drug was approved for and the conditions and the species that it was approved for, and that if it is ineffective for what is on the label, that is one point.

We are talking about AMDUCA, which is off-label use and I personally don't feel we are in a position to make a decision about how ineffectiveness would play in your regulatory process. I guess my own personal feeling and my suggestion would be if you could just stick to what is on the label and look at whether it is effective for the things that are specified on the label, that would be satisfactory to me. The ineffective information from AMDUCA is very interesting for the veterinary profession, but not necessarily something from a regulatory manufacturing point of view you have to do anything about. Does that make any sense?

MR. GARZA: It makes sense, and the first thing I do in evaluating complaints is, is it an expected side effect? If so, then I don't put as much weight on the report. If it is unexpected, then you try to evaluate how many other reports, how many other practitioners, how many same lot number, different lot numbers. In evaluating the time and effort, I am going to try look into it to see if, in fact, there is a manufacturer's problem, a practitioner's problem, a transportation problem or some other activity that may have led to that. But when you go to a farm and you get quite a number of complaints, that is one of the things I look at.

Another issue is that, yes, it is off-label and that is not an issue to be concerned with, but you may still pick up evidence of subpotency because you are using off-label. That is one thing to consider. If, in your estimation or your professional opinion, that is a contributing cause, you need to consider whether we should know about it and begin an early investigation into that issue.

DR. GERKEN: Yes, but that would be for the labeled specifications, not for the extra-label specifications, I would think.

DR. WOLF: I can see Dr. Garza's point. What it

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comes down to is that I may be using a drug that is not labeled to treat urinary tract infections but I have my culture and sensitivity data to say that it ought to work in this particular patient. Once I have ruled out all the patient factors -- it doesn't have a urinary stone or something like that which is an underlying cause that I haven't dealt with, if the drug is ineffective based on culture and sensitivity data, then even though I am using it in an off-label manner I might make that report because that may be a subpotency problem. So, I don't think that that is going to change.

MR. GARZA: Right, and I appreciate those type of comments and in your professional opinion, if that is relevant, then we should know about that.

DR. LEIN: I think the other thing too is that data is collected on the off-label use basically, or I should say extra-label use, as much as we can, and I am sure specialty groups do this, because I have sat on some of those where that data is shared, that this is something that we are seeing today that at least is responding to an extra-label use, especially in those species where we have no licensed drugs, or minimal. Certainly that is shared usually by the species group. We see that done quite frequently.

DR. STERNER: Mr. Garza, implicit in the AMDUCA is the fact that my therapeutic decision process there puts me in uncharted waters. However, it again gets back to professional judgment. If there is an adverse reaction that clearly could not be foreseen, either in terms of subpotency or a suspected contamination incident where we had taken reasonable precautions to assure that we would garner an expected response, then, in fact, it seems reasonable to report it as an adverse reaction. But I guess, as a practitioner, my expectation would not be that you are going to necessarily hold production of this pharmaceutical product for labeled uses, but it might certainly merit investigation in terms of a contamination or containing some product which caused those adverse reactions.

MR. GARZA: Well, as I said back in May, there are numerous other GMP issues that would come into play if I were to consider all the off-label uses that you in the field are actually using. Right now, if you expand off-label use to the point of perhaps relaxing some GMP controls, you could have different scenarios to consider. Thank you.

MS. DUNNAVAN: I would like to comment on Dr. Sterner's first question about CVM commenting on this definition. I don't believe I am speaking incorrectly here,

I believe that we were seeking information from you on this topic with the thought that we would be providing guidance on this issue, either separately on this subject or as part of a broader guidance document, and that would clearly be a level I document that would get further comment. So, even though we may think it is wonderful right now, I think there will be some further discussion not only within the Center but from the public.

DR. LEIN: Other comments on the first part of this question 1? Hearing none, we will go to question 2: "How should a veterinarian go about determining whether a drug is clinically ineffective for a labeled indication, i.e. what steps should he or she take in making that determination?"

What came back from AVMA is that "practitioners should use their scientific training, experience and clinical judgment to determine when a pharmaceutical product has been or would be deemed clinically ineffective. There is an extraordinary scope of species and clinical circumstances which are of a subjective nature. In general, use of the veterinarian's oath may serve as a guideline."

We have essentially the same thing:  
"Practitioners should use their scientific training, experience and clinical judgment to determine when a

pharmaceutical product has been deemed clinically ineffective. There is an extraordinary scope of species and clinical circumstances which are of a subjective nature. In general, use of the veterinarian's oath may serve as a guideline."

So, I don't think anything is changed there. Go ahead.

DR. CLELAND: I guess my question is, after having changed the language on the first one to "is not likely" do we need to do something similar to "or would be" which was added because, again, it is the same sort of thing as "has been or is not likely to be deemed" -- or "is likely," I guess, "to be deemed."

DR. LEIN: Yes, I see what you mean. Others? Yes, Dr. Wolf?

DR. WOLF: Just a couple of syntax things, we need a comma after "experience" in the first sentence. and, if we say "has been or would be likely," should we just say "likely to be" not "likely to be deemed to be clinically ineffective?" Just take out the "deemed?"

DR. LEIN: I like that but maybe we will find out if someone else doesn't like it.

DR. STERNER: Now you are speculating on the future and this is after you have used it and your judgment

now says that it is clinically ineffective.

DR. WOLF: Well, they have "would be."

DR. STERNER: But "would be" means after you have looked at it and found it to be clinically ineffective.

DR. WOLF: Can we get back to that in a second? Let me just ask you about a couple of other things. The second sentence, "there are an extraordinary number of species and clinical circumstances" and change "which" to "that are of a subjective nature."

DR. LEIN: Sounds good.

DR. WOLF: To make our cases match.

DR. LEIN: Right.

DR. WOLF: "There are an extraordinary number of species and clinical circumstances that are of a subjective nature."

DR. LEIN: You are changing scope to number?

DR. WOLF: To number.

DR. LEIN: Let's go back to "would be" and "is likely" situation. Dr. Fletcher?

DR. FLETCHER: It sounds like it would be "determine when a pharmaceutical product is or has been clinically ineffective." Then we wouldn't be projecting into the future. It is a fact right now.

DR. LEIN: "Is and has been."

DR. WOLF: That sounds good -- "or has been" or "and has been?"

DR. FLETCHER: I think "or."

DR. LEIN: It can't be both. We are taking "deemed" out of that. "Likely" is out of there too. Let me read this and see if I have this in my mind: "Practitioners should use their scientific training, experience and clinical judgment to determine when a pharmaceutical product is or has been clinically ineffective. There are an extraordinary number of species and clinical circumstances that are of a subjective nature. In general, use of the veterinarian's oath may serve as a guideline."

DR. GLOYD: Do you mind pluralizing number?

DR. WOLF: There are a number.

DR. LEIN: Yes.

DR. LEIN: If you just said there are numbers, but if you say there are an extraordinary number.

DR. GLOYD: That is why I say, you don't say there are a number.

DR. WOLF: There are a number.

DR. LEIN: Are there other concerns?

DR. KEMP: Does the term clinical judgment have the same breadth as does professional judgment? I am not trying to pick on clinicians in the group.

DR. STERNER: Clinical judgment, to me, implies that you have, in fact, looked at these animals, made examinations and come to a determination on site involved in the diagnosis of the case, rather than from afar.

DR. LEIN: Why don't we just add "training, experience, professional and clinical judgment?"

DR. WOLF: Then in the first statement we just used professional judgment to cover the clinical situation. Is it different in the second circumstance?

DR. STERNER: Because you can give professional judgments from afar without having seen the animals. I give my professional judgment all the time on the telephone.

DR. LEIN: Bob brings out that putting in scientific training, experience and clinical judgment all come back to professional.

DR. WOLF: So, just say "professional judgment" and eliminate the rest of it. It makes sense.

MR. GUIDOS: Professional judgment encompasses those three criteria and those three criteria may define professional judgment referred to in your first definition. Practitioners should use their professional judgment, including scientific training, experience and clinical judgment.

DR. STERNER: The discussion, as I recall, last

time related to using those tools that we, as professionals, are trained to use in making the clinical judgment category rather a priori coming up with this is not likely to be effective. In other words, we were going to employ our scientific training, not just some subjective criteria for determining clinical effectiveness.

DR. FLETCHER: I think what Keith said makes sense to me, to leave it "clinical judgment" here. In the first statement we had "attending veterinarian" and, to me, attending veterinarian conveys the veterinarian-client relationship. So attending veterinarian gets at the clinical judgment. Then in the second one I would prefer "education" but "training" is okay. We do more than just training.

DR. KEMP: I agree with you. Training, you think about dogs and horses and stuff. We like to educate the veterinarians.

DR. STERNER: I have been called unteachable by my spouse!

[Laughter]

DR. LEIN: We could do education and training if you want to get a lot of words in here. Education includes training. So far I hear that "professional" is out of this second statement.

Let me read it again: "Practitioners should use their scientific education, experience and clinical judgment to determine when a pharmaceutical product is or has been clinically ineffective. There are an extraordinary number of species and clinical circumstances that are of a subjective nature. In general, use of the veterinarian's oath may serve as a guideline."

DR. KOONG: I guess when you change "training" to "education," as I read this again, "practitioners should use their scientific education" -- is there unscientific education?

DR. WOLF: Yes.

DR. LEIN: You could put professional there now if you want to, instead of scientific.

DR. FLETCHER: I was going to say economics.

DR. LEIN: This is getting a little bit too biased!

[Laughter]

Is everyone happy with what is there?

DR. KOONG: So moved.

DR. WOLF: Second.

DR. LEIN: Discussion?

MR. KOONG: Mr Chairman, I have a question that is not directly related to the verbiage here. When a

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practitioner, obviously based on experience, has found that this particular drug is clinically ineffective is there a requirement for documentation of that specific case?

DR. LEIN: Well, it is certainly going to be in the records that are kept at the farm. He has to do that.

DR. KOONG: Okay, so there is.

DR. LEIN: There is documentation, yes, under AMDUCA. Other questions? Yes?

DR. BEAULIEU: I hesitate to insert myself into this discussion --

DR. LEIN: No, please do.

DR. BEAULIEU: I am having a hard time interpreting species of a subjective nature.

DR. WOLF: I thought that was two separate statements.

DR. BEAULIEU: And circumstances are of a subjective nature?

DR. LEIN: Clinical.

DR. WOLF: Clinical circumstances.

DR. GERKEN: I see what he says, though.

Can you shorten it to, if that's what you want, two separate things; clinical circumstances of a subjective nature which means you eliminate that other phrase which may modify both species and clinical circumstances.

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DR. LEIN: So we are making this into two sentences, then?

DR. WOLF: No.

DR. LEIN: Okay.

DR. WOLF: We need a journal editor here.

DR. LEIN: "There are an extraordinary number of species in clinical circumstances of a subjective nature." Shall I read the whole thing again? Basically, does the mover and the seconder--

[Amendment moved and seconded.]

DR. LEIN: Let's just stay with the laws here. "Practitioners should use their scientific education, experience and clinical judgment to determine when a pharmaceutical product is or has been clinically ineffective. There are an extraordinary number of species and clinical circumstances of a subjective nature. In general, use of the veterinarian's oath may serve as a guideline."

DR. KEMP: Why do we need "of species" in there? Clinical circumstance incorporates all these different things, and species is just one of those variables.

DR. STERNER: I think because it implies the extraordinary breadth of what a veterinarian may be called to make a clinically ineffective judgment. It isn't just

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the circumstances but the fact that you may have a species which reacts uniquely, or doesn't react in this case uniquely, to an expected outcome.

DR. KEMP: You want some enumeration of at least that one circumstance.

DR. STERNER: That's correct.

DR. KEMP: That's fine.

DR. STERNER: The fact that different species may, in fact, not show the expected clinical response under our AMDUCA privileges.

DR. LEIN: Other questions? Hearing none, all in favor, say "aye," please.

[Chorus of ayes.]

DR. LEIN: Opposed, same.

[No response.]

DR. LEIN: So, unanimously, we pass this on to CVM.

DR. GLOYD: Could you read it one more time? I think I slept through it.

DR. LEIN: It has been voted on, Joe.

DR. GLOYD: I just want to know what it said.

DR. LEIN: No; I'll do it. "Practitioners should use their scientific education, experience and clinical judgment to determine when a pharmaceutical product is or

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has been clinically ineffective. There are an extraordinary number of species and clinical circumstances of a subjective nature. In general, use of the veterinarian's oath may serve as a guideline."

DR. GERKEN: Don, the real test is if, at the next meeting, you read it and everyone wants to accept it as it is, we have done something, maybe.

DR. LEIN: Hopefully, I won't read it at the next meeting.

DR. KOONG: Mr. Chairman, I think that question is legitimate because I think we, as a member of this committee, should recognize this as an advisory committee. Anything we pass along to CVM is advisory to the Director.

DR. LEIN: Exactly.

DR. KOONG: The staff have a choice of whether to accept it or modify it.

DR. LEIN: We may see it again, or in a different form.

DR. STERNER: The people who sign off on this are not present.

DR. LEIN: I am sure it will be discussed within CVM and, obviously, also our profession is going to look at it. If it holds, basically, they will also be looking at it.

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DR. STERNER: But isn't it also remarkable, Mr. Chairman, that it did go through both DAC and COPTA, statement 2, and there were no wording changes.

DR. LEIN: True.

DR. STERNER: Obviously, they had no journal editors.

DR. LEIN: We are open for any other additional issues that people would like to raise although it came up really stating that these were issues from the 1997 May meeting of VMAC.

DR. HUDSON-DURAN: I have to go back and address this problem--I have talked internally, but I still don't know a solution. We have a number of embryo transfer veterinarians that have no FSH and I really don't know how to handle this. We have talked about this but if there could be some--if I could go back and say, "We are working on it. We are following up on it," or something because it is a tremendous industry in my area. Right now, we are having problems getting FSH.

DR. GLOYD: I think somebody else wants at this table to answer that question a lot better than I can. Why don't you go ahead with it.

MS. DUNNAVEN: The only thing I can tell you is we did lift the import alert because the product was not

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available. We lifted the import alert which said it can come into this country from somewhere else and we wouldn't object to that.

Now, I understand from our conversation that there is some problem beyond that between the two companies about getting the product in. The only thing I can tell you in response to that is that I can take a look at that and try to get some further resolution.

Our intent here is not to make this product not available and we were trying to make it available by lifting the import alert. So we are working on it, if that helps. It is not really a very good answer for you, but, at this moment, it is probably the best I can do.

DR. GLOYD: I would advise you to either contact Dr. Holzer or Don, who is the executive secretary of the Embryo Transfer Association.

DR. LEIN: I am trying to think of his name, too. Dr. Holzer's address, I think, is on this letter, isn't it, Sue?

DR. HUDSON-DURAN: They are having problems. I have been there a long time. We have practitioners all over the United States. My understanding, as of right now, is that the Canadian companies will not sell to us because they are afraid of litigation by the product. Even though it is

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not currently available, it is being marketed.

DR. GLOYD: The litigation, as I understand it, this is from a phone conversation that I had with Dr. Holzer yesterday, has been more or less been dropped.

DR. HUDSON-DURAN: Thank you.

DR. LEIN: Other problems, concerns, statements? Hearing none, I would like to again thank our members that are leaving the Board; Dr. Wolf, Dr. Koritz, Nancy Jaax who is not here but will hear this, I'm sure, from Dr. Sundlof, and Sue Duran, for all of their help. We may see you back on here again as a consultant or god knows what.

But, again, thank you very much and, for those that are still members, we will try to see you again in another time frame.

I don't know about next year's meeting. Is there going to be a spring meeting, do you know?

MR. GUIDOS: There is nothing planned at this time.

DR. LEIN: There is nothing planned at this time or any topics at this point.

MR. GUIDOS: No.

DR. LEIN: So we will hear more from that--at that time, we have a chance to, at least, talk about conflicts of dates or other things if that is going to happen.

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Other than that, why I thank everyone and the audience that stayed to the end, here, and those that left before for their participation.

Thank you.

MR. GUIDOS: I just want to let you know that I enjoyed my Acting position here and I will carry back the compliments that were extended to Dick Geyer for the hard work that he and Jackie Pace and others have done to prepare for this meeting. I thank you all.

DR. LEIN: Also, if you would relay our sympathy, the committee, to Dick Geyer--I think that is very important at this point--on the loss within his family.

MR. GUIDOS: I will do that.

DR. LEIN: Thank you everyone. Have a safe trip home.

[Whereupon, at 11:45 a.m., the proceedings were concluded.]