

SECTION I

FUNDAMENTAL LEGAL, STATISTICAL, INDUSTRIAL,
AND REGULATORY BASES FOR DOSE DETERMINATION

DISCUSSION PERIOD

(PART II)

DR. GUEST: If the last group of speakers will come forward, we will begin the last discussion period of this section.

DR. KRATZER: Jean, what correlation should exist between MIC's and clinical efficacy to use Dr. Mercer's techniques for divergence from label to dosage?

DR. J. POWERS: I'm glad you asked that, because that's another one of those things that I was forever telling Dr. Mercer. The correlation coefficient is the statistician's toy inasmuch as it has nothing to do with cause and effect. It is only a mathematical relationship, hence I'll let one of the pharmacologists answer that question.

DR. HARVEY: Dr. Gingerich, you said that dose titration studies are not necessarily the sole basis for dose determination; have you any experience where a laboratory dose did not pan out in the field? If so, were clinical dosage modifications made during trials and ultimately the new dose accepted based on clinical findings?

DR. GINGERICH: I think I can get off the hook on that one by saying that the answer to number one is no. I can cite some examples, such as penicillin. I don't have any personal experience where a laboratory dosage titration experiment or a conclusion therefrom has not panned out in the clinic.

DR. DAVIS: If there's no legal requirement for dose determination, how can dosage adjustment by a practicing veterinarian be construed to be extra-labeled use?

MR. MURPHY: Well, let's go back to the basic question; I said at the beginning of my talk that obviously dose determination is important and there are a lot of reasons for doing dose determination. It's the methodology and the way it's being asked by FDA to be performed that is your concern here. Once a dose has been determined, or at least a product has been labeled, what is the requirement of the practicing veterinarian to adhere to that? We'll refer back to Dr. Mercer's talk again.

DR. FARNHAM: What about drugs which have been used effectively overseas for 3-4 years; if clinical trials in the U.S. demonstrate efficacy, should FDA require additional dose titration work in order to grant approval for use here? Dr. Gingerich, I'll ask you first, then Mr. Murphy, and finally, Dr. Guest.

DR. GINGERICH: No.

DR. GUEST: Mr. Murphy, would you care to comment?

MR. MURPHY: No.

DR. GUEST: Yes.

AUDIENCE: You're overruled!

DR. GUEST: There's obviously some judgment involved depending on the organism you're talking about and whether it's a bacteria or whether you're talking about a parasite and just what the conditions are in the countries you're referencing. I think we clearly have had some change in our attitude toward foreign studies and will continue to improve on that. I think the future's bright in terms of international cooperation on studies; I think parasitology has led the way on that and microbiology is coming along very very quickly.

DR. HARVEY: Mr. Murphy, you've said neither the Act nor the regulations specify the need for dose determination. What is your view about the usefulness of FDA promulgating regulations through notice and comment for dose determination as has been done for human drugs?

MR. MURPHY: The promulgation of a regulation based upon opportunity for comment, opportunity to have the proper scientific input, is the correct method to go with. Is it proper for the Agency to promulgate a regulation by other than the guidelines which say that dose determination is necessary; is that consistent with the Act? I think it could be argued that it would be consistent with the Act depending on what the science was that was contained in it.

DR. POST: Does Dr. Jean Powers advocate the Animal Care Committee in the research institution to advise on ethical judgments?

DR. J. POWERS: Idealistically, the Animal Care Committee has veterinarians on it -- at least I would hope so; therefore, I would hope that they would keep the researchers along the straight and narrow as far as caring for the animals and treatment of the animals throughout the investigation. I've seen some things appear in the literature that were done (certainly not at Ohio State) by veterinarians who feel that just because they have used anesthetics when they do whatever they do to their animals, that they are justified in using that procedure. However, concern should also be directed to possible pain after the animal recovers from anesthesia. In these cases, you as the veterinary profession should be self-monitoring. In this case it was specifically a veterinarian who carried out some of these experiments and independent of the outcome of the experiment, I think some of the things that were done were really not in the best interest of the animal, to say the least.

DR. CARNEVALE: You spoke about combination drugs, Mr. Murphy, and don't you think it's important to determine an optimum dose of each individual drug in a combination so as to give us an idea of whether one drug given at an adequate level may take the place of the two or three drugs in the combination, thereby preventing this mixture development?

MR. MURPHY: I think that is a reasonable goal, but I also think that the answer to it is not a legal question; that is a scientific question as to whether or not that's correct.

DR. CARNEVALE: Well, how would you legally determine whether the two or three drugs have been proven to be safe and effective; or the combination as a whole to be safe and effective? How would you legally justify say two or three drugs in a combination if you didn't know that each individual drug is safe?

MR. MURPHY: I was saying you have to be able to determine that the individual entity, each of them in the combination, has met the basic standards of safety and efficacy. As to an optimal dose, I don't know what an optimal dose is; I don't know how you're going to determine that.

DR. CARNEVALE: Dan, would you like to comment on that?

DR. GINGERICH: Is the question, is it a legal requirement that all components of a combination be shown to make a contribution?

DR. CARNEVALE: Well basically yes, I'm asking if you had a

product that was indicated for a single claim and you wanted to put two drugs in that combination indicated for that single claim, don't you think it's important to determine what the optimum doses are of each of those drugs vs. that single claim first?

DR. GINGERICH: Yes, I think scientifically that is important; I wouldn't argue with you over that at all.

DR. CARNEVALE: Well, I guess then what I'm asking is how would you get around the dose titration concept and know that?

DR. GINGERICH: I would agree with Dr. Muser from his talk this morning and state that it is up to the firm to develop the rationale for the combination to their satisfaction and to the satisfaction of the scientific community. I think that what you're asking is, are we going to show you in the Bureau those data. The answer to that from most firms, I think, would be of course we're going to submit those data.

DR. CARNEVALE: So what you're saying is that there's a legal requirement and a scientific requirement and we can't just say it's not required because it's not required in the law. The science would demand that we do certain things; where you would take issue is the flexibility of the science.

DR. GINGERICH: Exactly. I would take issue with a rigid requirement. I would say that if I can show that both drugs are effective by whatever methods are reasonably applicable and that both make a contribution to my combination, then I would owe you the courtesy of showing you that evidence. I think that's about where it stops. From then on, the approval process should concentrate on the safety and efficacy of the combination rather than on the individual components of the combination.

DR. JENKINS: Recognizing that MED's and MTD's can only be derived statistically with all the concerns which you covered in your presentation, surely it would be more rational to deal with dosage ranges rather than a single dosage rate.

DR. J. POWERS: I think that was my exact point, that there is no single dose that is best. There's a dosage range and, like we said, if you have a neonate and you are giving that animal one dose, certainly one would not expect that, under some circumstances, that same dosage to be effective for the mature animal. So you definitely need a range and I don't think that one single dose will always work.

DR. BALDWIN: At one time, all NADA's for use in food animals were also food additives. Section 409 requires that no more drug be used than is necessary to accomplish the intended effect. This concept was carried over in implementing 512. Would you care to comment, Mr. Murphy?

MR. MURPHY: Let me get right to the point of why I didn't go specifically to that particular section you're looking at. First, my topic was substantial evidence which is a term of art and applies to the efficacy section. Secondly, the reason I didn't discuss it is that it does only apply to food-producing animals; since our topic was all drugs, that's why I didn't put it into the beginning. But neither the statute nor the regulations on that section really mention dose titration and the timing of the use of titration as it's been required by the Agency is such that the optimal dose has already been determined before the residue analysis under the section is called into play. If this section of the Act were to have meaning, then the residue analysis would have to be a part of the titration trial itself. Also, as I understand it (and now we're getting out of legal as far as I'm concerned; now I'm sort of quoting the scientists who feed me information), that the approved residue level could be exactly the same with different dosages but with different withdrawal times and they may or may not be significant, then the basic question of the scientific validity of the methodology is not changed whether it's performed for efficacy, safety, or the human health safety considerations of the food additive amendment. Good public policy requires good science.

DR. GUEST: The difficulty for us in a regulatory framework is how to test for all those situations and then, how do you label and how do you communicate it. I think a lot of what we're talking about today, all of us sit around and nod, then when it comes down to how that company or how we communicate it, that's when it really gets tough because there's so many variables involved in that biological system.