

DR. SIMMONS: Thank you, Dr. Gunderson.

Our next two speakers will give comments on animal models. The first of these will be Dr. James Colaianne. Dr. Colaianne received his B.S. degree in 1966 from Pennsylvania State University and his M.S. and Ph.D. degrees from Purdue University in quantitative genetics and statistics. He did post-doctoral work at Argon National Laboratory. Dr. Colaianne joined the Bureau of Veterinary Medicine's biometrical staff in 1973 and is currently serving as Chief of the Biometrics Group. Dr. Colaianne...

DR. COLAIANNE: Thank you. I find myself in the same situation as Dr. Gable; I'm trying to remember how Dr. Tom Powers talked me into doing this. I find it interesting that I've sat across the table from almost everyone in this room at one time or another but when you're up here, it's a much more imposing group; especially the FDA'ers -- I didn't even recognize Don Campbell! Again, like Dr. Gable I received my copies of these papers around Monday of this week and really haven't had an opportunity to make a lot of specific comments on the models presented. However, unlike Dr. Gable, I don't have 25 minutes worth of comments, I have about three, so this is going to be brief. I'd like to try to give you a little bit of a statistician's perspective and some feeling for what an "inside" FDA'er has been feeling the last two days while listening to all these presentations.

COMMENTS ON THE USE OF ANIMAL MODELS

Dr. James Colaianne

As a statistician, animal laboratory models are very appealing. They have a number of characteristics that we just dearly love -- things like: they are generally very simplified systems, they have very well-defined and repeatable conditions, and usually the animal variability is relatively small which means the numbers we can work with are small (statisticians don't really like numbers in the thousands, not if we can get by with 10's or 20's -- it's just that we have a little different feel for the problems in using small numbers). There is also usually a lot of control over the randomization process in animal models and that is certainly an area that's geared to the statistician. Statisticians love to be able to randomize because we've seen time and time again how easy it is to introduce unintentional bias when you can't randomize. Another positive aspect of models is the ability to use placebo controls and unmedicated groups. I don't entirely agree with Jean Powers, I see a very strong need for these types of controls but I do have a lot of reservations about using them under field conditions and I'm extremely happy when we can do this kind of thing in a model environment. And, finally, in an animal model, usually the successful treatment is very well defined in terms of objective criteria. Again, this is difficult in the clinical setting.

All of these characteristics could exist in the clinical setting but as we all know, they're very difficult to achieve. So the point is, that since these are all features near and dear to the heart of any red-blooded statistician, I've been an advocate of animal models since coming to FDA. I've pushed most of you out there very hard for model development and I think we've had a lot of success. Many of the things that have been said in the past two days, contrary to indicating that animal models are no longer useful, really seem to indicate that we've learned a great deal about them and that we have such a great variety of them that we're beginning to learn more about their limitations. However, the ultimate test of the usefulness of any animal model has to be whether the data collected in that model is relevant to the real world. We heard a lot of comments yesterday in particular that suggested this may not be the case and that worries me. However, my experience has been that it's not as

bad as might have been implied yesterday. We at FDA have used a lot of model data in our drug approvals and the doses coming out of those models have generally held up (I hope Tom Powers doesn't jump me now because he's probably got a half dozen good examples where I'm wrong). In general, though, models have been fairly effective in determining, I won't say optimum doses, but at least useful doses for the field.

By the same token, I don't believe and I don't think anyone here believes after hearing what's been said for the past day and a half, that animal models are the answer for all of our problems, or that they are the only way to collect dose titration data or dose determination data. Dr. Keefe has suggested we probably need all three of the areas we have been discussing; I certainly wouldn't refute that. I'd love to see titration data in clinical trials but you have all told me that's impractical. I really enjoyed seeing these animal models progress as they have; we've been collecting dose titration data there and it seems to be working. I am very unfamiliar with the pharmacokinetic area, although that seems to be where we are headed in the future.

From the viewpoint of a BVM scientific reviewer, the critical issue is really not whether a new drug has been dose titrated as much as whether the proposed dosage has been justified in some scientific sense. Most BVM reviewers are open to reasonable scientific justifications for the dose that the drug sponsor wants to propose. They are not open to arguments that this is the dose that has always been used or the dose that marketing says must be used for economic reasons.

Dr. Harvey indicated yesterday that the Bureau has a standing dose determination group. That group is basically charged with reviewing our dose determination, dose titration, requirements across the board with reference to all the various products we review. We are thinking about changes and we are open to your arguments and your recommendations. The four models that were just presented are very encouraging. I have seen Tom Powers' model before but the other three were new to me and they suggest to me that we are still making considerable progress in the model area. We, at FDA, want to see more of this progress. We are particularly anxious to see what will happen with the pharmacokinetic model.