

SECTION I

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

DISCUSSION PERIOD .

(PART I)

DR. MILLER: We're ready now to have our discussion period. I think these are really stimulating and productive sessions and I certainly want to encourage each and every one to participate. I would like to ask Dr. Harvey, Dr. Mercer, and Dr. Muser to come up and join me on the podium for the discussion period.

While they're coming up, I have to mention one thing that just happened to flash through my mind. There are a lot of people here from Ohio State and not only do they play good football, they've got a pretty good veterinary college. When I was a student at Ohio State, there was a pathology professor by the name of Dr. Goss who told us, "Gentlemen, 95% of the patients you treat are going to get better regardless of what you do and 2% are going to die regardless of what you do. That leaves 3% that you might help if you don't kill them with drugs."

Now we are open for the discussion period.

DR. DAVIS: I'd like to make a couple of comments on Dr. Mercer's paper. Since he cited work that we did in Illinois with tetracycline, I'd like to say that your presentation was quite elegant, Dwight, and that we, too, teach our students in this manner. The thing that wasn't brought out in the discussion, however, is within the clinic we use this information to treat metritis in our cows and even though we define the parameters for tetracycline, we find that most of the isolates we're dealing with are not sensitive to dosage ranges that we're able to use of tetracycline. As a result, we're currently doing the same type of work with chloramphenicol and the reason for this is because of the sensitivity pattern with the pathogens that we're now encountering. I think 25 years ago tetracycline would work very nicely and take care of most infections and I wish we'd had the data that you cited this morning to have guided us 25 years ago. But, that's why we're stocking chloramphenicol; it's not because we're dedicated to go contrary to regulations, or break the law, or anything else; it's because on both empirical and scientific grounds, that's the only way we can benefit these owners and their animals.

DR. MERCER: Thank you, Dr. Davis. I was hoping to portray the concept of tissue levels rather than focus on the drug itself. Obviously there will be other drugs after chloramphenicol because microorganisms will adapt to whatever antibiotic is in use.

DR. COPELAND: Dr. Mercer, do you also do calculations to determine residues so a proper withholding period can be established?

DR. MERCER: Well, fortunately for chloramphenicol, Dr. Nouns and his group in the Netherlands did a very thorough residue study on chloramphenicol better than 10 years ago. The depletion time for most residues of chloramphenicol was found to be about 21 days. I am a firm believer that pharmacokinetics can go a long way towards elucidating the drug depletion pattern. If we knew a lot about the kinetics of a drug and how it's eliminated from the body, and realizing that metabolites are in general more polar than their parent compound, the only ones we'd really have to worry about are the ones that are unique.

I'm very pleased with some of the efforts that USDA is doing now from a positive standpoint to promote distribution of residue information to the producer. I believe the practitioner has to use his judgment; I believe he must be part of a team; I believe he's the guy that stands between the FDA and the ultimate consumer. And when he does use a drug, even if it's an approved drug, he still has the potential for the same problem. It doesn't make any difference whether it's an illegal or a legal residue, they pose a real concern. So the clinical judgment has to be there. My pitch would be to direct our efforts so that we can bring the practicing veterinarian into a role as an expert advisor and counsellor to his clients, to the public, as far as what drug residues are all about. Right now he doesn't have a good feeling about what we're doing in terms of drug residues.

DR. BALDWIN: Dr. Mercer, most products for use in animals are developed for over-the-counter use. How would you suggest adapting your approach to therapy under these conditions?

DR. MERCER: Well, I think in over-the counter use of drugs, Bob, the only way that will work is if you have the same kind of concept they have in human medicine. There has to be a fairly clear definition of what over-the-counter drugs should be and I don't think at this point that we, meaning all of us -- FDA, industry, and academia -- have really ever made much progress beyond the time the law was written that says

the owner has a right to treat his animals. We made some decisions; we've said that if it's very toxic, if it's not safe, and if it can't safely be used by that client, then it's on prescription to the veterinarian. Somehow in that process there is more latitude in the veterinary profession than there is in the human profession in terms of consumer judgment in using the over-the-counter drug. I don't think we can resolve that issue. You obviously have to label it to the best of your ability and you've got to assume that a non-trained individual is going to use it according to the label. And there is a place for that -- no question about it. But let's not assume that drug residues are a simple problem.

DR. MUSER: Not being asked, may I add something anyway? I propose to remember what I said earlier, that we have to look at each drug individually. Obviously there are drugs that are suitable for O-T-C use and others that are not. I think Dr. Mercer's comments were mostly referring to those in the hands of the veterinarian for prescription use. I totally agree with him that drugs for O-T-C use must be drugs that are easy to use and have a standard set of recommendations; one could not apply to them what he has discussed.

DR. GUEST: Drs. Mercer and Muser, how would you reconcile the variation in dosage needed for the individual animal and the disease condition with a need for label directions? Can we do better with labels? What would you suggest?

DR. MERCER: I can only give you my thoughts on this in terms of how I would approach it. Many times, when I look at a label on a drug, I would very much like to see some kind of table that indicates that at a certain dose I have a certain blood level. If you go to the other end and decide that you need a certain concentration of drug to be effective for that particular organism, that particular site, then all you really want to know is what dose is required to give you that concentration. So if our labels had the kinetics worked out, if we had the volume of distribution, biological half-life, and bioavailability, we would have the key parameters that we need. I think the clinician could make a better judgment as to what he needs for the case that is on the examining table. Sometimes he guesses and he gives 3 to 4X doses when he may need to give only 2X the recommended dose. If he had the data on the label to make that clinical judgment, perhaps he could do a better job in treating that case and would not have to make so many estimates or judgments in the process.

DR. MUSER: Again, may I say that I believe there are different types of drugs; for some drugs we may be able to come up with very clearcut and strict recommendations, but for other drugs, as Dr. Mercer just mentioned, we may be better off having a descriptive label rather than a label with strict recommendations. One way to use drugs, and again I'm talking about the veterinarian using drugs (I don't think this would be possible in the hands of a lay person), is to measure the effect and then modify the dose by various ways -- for example, measure clinical pathology parameters, blood levels of the drug, or maybe sometimes just look at the animal. With that I believe we can arrive at suitable labels. I don't think we can ever write a label covering all the possibilities that may occur under field conditions. We have to call on our colleagues in academia to educate the veterinarian so that we can take the proper steps.

DR. HARVEY: Bob, if I might interrupt here, I'd like to ask Rainer what his views are in terms of providing that pharmacokinetic data to the end user as you rightly pointed out -- what would you give us from an industrial point of view on this?

DR. MUSER: I could see that we describe serum or plasma levels, for instance, after a given dose. But it has to be pointed out also then that there may be differences in the pharmacokinetics depending on the disease. For example, we mentioned renal impairment as a factor to be considered. If that is pointed out in the package insert, and if you describe this dose in cattle will cause that blood level, and that blood level has been found to be effective against whatever bugs there are, then you have a label that is useful for the veterinarian, I believe. With other drugs, it may be enough to start with a certain dose, for example, and if you don't see an effect, give some more. We are quite familiar with diuretics in our company; their effect is easy to see and the diuretics we have been working with have, fortunately, a reasonable safety margin. Therefore, we could say this and it would be all that is needed in this respect. So again, you have to look at each drug on its own merit.

DR. COPPOC: Dr. Mercer, I am a devotee of kinetics but I wonder if we are as advanced as you imply. Isn't steady state less appropriate than trough level, particularly for static antibiotics? What is the appropriate site in your example? What about free vs. bound drugs?

DR. MERCER: Gordon, I'll see you tonight and we'll work on that for about 2 or 3 hours! There's no question about it, Gordon, I don't think pharmacokinetics are infallible; I think we have a lot of information yet to generate in this area. However, I think what I see in pharmacokinetics is that it finally gives us a tool so we can begin to "crank" some science into the whole issue of dosing. Surely there are drugs with which the peak and trough levels are important. There are other drugs in which the steady state is perhaps the most desirable, but it is an imprecise science at best. All I'm saying is that the kinetics give us a little better mechanism to deal with a complex issue and move it a little further away from the art to the science of dosing.

DR. VARMA: Dr. Mercer's talk prompted me to ask some questions on extrapolation since we are going to talk about dosage regimens and dose determinations and extrapolation. You gave an example of gentamicin and other aminoglycosides which I believe would work very well; the extrapolation can be done in the same species or in different species because physiochemically, these antibiotics are the same and also, we know the mechanism by which they are excreted from the body. Now, my question is, what do we do with the drugs which we know are excreted or metabolized at more than one site? How do we extrapolate those in the same species? And if we want to go to a different species for extrapolation and if the drug is being metabolized in the liver and we know there's lots of differences in the hepatic drug metabolizing systems in the livers of various species, how do we address that issue? For example, consider the case of tetracyclines or cephalosporins or even chloramphenicol.

DR. MERCER: I think you're exactly right. When you look at extrapolation across species, that is one of the toughest areas that a clinician has to deal with. When he gets a drug on the market that's approved only in one species, the first thing he starts doing is looking around to see how many other species he can use it in. He does, in fact, and if you don't believe it, let's talk about the ivermectins for a few minutes. So how do you deal with the problem of cross-species extrapolation? I come back to the contention that pharmacokinetics, which is a cheap, easy and quick way to define the characteristics of a drug, gives us the best tool to make a decision as to whether or not this drug can be extrapolated across species. A kinetic study can be run in a matter of hours or days and does not cost that much. Pharmacokinetics, in my opinion, provides a reasonable tool to make those assessments.

DR. JENKINS: Would you agree, Dr. Mercer, that the pharmacokinetic parameters you use are derived from studies in normal animals? There is accruing evidence that these parameters are distinctly different in the diseased state.

DR. MERCER: Bill, I think it depends on the case. And as far as the diseased vs. normal data, yes, I think you need that information. Current studies have looked at the normal and abnormal cattle in the oxytetracycline study I referenced and they found no difference. That may be unique to that particular class of drugs and with that particular species. I think you need to know that and I would place a greater value on having the kinetics in the abnormal animal than in the normal animal because that's what you have to treat. I'd like to see that kind of data generated. I think we've basically got a lot a data in normal animals now and I'd like to see some in abnormal animals with a variety of drugs.

DR. MUSER: Again, not being asked, I'd like to comment. I would hate to be quoted later on after we go home from here that I share the opinion that we have to quote pharmacokinetics of each drug on each label. I think pharmacokinetics is one parameter that may be very useful but it may not be needed with every type of drug you are using.

DR. TRACY: Dr. Mercer, do you think we should be placing more emphasis on levels of drugs in tissues vs. plasma or blood levels?

DR. MERCER: I think somewhere down the line in the development of a drug you've got to know what the tissue levels are, but realistically, when you get down to using the drugs, the blood levels remain our most accessible fluid or tissue to monitor. So while you need to know what the tissue ratios are, I think that's all you need to know to calculate a dose.

DR. KEEFE: If you pick your dose based purely on pharmacokinetic principles, what about host defense in certain animal disease? What about the activity in dealing with bacteriocidal antibiotics -- are we over-simplifying picking the dose?

DR. MERCER: Well, what are we doing now? You don't look at that now, so what's the difference?

DR. KEEFE: Well, yes, we do by using clinical field studies. We can look at the activity of the drug even though I realize the limitations there very well.

DR. MERCER: You're not going to tell me you know what the immune status of that animal is on clinical field trials, are you? We aren't doing that now. So again, what's the most precise effective way to deal with that? Regardless of how hard you look at it, you come down to the relationship between the organism you're dealing with and the antibiotic blood levels you can produce. I still think that's the best predictor. There are other things involved certainly; the immune status of that animal, certainly. But we aren't doing that now with clinical field trials. I don't think we're over-simplifying things, we are simply trying to be more precise.

DR. J. POWERS: Dr. Mercer, if we plan to use kinetics to determine dosages -- and I agree with you that it is a good idea -- what do you recommend or do you plan to recommend a standardized statistical method for determining these different kinetics, because there are many different methods on the market today and they get all sorts of different answers. If we're going to use kinetics, shouldn't we get comparable answers someplace along the line?

DR. MERCER: You must have forgotten that you told me a long time ago that many of the kinetic estimates are not normally distributed and therefore, most of the statistical tests we run are not applicable. Perhaps if we could decide how they're distributed, then maybe we could answer that question. We will still depend on the statisticians to help us in that regard, Jean.

DR. PAUL: Dr. Harvey, you referred to the responsibility of the members of the animal health scientific community to consider animal welfare issues. Sometimes that's difficult in view of the guidelines, particularly those guidelines associated with safety in the target species. I wonder if you could comment on how we can reconcile our moral and ethical responsibilities and the guidelines that sometimes could require needless killing of animals.

DR. HARVEY: Good question. There were various symposia in Washington just this past week on that subject; a task force has been appointed within FDA and perhaps within the Public Health Service to study all of the FDA requirements and their impact to animal welfare concerns. So let me answer

your question by saying -- it's under review internally and will be a major issue for the Agency. The second thing that I would add to this is that a lot of the data that I see is wasted data. Rainer talked about cost and time and those are important things for industry; they're also important things for the Agency. I'm not talking about the direct cost of development, but time is very important. What I'm talking about is garbage in/garbage out. I've seen many, many volumes of data that I would not submit or have sponsored. I think what we need to do, and that's the purpose of this Symposium, is to hone that effort. For example, I don't want to see 300 sloppy cases, I want to see 50 good cases, and if there's any message I can give you on that conservation theme, that would be it.