

PROCEEDINGS OF
SYMPOSIUM ON
DOSE DETERMINATION WITH ANIMAL DRUGS

Edited by:
Jean D. Powers
Thomas E. Powers

Published by:
The Ohio State University Press
Columbus, Ohio
1984

Held at
Ramada Inn, Old Town
901 N. Fairfax St.
Alexandria, VA

November 16-17, 1983

Presented and Co-Sponsored by:

AMERICAN ACADEMY OF VETERINARY
PHARMACOLOGY AND THERAPEUTICS

Co-Sponsored by:

FOOD AND DRUG ADMINISTRATION
BUREAU OF VETERINARY MEDICINE

In cooperation with:

AMERICAN ASSOCIATION OF INDUSTRIAL
VETERINARIANS

and

AMERICAN VETERINARY MEDICAL ASSOCIATION

Planning and Coordinating Committee

Thomas E. Powers, D.V.M., Ph.D., Chairman
Harlan Bigbee, D.V.M.
Jerry Brunton, V.M.D., Ph.D.
Joe Gloyd, D.V.M.
Terry Harvey, D.V.M.
Thomas Keefe, D.V.M.
Dwight Mercer, D.V.M., Ph.D.
John Paul, D.V.M., M.S.
Jean Powers, Ph.D.
Richard Teske, D.V.M., Ph.D.

Program Committee:

John Paul, D.V.M., M.S., Chairman
William Miner, D.V.M.
Nancy Langwith, D.V.M.

Secretarial Assistant:

Carolyn Walters

Preface

At the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) business meeting held in Salt Lake City in July 1982, Dr. Terry Harvey, speaking for the Food and Drug Administration (FDA), Bureau of Veterinary Medicine (now the Center for Veterinary Medicine), proposed a symposium to address the issue of dose determination with animal drugs. Dr. Harvey invited the AAVPT to present the symposium and to join with the FDA as co-sponsors. The American Association of Industrial Veterinarians and The American Veterinary Medical Association also cooperated in the planning and support of the symposium.

The Symposium on Dose Determination with Animal Drugs was developed following a similar format and objective as the 1982 AAVPT Symposium in Columbus, Ohio: To improve the animal drug approval process and provide a more scientific approach to veterinary therapeutics. In addition to the presented papers, the valuable discussions from the floor are included in these proceedings. These discussions represent the very important scientific intercommunication from the regulatory, academic, and pharmaceutical industry, as well as practitioners of the veterinary community.

During the Symposium, the AAVPT presented a citation to Dr. Thomas E. Powers "IN RECOGNITION OF HIS IMPORTANT CONTRIBUTION IN ORGANIZING AND DEVELOPING SCIENTIFIC SYMPOSIA." Subsequently, the Food and Drug Administration presented the Commissioner's Special Citation to the AAVPT "FOR SIGNIFICANT CONTRIBUTIONS TO THE AGENCY'S ANIMAL DRUG REVIEW PROCESS BY FACILITATING SCIENTIFIC FORUMS AND SYMPOSIA ON CONTEMPORARY ISSUES IN DRUG THERAPY."

We must now take the necessary steps to insure that the recommendations made by the Symposium Task Forces are implemented and fully employed to improve the drug approval process as well as encouraging a more scientific approach to veterinary therapeutics. With the success of this and previous symposia, we should plan another symposium with the objective to once again provide the opportunity for positive interaction between the regulatory, academic, and industry sectors to address an important scientific issue -- clinical studies with animal drugs.

John W. Paul
Secretary-Treasurer
AAVPT

Speakers

Dr. Carl Aronson
University of Pennsylvania

Dr. Stephen Bai
North Carolina State
University

Dr. Robert Baldwin
Food & Drug Administration

Dr. Harlan Bigbee
Schering Corp.

Dr. Wally Brandt
Hoffmann-LaRoche, Inc.

Dr. Jerry Brunton
Animal Health Institute

Dr. Donald Campbell
Food & Drug Administration

Dr. Richard Carnevale
Food & Drug Administration

Dr. James Colaianne
Food & Drug Administration

Dr. Lloyd Davis
University of Illinois

Dr. Robert Furrow
Food & Drug Administration

Dr. Donald Gable
Food & Drug Administration

Dr. Daniel Gingerich
Bristol Laboratories

Dr. Gerald Guest
Food & Drug Administration

Dr. George Gunderson
Burroughs-Wellcome Co.

Dr. Terry Harvey
Food & Drug Administration

Dr. William Jenkins
Texas A & M University

Dr. Thomas Keefe
Beecham Laboratories

Dr. Gary Koritz
University of Illinois

Dr. Jerry Ling
University of California

Dr. Robert Livingston
Food & Drug Administration

Dr. Dwight Mercer
Mississippi State University

Dr. Robert Miller
A. H. Robins Co.

Dr. Bill Miner
Sterling Drug Co.

Mr. T. Jefferson Murphy
The Upjohn Co.

Dr. Rainer Muser
American Hoechst Corporation

Dr. Jean Powers
The Ohio State University

Dr. Thomas Powers
The Ohio State University

Dr. J. Edmund Riviere
North Carolina State
University

Dr. Robert Simmons
Beecham Laboratories

Dr. Richard Teske
Food & Drug Administration

Table of Contents

SECTION I

Fundamental Legal, Statistical, Industrial, and
Regulatory Bases for Dose Determination

Chairpersons: Gerald Guest and Robert Miller

	<u>Page</u>
Interface of FDA Product Decisions and Science Terry Harvey	3
Clinical Dose Determination Dwight Mercer	11
The Impact of Dose Determination on Development of Animal Drugs Rainer Muser	20
Discussion	27
What is Statistical Significance in Dose Determination? Jean Powers	37
What is an Adequate Base for Dose Determination? Daniel Gingerich	45
Dose Determination: What is Substantial Evidence? T. Jefferson Murphy	64
Discussion	78

SECTION II

Pharmacological Basis of Dose Determination of
Antimicrobial Drugs

Chairpersons: Richard Carnevale and Bill Miner

	<u>Page</u>
The Value and Limitation of Pharmacokinetics in Predicting Dosage Regimes. Richard Teske	86
	Gary Koritz 89
	J. Edmund Riviere 99

	<u>Page</u>
(SECTION II, cont'd)	
Comments on Pharmacokinetics	Stephen Bai Jerry Brunton
	120 124
Some Scientific Bases Used in Extrapolation	Thomas Powers
	128
Human Food Safety Aspects of Dose Determination	Robert Livingston
	142
Discussion	150

SECTION III

Experimental Design of Dose Determination Studies with Antimicrobial Drugs

Chairpersons: Carl Aronson and Robert Simmons

	<u>Page</u>
Use of Clinical Trials for Dose Determination	Thomas Keefe Harlan Bigbee Wally Brandt
	164 177 182
Comments on Clinical Trials	Donald Gable Lloyd Davis
	186 190
Discussion	194
Use of Animal Models for Dose Determination of Antimicrobial Drugs	Donald Campbell Robert Furrow Jerry Ling George Gunderson
	200 208 215 219
Comments on Animal Models	James Colaianne William Jenkins
	235 238
Discussion	242
The Future for Dose Determination . . .	Robert Baldwin
	246
Task Force Report and Recommendations	254

SYMPOSIUM ON DOSE DETERMINATION WITH ANIMAL DRUGS

Good morning. My name is John Paul. I'm with the American Hoechst Corporation and I would like to welcome each of you to this Symposium on Dose Determination with Animal Drugs. I very much appreciate the strong support that we've had from all of you and we look forward to a very interesting and productive symposium. I'll be making some announcements later this morning but in order to stay on time as we have a lot of things to do today, I'd like to introduce a man that I think we all know -- he really needs no elaborate introduction. Dr. Tom Powers of The Ohio State University would like now to make some introductory remarks. Tom...

Introductory Remarks

Thomas E. Powers, D.V.M., Ph.D.

Thank you, John. Good morning, everybody. I guess there are no lawyers in the audience; Bob Becker told us at the last symposium that they sleep until 10:00, so we won't have to worry about them being present until then.

The reason I have been asked to make a few introductory remarks is to try to bring you up to date historically as to why we sit here today. As many of you know, we had a symposium in Ohio in April, 1982, which addressed the NADA process. Prior to that symposium, two gentlemen from the Food and Drug Administration phoned me in 1981; Dr. Jim Heavner and Dr. Terry Harvey said they had listened to several academicians complain about the fact that the way we presently teach dosages in school is not always compatible with what is in the package insert. They then requested that we should seriously consider conducting a symposium that involved the FDA, industry, and academia. I asked Terry to propose this to our American Academy of Veterinary Pharmacology and Therapeutics at the meeting held in Salt Lake City. The Academy was very much interested in such a symposium and they endorsed it highly. I immediately went to Dr. Lester Crawford, Director of the Bureau of Veterinary Medicine, who also backed our efforts and with that a committee was appointed which met in the spring of 1983 at the Animal Health Institute to plan this program.

From that Planning Committee came the charge to the Program Committee. We decided we couldn't tackle all the problems regarding dosage in a single symposium so we selected a central theme to follow. That central theme was to consider only the most commonly used drugs, prescription antibiotics. That doesn't mean that some speakers won't move away from that central theme at times; however, there are certain things we are not going to address in our discussions. We're not here to resolve the problems of over-the-counter products; nor are we here to resolve the problems of bulk drugs. We are here to try to discuss in detail how we can handle prescription type antibiotics.

We are planning on conducting the meeting as we did the meeting at Ohio State University in April 1982 and that is, you'll notice there are microphones in the aisle -- whenever you have a question or want to make a comment, we hope you'll go to the microphone, identify yourself, and then make your comment.

One thing I want to emphasize is let's make this a very positive experience. We all have things we might like to "grind a bit," but those are our own personal problems and we do not wish to get off into these problem areas. We want to make this a very positive meeting as to what we can do and not what we CAN'T do -- we assume we can do anything. As Dr. Les Crawford told us at the Ohio meeting, "You should take the attitude that you can do anything."

In addition, I would like to announce that the Academy has appointed two Task Forces. These twenty people have already been notified. There are 10 members on each of the two Task Forces. One Task Force is headed by Dr. Terry Harvey and the other by Dr. Dwight Mercer. It's their charge that during this meeting they will be paying very close attention to what the speakers say and what the comments are from the floor and then at the end of the meeting (tomorrow afternoon), they will have the opportunity to work for another 4 or 5 hours to draft the report of this meeting, which will be proposed to the Food and Drug Administration as the recommendations of this particular group regarding what may or may not be needed to be changed with the drug approval and labeling process for prescription type antibiotics.

I would also like to acknowledge a special guest of this Symposium who was one of my teachers many years ago -- Dr. Fred Kingma. Dr. Kingma has served the veterinary profession in several roles during his distinguished extended career. He has been both a practitioner and an academician. In the academic community he rose to the rank of Professor and Chair-

man of the Department of Physiology and Pharmacology at the College of Veterinary Medicine at The Ohio State University. Following this, he worked in the pharmaceutical industry for several years. The latter years of his career were spent in Regulatory Veterinary Medicine from which he recently retired while holding the position of Associate Director of the Bureau of Veterinary Medicine. We are glad to have you here, Fred, and we welcome you aboard.

Just as Dr. Kingma has to claim me as one of his students, I look around and see about 25-30 of my students in the audience. If you go back, and especially those of you who remember back 25 or 30 years, one of the things I commonly stressed in my lectures was that in the 50's and 60's we had a tendency to underdose antibiotics and to overdose corticosteroids. For example, we'd take a small dog that had a skin condition and treat him with 25 or even 50 mg of prednisolone when 1 mg, 2 mg, or less would have been adequate. On the other hand, we'd treat a cow with 1 mgm per pound of oxytetracycline when we may have needed 5-10 mgm per pound. We did this to save on the cost of the drug.

The point is, we have a problem. If you talk to an anesthesiologist, he will say -- don't tell me what dose to give, I'll give the drug to effect. Talk to the chemotherapist in the veterinary school and he will probably say, I'm going to do the same thing with antibiotics.

It's been said in human medicine, and I think it equally applies to veterinary medicine, that there are more failures due to improper dose than due to the use of the improper drug. I think we should think about this as we proceed. Let's have a good symposium and let's take a very positive approach; sit back and relax and when you have an opportunity to add something, please do so -- and enjoy yourself. Have a good day!