

look at what that active control is, whether it contains something like contemporary data, and if it doesn't, then we have to look at the science of it and not just the legalities.

DR. DAVIS: I have a question for Dr. Ling. Do you have any information in terms of spontaneous remission following infection in your dogs? That is, if untreated.

DR. LING: We do have some data in that regard. The spontaneous "cure rate" is quite low, probably less than 5% and occurs at that level only after about 3 to 4 weeks.

DR. DAVIS: The reason I asked that is that we just heard a paper in Chicago this week - a cystitis model - in which the dogs would recover spontaneously in 4 days. Many of us were wondering how one could use such a model as this to thoroughly evaluate an antimicrobial product.

DR. SIMMONS: If there are no other questions, I'd like to take this opportunity to thank the preceding speakers for their fine presentations and say that we appreciate their work.

Our final speaker for today and for this Symposium will be Dr. Robert Baldwin who will be talking on the future of dose determination. Dr. Baldwin received his D.V.M. degree from Michigan State University in 1951 and his M.S. degree from Colorado State University in 1964. He interrupted 14 years of practice in Wyoming to receive his M.S. degree. Dr. Baldwin served with the FDA/BVM for 17 years and is currently the Associate Director for Scientific Evaluation. Dr. Baldwin...

THE FUTURE FOR DOSE DETERMINATION

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I. PRESENT STANDARDS

Before I speak of the future of dose determination, let me tell you where we are, presently, regarding the establishment of dosage.

For the past year we have had a Dose Determination Group within Scientific Evaluation (SE) under the chairmanship of Dr. Terence Harvey. The group made a report to me in February 1983 utilizing an approach for considering dose determination on a drug class basis. Their first report was subsequently accepted by both my office, the SE Council, and partially by the BVM Council. This report involved three drug categories: Production drugs, physiologically acting therapeutic drugs (diuretics, anesthetics), and anthelmintics. Similar reports of the committee will follow on additional drug classes.

We have established standards for those sulfonamides covered by 21 CFR 510.450 (Sulfamethazine, Sulfapyridine, Sulfanilamide, Sulfamerazine, Sulfaquinoxaline) and other NAS/NRC/DESI reviewed products. Finally, we have altered the standards for combination drugs. Briefly, this is where we are on the following 6 drug classes.

1. Production Drugs

Dose determinations for this product class should continue to be accomplished by three non-zero point studies, except for combinations, wherein the newly revised combination drug guidelines are the standard. The rationale behind this position is the nature of the intended effect of such drugs and the relatively small differences of drug effects to be measured against control groups.

Pharmacological testing in-vivo and dose range finding are of insufficient sensitivity for establishing the best dose level under production claim circumstances. Additionally, the statistical power of the test has a definite effect on the results obtained. Techniques for most production claims are standardized and well accepted by the scientific community.

2. Physiologically Active Therapeutic Drugs

This product class includes agents such as diuretic and anesthetic agents. We considered setting an effectiveness standard in lieu of dose titration for this class but rejected it. These drugs often have relatively low margins of safety which makes specific dose determination and titration more necessary. Also for most drugs in this class, finite testing end points are available, e.g., urinary output, sleeping time, etc. These end points are easily monitored with test subjects often serving as their own control. Active treatment controls are also readily available. Consequently, we believe that this type of product is best examined utilizing the three non-zero point strategy. Exceptions could occur on a case-by-case basis depending upon the physiological effect of interest, e.g., an antidotal drug when the dose is directly correlated to the amount of toxic substance ingested by the animal.

3. Anthelmintics

For anthelmintic agents intended for treatment or control of certain parasite species, as indicated in previous presentations, we have established effectiveness standards in lieu of the three non-zero point strategy, thus utilizing an alternate means of dose determination. We have lists which show those adult parasite forms and target animal species for which the effectiveness standards can now be used. The lists are available upon request.

Essentially, the threshold for minimum adult anthelmintic effectiveness should be no less than 90%. New approvals would not escalate the standard upward as many of the newer anthelmintics have effectiveness levels approaching 100% for certain parasites. However, we believe the 90% standard is adequate to account for experimental variations and clinical needs and practicality.

The basis for our position lies in the percent effectiveness established by recent (primarily within the past 5 years) approvals as published via FOI summaries or other published data. Institutionally, the net effect of a percent effectiveness level becomes the minimum threshold for future product approvals. Also, the primary basis of the effective dose level is determined by the controlled and/or critical study techniques which are accepted worldwide.

Under this new approach, a sponsor would be able to conduct range finding studies to determine a dose likely to reach the minimum effectiveness level. If the sponsor then chose to test only that level in critical and/or controlled studies and the results equalled or exceeded the effectiveness standard for that parasite in the target species, no further dose determination work would be required. Of course, clinical or field studies would be required at that dose level for a showing under actual use conditions that the drug is safe and effective.

4. Sustained Release - 21CFR510.450 Sulfonamides.
(sulfamethazine, sulfamerazine, sulfaquinoxaline, sulfapyridine and sulfanilamide for cattle, swine, sheep, rabbits, chickens and turkeys):

For purposes of target animal safety and effectiveness, the sustained release and other forms of the above-mentioned sulfonamides will be considered safe and effective on the basis of either (1) bioequivalency to a marketed DESI-finalized product, (2) bioavailability data where referenced drugs are unavailable (sulfathiazole, sulfamerazine) documenting that the sustained release formulation achieves a blood level of 8 mg/dl throughout the labeled intervals of administration, or (3) particularly for poultry products, a controlled disease challenge study with a control group administered the effective dosage regimen of the conventional sulfonamide drug product.

5. Duplicates of NAS/NRC/DESI Effective Therapeutic Products and Pre-1969 Certifiable Antibiotics (chlortetracycline, tetracycline, the bacitracins, the penicillins, the streptomycins and chloramphenicol)

The standard for duplicates of NAS/NRC/DESI effective therapeutic drug products as well as pre-1969 certifiable antibiotic products is a comparison (blood level, clinical, whichever is appropriate) to the product reviewed by NAS/NRC/DESI and found effective or moved to the effective category by FDA. Certifiable antibiotics approved prior to implementation of the 1968 Animal Drug Amendments to the FD&C Act also qualify for this approach. Most of the NAS/NRC/DESI products in this category are designated in the 21 CFR 500-599 with a footnote explanation. A few exceptions to this requirement for in-vivo comparison between products include identical true solutions for intravenous administration only the inhalation anesthetic products. Such studies are deemed unnecessary for these products to achieve their intended purposes.

6. Combination Drugs

We are currently in the final process of changing the standards for combination drugs used in feeds. Briefly, the dosage established for each single drug would not have to be retitrated when combined with another drug.

Equally significant were moves made over the last several years to no longer require that vitamins and minerals when added to feed or water use products be required to show an additive effect as long as therapeutic claims are not made and the levels are shown on the labels. Some would want the same policy to apply to all dosage forms including tablets, capsules, etc.

So much for the past and current policies. Now let us look at issues relating to dose determination facing us now and in the future.

Bear in mind we are working under a law that requires us to make a product over-the-counter (OTC) if adequate directions for the safe use can be written. Over half of the approved products are OTC.

Future Considerations

As in the past, for preclearance purposes, the future for dose determination must relate to the end point we are seeking and the precision with which we can measure that end point. Where standards can be agreed upon and set, obviously, that should be done.

Where precise standards are less likely to be agreed upon, scientifically, but the objective is to obtain as high a "cure" rate as possible and the method(s) for measuring a "cure" is somewhat imprecise, then the future of dose determination with such agents is still likely to be a combination of clinical response, pharmacokinetics, animal models and knowledge about the basic pharmacology.* The hope for the future with these type products is improvement in the technology with which we can measure the desired response(s). I refer here to target organ drug levels that are correlated with "cure" or efficacy for example.

Dr. Mercer alluded to this briefly in his presentation.

Dr. Davis suggested we develop animal drugs in phases such as occurs for human drugs.

*The present need for these products is more and better pharmacokinetic data in the target species using the product to be marketed.

The papers presented at this conference will help us to mold dosage determination standards for antimicrobials. We will be pouring over their content and meaning for some months to come.

In addition, we have the following issues before us relative to dose determination which we are or will be addressing in the near future.

1. The Scientific Evaluation (SE) dose determination group has been charged to look at the methods we use for determining the dosage of antimicrobial drugs and therapeutic drugs used in feeds and to recommend alternatives, if appropriate. This symposium will help them in this endeavor.
2. The AVMA has requested we change the combination drug policy relative to the use of therapeutic drugs used in feeds while animals are on long term, low-level growth promotants or estrus regulators in feed. A final determination on that subject is under active review.
3. Improving clinical study design and execution. We believe better use should be made in the clinical data that is collected. For effectiveness, at least, we must have statistical significance as well as medical significance in either valid models or in the clinical setting for each major claim, e.g., respiratory tract infections. Are there valid scientific alternatives to this standard? Dr. Gingerich presented some. What does the Academy think?
4. Effective dose ranges in labeling have been allowed for many years for non-food animal prescription products. We think this should be continued. Such dosage ranges are facilitated by appropriate pharmacokinetic data. We allow dose ranges in drugs for use in food animals also as long as human food safety considerations are met and we can write adequate directions for use.

In this regard, pharmacokinetic studies are part of the data requirements for most products submitted to the National Center for Drugs and Biologics, (NCDB). We have been considering this for some time in SE. Perhaps the Task Forces would address this issue and make a recommendation to the Bureau. The task forces may also wish to address the issue of dose ranges for OTC drugs.

5. The use of published data to support dosages as well as claims has been accepted by the NCDB and BVM. The extent to which we are willing to use such data is under active consideration in the Bureau at this time. More will be heard from us later on this issue.

6. The combining of food safety considerations with target animal safety and efficacy data requirements as they pertain to bioequivalence, is under active discussion.

The issue here is whether or not two products which have been determined to be therapeutically bioequivalent, based on the absorption and distribution phases of the curves would in fact, have comparable excretion and tissue depletion phases, i.e., can the Agency accept bioequivalency data for both efficacy and human food safety requirements? The Task Forces may wish to address this issue.

7. Keeping package inserts current regarding not only dosage but adverse reactions and cautionary information is a major task now and in the future. It takes the cooperation of everyone in the profession; particularly the practitioner, academia and the drug industry to accomplish this.

Finally, it goes without saying that animal welfare must be a major consideration in all studies whether dose determination is related or not.

Since the time was short for me to speak to the future of dose determination, I have been purposefully brief. However, the BVM members of the Task Forces are prepared to elaborate on the above 7 issues so that meaningful discussions may ensue regarding them.

We in SE look forward to the suggestions and recommendations that come out of this symposium.

I wish to thank the American Academy of Veterinary Pharmacology & Therapeutics, the American Association of Industrial Veterinarians and the American Veterinary Medical Association for co-sponsoring this symposium with the Bureau.

In particular I wish to thank the speakers for their thoughtful presentation.

DR. PAUL: Thank you, Dr. Baldwin.

Dr. Tom Powers will now make a very brief closing statement.

DR. POWERS: I want to take this opportunity to thank all of the organizations who have participated and supported this Symposium. I also want to thank all the participants from the stage, as well as all those of you in the audience who have contributed to the Symposium. The proceedings of this Symposium will be published as soon as possible and will be available to all participants.

I hope that this is the second in a series of similar symposia and that we'll keep going on to the third, fourth and fifth. I hope the Bureau, industry, academia, and the American Academy of Veterinary Pharmacology and Therapeutics look forward to the next one as they leave here today. I could suggest a good title - Clinical Trials - or, Over-The-Counter Products, as Bob suggested.

I would certainly be remiss in my final remarks if I did not acknowledge a real warrior who has done an enormous amount of work with his committee; and you watched him get gray hair from it. So before adjournment, I'd like all of us to give a standing ovation to Dr. John Paul.