SECTION II

CLINICAL TRIALS--EXPERIMENTAL DESIGN

Chairman

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Considerations in Designing Protocols for Antimicrobial Drugs

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The objective of this paper is to discuss the various factors that must be considered in designing protocols to demonstrate the safety and efficacy of an antimicrobial drug. This paper is based on personal experience obtained from 16 years of dealing with this subject.

The pharmaceutical company's objective for initiating a clinical field study is to obtain FDA approval for the test drug. To obtain approval of a new drug, the Agency requires that the firm demonstrate "substantial evidence of the drug's effectiveness and safety." This requirement certainly sounds reasonable since any ethical pharmaceutical company would want to meet such minimal standards. The problem comes to life when the term "substantial evidence of effectiveness" is defined. Note I excluded the word "safety" from the last statement. Safety has never been a serious issue with the Agency. Personally, I believe more emphasis should be placed on safety, and less on efficacy. The practitioner is in a better position to judge efficacy than safety.

For the purposes of this paper, the subject of dose titration will not be discussed and the reader is referred to the Proceedings of the Symposium on Dose Determination with Animal Drugs published by The Ohio State University Press in 1984. It is obvious that the optimum dose must be determined in nearly every instance prior to initiating a clinical field study. The optimum dose for an antimicrobial is generally selected by evaluating the following factors: pharmacokinetic data, in-vitro microbiological data, extrapolation of human data and experimentally induced infection studies. In a few cases, such as bovine mastitis, the dose may be determined during the clinical field study.

Once the optimum dose is selected, the clinical field R & D program is designed. This clinical program involves the development of protocols, FDA approval of these protocols, enrollment of clinical investigators, monitoring of the study(s), target species toxicity and breeding studies, summarization of the data and submission of the NADA.

In designing an R & D program, it is essential to keep in mind the FDA's requirements of "two well-controlled studies." This requirement can be met by having at least one experimentally induced infection study in the target species and a large multicentered clinical field trial. Each of these various steps in designing a clinical field study with an antimicrobial will be discussed.

PROTOCOL DEVELOPMENT

Early in the R & D program, it is essential to carefully select the proper label claim. This may seem elementary but it may be a key factor in the eventual regulatory approval and marketing success of the

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product. Obviously, the medical considerations are the primary importance and they are the easiest to define. Regulatory considerations are more difficult.

Ten years ago, we picked the indication by system such as skin/soft tissue or respiratory tract infections and simply listed the organisms for which we demonstrated efficacy. Now it seems the diagnosis, or rather subdiagnosis, must be more specific (abscess, wounds, abrasion, cellulitis, etc.); however, if the diagnosis is too specific, generation of an adequate number of cases will be difficult.

An extensive review of the literature for various indications selected is also necessary as well as discussions with qualified experts. This is particularly important in order to be sure to include the most advanced and sophisticated methods of diagnosising the condition and evaluation of the response to treatment. Always try to build in as many objective measurements of efficacy as possible.

The protocol itself is a detailed plan of action and should describe your clinical study in minute detail. Protocols are becoming extremely complicated in order to meet FDA requirements, which in turn causes serious start-up losses due to protocol violations. The protocol must be very carefully worded due to the large number of people with a variety of backgrounds that will be criticizing and interpreting the protocol. The protocol should be reviewed by an internal review committee prior to submission to the Agency. The advantage of their review is to gain insight as to how non-veterinarians will interpret the protocol.

Our protocols are divided into the following categories: Objectives, Test Drugs, Study Design, Selection of Subjects, Treatment Regimen, Concurrent Medication, Clinical Pathology, Clinical Symptoms, Labeling, Evaluation, Termination, Laboratory Supplies, Drug Control, Side Effects, Statistical Analysis and Miscellaneous.

The protocol must carefully define the criteria of animal selection. The animal's condition must be representative of the population that is to be treated once the drug is approved. A list of exclusion criteria such as tracheobronchitis in a tonsillitis study is a practical way of helping the investigator decide upon eligibility of a given case.

It is also very important that the protocol specify the exact treatment schedule in regard to route, dose, frequency of dose, duration, etc. Variations from this schedule are not permitted.

Prior to the early 1970's, the clinical evaluation of veterinary pharmaceuticals was less than desirable. In recent years, however, the use of well-controlled, randomized studies has improved the quality of

the data generated from clinical trials. There is no question that clinical field trials should be well-controlled. The results by necessity are based upon a limited number of cases with inference on how effective the treatment will be on the target population. Due to the biological variation seen in infectious diseases, the proper interpretation of data requires that the clinical field studies be well-controlled. Generally, with the use of proper controls, blinding and randomization, a well-controlled study is possible.

The FDA currently accepts four types of controls: no treatment, placebo, active control and historical. The specific control used obviously depends on many factors, the condition being treated, owner of the animal, availability of active controls, etc.

The no-treatment group causes a problem in blinding unless two investigators are used. However, this control procedure works very effectively in subclinical bovine mastitis studies. The placebo provides an excellent control from a scientific point of view, however, it should be used only in non-life-threatening situations such as a topical antibiotic study. Placebos are often used in experimentally induced infection studies where the company owns the animals.

The utilization of an active control drug is the most common type of control used in field studies. With proper blinding and randomization, this procedure provides an excellent study. The primary problems encountered with the active control are blinding and dosage instruction. The active control drug selected must have an FDA approved label with similar claims to those being sought with the test drug.

I have no personal experience with historical controls. According to the Code of Federal Regulations (§514.111), historical controls are acceptable in certain diseases which have high and predictable mortality rates (leukemia or tetanus), with signs and symptoms of predictable duration or severity (bovine hypocalcemia), or in the case of prophylaxis where morbidity is predictable. I urge caution to anyone planning to conduct a study using historical controls.

The ethical issues of the use of placebos and no-treatment groups must be considered very seriously, particularly with the increased pressure from animal welfare people. We, as a profession, must temper our desire for a "perfect study" with that of compassion for the animal. We must assure ourselves that there is no unnecessary suffering. The potential benefit of such a study must outweigh the risks and suffering.

For the past 15 years, we have routinely incorporated blinding into our clinical studies. To conduct a pivotal clinical study without a

reasonable attempt to blind the investigator is unacceptable in today's world. At the same time, the practicality and economics of veterinary medicine must be taken into account.

The biggest single obstacle in blinding veterinary antimicrobial studies is the lack of unit dosing, particularly in dogs. Due to the extreme weight variation of dogs and the common use of mg/lb dosage, it is difficult to totally blind a study without using two investigators.

When dealing with a non-unit dosing, we nearly always use a drug code such as treatment A Vs. B along with a predetermined treatment schedule based upon a computer generated randomization schedule. This procedure, which a few statisticians may criticize, is adequate and practical for veterinary antimicrobial drugs. Before insisting upon total blinding, one must assess just how serious or minor any bias might be compared to the problems of protocol compliance associated with total blinding. A compromise is often needed in order to achieve an adequate number of medically acceptable cases. When a good effective active control is used, very few investigators can truly break a code (A vs. B) even if they try. Many of our investigators tell us that they really do not try to do so.

In the case of a unit dose such as an oral antibiotic in cats, blinding is relatively easy by use of numerical codes (1-20) with a predetermined randomized treatment schedule. This procedure obviously eliminates any bias and is preferred when possible, but is only really suitable to unit dosing.

The use of two clinical investigators to blind treatment groups presents many problems. We use this procedure only as a last resort, although I foresee this method of blinding increasing over the coming years. Without company controlled blinding, I am concerned with investigator bias and protocol noncompliance.

Regardless of the method of blinding, all animals should be randomly assigned to a treatment schedule. This assures us of no bias in assigning a prospective animal to a treatment group. The use of alternating assignment, such as date of birth (odd/even = test drug/control) or date of presentation, are not sufficiently well controlled due to possible selection bias. Assignment to test group should not be left to the discretion of the investigator.

SELECTION OF INVESTIGATORS

The selection of the proper investigator is an important factor in the eventual approval of an application. The ever-increasing amount of paperwork, laboratory tests and now FDA inspections, is making the good clinical investigator an endangered species. A really good productive investigator is the key to a successful study.

In a statement before the HEW Review Panel on New Drug Evaluation, Dr. R. Gifford, Jr., President of the American Society for Clinical Pharmacology and Therapeutics said, "Protocols have become so complicated, yet stereotyped, and reports so voluminous that many clinical investigators have given up or sharply curtailed the evaluation of new drugs." I am finding this statement to be true on the veterinary side.

There is no way in which to judge or pick a really good productive investigator. A lot of luck is essential. Some of my best prospects never produced or what they did produce was worthless, while some of the most unlikely prospects turned out to be truly productive. I will outline some of my thoughts on how to select good clinical investigators.

Do you chose a college clinician or a private practitioner? After 16 years of asking and trying to answer this question, I believe on average I have had better success with the private practitioner. Some of my greatest disappointments over the years have been university investigators. You would think that with their academic positions, records, expertise, laboratory support, interest in the new compound, they would do the best job. I believe there are many reasons for their lack of productivity. The client not returning for follow-up evaluation due to long distances is a very valid problem. Unwillingness to follow the protocol is also a major problem. Over-commitment of time is often a problem. In many cases, they feel the clinical study is below their level of expertise. Finally, due to university overhead, which may be as high as 60%, they are pricing themselves out of the market. Our best success over the years has been with the busy private practitioner with a sincere interest in medicine who practice an above average level of medicine. This type of individual seems to be more productive.

In order to obtain a balance in our program, a total clinical impression of a drug's performance, and to ensure having an adequate number of cases, we generally have no more than one/third of our investigators from universities and two/thirds from private practice. Generally, one out of every three new investigators will be productive!

When setting up a large clinical field study, it is tempting to go to the large multi-person clinic in order to obtain a large number of cases in the shortest possible time. My own personal experience suggests that the smaller (1-2 veterinarians) clinic is superior to the large (4-6) multi-person clinic. The primary problems in the large clinic is inadequate follow-up, too many different clinicians, the "other guy syndrome," and possibly, less individual economical incentive.

The facilities obviously must be adequate to meet the protocol's requirements. Generally, any investigator practicing a high level of

medicine will have adequate facilities. The newest, most expensive looking clinic in town is not necessarily the best clinic nor most productive.

The ever-increasing need of laboratory support is becoming a major factor in the selection of potential investigators. Due to the need of good microbiological data, we are now essentially selecting the laboratory first and then selecting the investigators. I do not think this is the way it should be done, but it seems to be the only way to obtain adequate microbiological results. Since bacteriological elimination is the primary objective measurement of efficacy, the use of a few good central laboratories is essential.

The two words you must impress on any potential clinical investigator are "detailed records." An investigator must keep outstanding records to meet the industry's and FDA's requirements. The typical veterinarian's medical records are usually inadequate for the purpose of the study.

The FDA requires geographical distribution in the clinical field program. I personally feel this is a waste of resources. In the 16 years in which I have been involved in antibiotic studies, I have never seen a study where there was any true geographic effect on efficacy or safety. In large animal studies, husbandry may have a much greater effect. The Agency requires that the clinical field study be conducted in at least three different locations. In order to meet this requirement, we generally select four to five different geographic locations. This surplus is a safeguard in case of non-producers. On a typical small animal oral antibiotic trial, we will have 15-20 investigators, while a bovine mastitis study will have 6-10 investigators.

ENROLLMENT PROCEDURE

The proper initial contact and explanation of the clinical field study is a major factor in an investigator's productivity. Where the program was not fully explained, we had a higher dropout rate and often never receive a completed case.

Our enrollment procedure involves a telephone call to set up an appointment with the clinician. We generally figure 1-2 hours to cover all the details. During our discussions, we go over the Product Introductory Brochure, which describes everything you ever wanted to know about the drug and more, the protocol in minute detail and then actually complete a case report form. The completion of the case report form is very helplful in raising questions and points that were not adequately covered in the earlier protocol discussions.

The number of cases per investigator varies depending on the type of study. In the typical small animal oral antibiotic study we will ask

each clinical investigator to do 20-25 cases. A few will do more; most will do one-half of what they tell you they can do.

Our human colleagues are required by the Code of Federal Regulations to obtain client consent; however, as I understand the regulations, this is only suggested and not required on the veterinary side. Due to our payment policy, most of our investigators do inform the client. Only a few investigators will ask the client to sign a release form. The client consent issue should remain an option on the veterinary side.

Due to the importance of microbiology in an antibiotic study, a great deal of time is spent on the laboratory procedures and our needs during the initial visit. Since we are using more and more outside central laboratories, we also visit the laboratory to discuss our needs and their needs as to proper identification of the samples, paperwork and reporting procedures.

During our discussions with the investigators, we emphasize the need for "better" record keeping. We explain that we will make periodic visits to compare the case report forms to their hospital records and also inform them of the possibility of an FDA inspection.

We also explain the need for keeping a close record of drug inventory and dispensing. We explain that at the end of the study, all unused drug must be returned.

Following discussion of the above details, our payment policy is discussed. Our investigators are generally paid by the case. The specifics will be discussed later.

The last thing we do during our initial visit is to have the investigator sign a Form FD-1573.

MONITORING PROCEDURE

Monitoring of a clinical study is extremely important. The primary functions of the monitoring program are to ensure protocol compliance and increase enrollment of cases.

Upon our return to the office from our initial visit, the FDA is notified that an investigator is going to participate in the study. Following this official notification, we send the necessary clinical supplies, case report forms, envelopes, laboratory supplies, etc. along with a cover letter re-emphasizing the major important points in the protocol.

In approximately two weeks, we contact the investigator by phone to check on the supplies and answer any new questions. We use the

telephone as a major monitoring tool during the course of the study. We try to call the investigators every 4 weeks to check on supplies and to remind them to enter more cases. Upon receipt of the completed case report forms, we often call to verify data or ask for additional information on the case report form. As a further motivator, we pay the investigator after every few case reports in an effort to stimulate more interest in enrolling additional cases. We also enter the case into the computer upon its arrival which helps pick up unnoticed errors, inconsistencies, and missing data.

Periodically, we visit the investigator during the course of the study as a motivating device, as well as to verify the data submitted. The frequency of these visits vary greatly depending upon the study and other priorities.

At the end of the study, we send the investigators a "termination" letter asking them not to enter any new cases, to complete any outstanding cases and submit them. We also ask that the unused drug be returned to us.

CONCURRENT THERAPY

We permit no concurrent antimicrobial therapy. Any case with concurrent antimicrobial therapy is automatically excluded from review (efficacy, but not safety). The use of non-antimicrobial concurrent therapy is discouraged to the maximum. Due to the unreasonable demands of the Agency in this regard, it makes many treatable indications impossible to study. It also significantly reduces the number of representative cases we are able to obtain. Now, I am not promoting concurrent therapy, but I am pleading that the FDA reviewer use some common sense in what and why he or she excludes a case from review. We are wasting thousands of dollars of valuable resources needlessly. The reviewer must use medical judgment. When bathing a dog with a non-medicated shampoo twice a month invalidates a deep pyoderma case, I think we have carried this no concurrent therapy a bit too far!

MEASUREMENT OF EFFICACY

The biggest problem of measuring efficacy is the true lack of quantitative yardsticks in most studies. Many of the factors we evaluate are subjective, not objective. Because of this built in limitation, it is essential that the pivotal clinical field studies be blinded and well-controlled. Then, any reasonable person with medical training can and must evaluate the data, even if it is subjective in nature.

In the case of antimicrobial drugs, generally the best and most objective measurement of efficacy is microbiological data. If the offending pathogen present on pre-treatment has been eliminated on

post-treatment examination compared to the control group in an adequate number of cases, then it is relatively safe to say that the test drug was responsible for this elimination. Bacteriological elimination is the primary measurement of efficacy. Yet, there are certain disease conditions, such as the skin infections, where normal flora causes a real problem in interpreting the data. In these cases, the Agency has been willing to accept a "healed lesion" as being a microbiological cure.

Another relatively objective measurement of efficacy is laboratory data. The improvement of urinalysis or hematology from pre- to post-treatment is often very supportive of efficacy. However, due to the wide variation in normal ranges, it is sometimes difficult to interpret these data. Other laboratory tests that may prove helpful are somatic cell counts (bovine mastitis) or histological improvement.

In our skin studies, we have encouraged investigators to take pre- and post-treatment photographs of the lesions. In many cases, these photographs are very supportive of clinical improvement or failure.

Body temperature may be another relatively objective measurement of efficacy in an antibiotic study. Unfortunately, not all infectious diseases produce high temperatures. This has not been a reliable parameter for us over the years.

Clinical response is a very important parameter in most cases even though it is subjective and nonquantitative. However, in a blinded, well-controlled study, clinical response is an important parameter to evaluate.

We do look at improvement in individual symptoms as well as overall clinical improvement. In many cases, definite trends are evident when individual symptoms are examined and compared across treatment groups. The relapse rate and outright failure are important factors to evaluate and compare. Time to improvement has also been valuable when comparing the efficacy of two antibiotics. Again, these are all somewhat subjective, but when the study has been properly controlled and blinded, they are valuable supportive yardsticks of efficacy.

Unless the study is blinded and controlled, these clinical parameters are often not valid. Open studies are not acceptable measurements of efficacy. They are confirmatory in nature but should not be used for the demonstration of pivotal efficacy. They can be very valuable in determining safety or incidence of side effects.

PAYMENT POLICY:

Over the years I have tried just about every type of payment from nothing, in other words "for the good of the profession," to "grants" to "by the hour" and "by the case." For most small animal studies, I believe the fairest policy is by the case. With this method, if an investigator does one case, he gets paid for one; if he does twenty, he gets paid for twenty. He gets paid for what he does and I only pay for what I get. This procedure also helps arrive at a fair payment per case as we simply list every item performed and place a fee for that service. We then pay for only the services they perform - if no blood chemistry, no payment. Thus, our payments may vary from $175 to $300 per case depending upon the work he/she does. If the case conforms to the protocol and we believe it will be acceptable to the FDA, we usually pay a bonus as enticement for better work.

PROBLEM AREAS:

There are several problem areas that I feel the AAVP&T, industry and FDA need to address.

1. Perfect Case Syndrome: The Agency is emphasizing the value of 10-20 "perfect cases" rather than an adequate number of good, medically evaluable cases. I am very concerned that if the Agency continues in this direction we are going to end up with inadequate dosages and unforeseen toxicity. The idea of greater numbers of "perfect cases" is absolutely out of the question due to the small size of our market and small financial return to the corporation. The Agency must change and reverse this perfect case trend.

2. Relaxation of Optimum Dose: Assuming an adequate safety margin, it is far better to overdose than underdose an antibiotic. The CVM is currently emphasizing the minimum optimum dose. This is the surest way in the world to increase resistance and make our antimicrobials less effective. Underdosing is a far greater threat than overdosing.

3. Cost/Time of Approval: The cost, and even more important,the "time" to approval of an NADA is becoming excessive relative to the size of our market. We cannot afford this luxury. There are too many good drugs not being developed for the veterinary profession due to the small return on investment due to time delays and costs.

   Just look at what is happening in the veterinary package pharmaceutical business. There is very little growth and I predict there will be even less in the future unless we can at least speed up the review process. The costs may be fixed and we may have to live with that problem, but why should it take 40 or so months to get an antibiotic approved for an indication in a dog after it has been used for years in human medicine for the same indication.

4. One Label Claim Syndrome: Industry fully realizes that the reviewers at the Agency are trying to do an excellent job. By doing an excellent job, they are demanding more and more data, more tightly controlled studies, more perfect cases, etc. As a result of trying to protect the public by doing a better job, they are in fact subjecting the public to greater risk. The reason for this seemly contradictory statement is that industry is not conducting as many studies due to these higher requirements, greater cost and longer time to approval. As a result, the practitioner will not have the latest pharmaceuticals with appropriate label claims.

   Unless there are changes in philosophy, we are going to see new antibiotics with one label claim in one species only. Then, the veterinarian will have to extrapolate the dosage, indications, organism sensitivity, etc. This will result in more misuse and greater potential side effects and toxicity. This policy will subject the practitioner to additional mal-practice. I sincerely believe the concept of "one label claim" and "extrapolate" is already here. It is up to this group working together for the betterment of our profession to change the direction in which we are heading.