

SECTION I

CLINICAL TRIALS--THE ISSUES

Chairman

Dr. Richard Teske
Food and Drug Administration

The Issues: Perspectives from FDA

Bob G. Griffith, DVM*

Introductory Comments

The Center for Veterinary Medicine is a relatively young institution. In the short span of 20 years we've been occupied with four basic tasks.

We first had to seek a clear definition and understanding of our responsibilities. Briefly stated, our objective is to assure and improve the quality of human and animal health, by fostering the development and safe use of innovative new animal drugs.

The second task has been to evolve an organizational structure that best suits our purpose. To do this we had to learn how to listen and communicate with all segments of the public we serve; how to effectively integrate the efforts of our scientific, administrative and legal staff; and finally how to selectively focus the efforts of our professional staff to maximize efficiency. More than at any time previously, with the recently implemented changes, we now have a logically designed, efficiently structured organization.

Our third objective has been to develop basic standards or guidelines to assess the safety and effectiveness of new drugs. We had to start from scratch. There was little or no precedent to rely on. Our initial efforts were understandably cautious in nature and attempted to anticipate all contingencies. A considerable number of these documents have been developed and are now available for mutual reference. With modification and refinement most have stood the test of time reasonably well.

We have progressed. As we acquired experience we gained confidence. Confidence has brought more reason, balance, and flexibility to our methods. Whether individually as a concerned citizen, as a public advocate, a member of the academic community or private industry, collectively you are the origin of many procedural initiatives the Center has taken.

The fourth major assignment we've obviously had is to continue to perform the essential review, research and regulatory functions on a day to day basis.

*Food and Drug Administration, Center for Veterinary Medicine, Parklawn Building, Room 6B-24, 5600 Fishers Lane, Rockville, MD 20857.

Salient Issues Related to Successful Clinical Trials

The preceding introductory comments summarize the Center's activities to date. Now let's turn to the subject of this seminar - how to properly test a new drug under actual conditions of use in a clinical field trial.

Frequently Encountered Deficiencies in Clinical Data

The need for this symposium is illustrated by the fact that it is not uncommon to receive applications with less than 50% usable data from the clinical studies. This occurs more frequently with anti-infective drugs, especially non-food animal drugs, perhaps because the closer client/patient relationship complicates post-treatment retrieval of the necessary data.

Often, many cases are unusable because of improper or inadequate diagnosis, failure to identify the etiological agent, misdosing, concurrent use of other drugs, failure to obtain data on the critical parameters, and lack of post treatment follow-up. If this symposium can identify the means to correct this problem, we will have performed a most useful service. The Center recognizes the barriers and inherent difficulties associated with obtaining sound clinical data, but we also stress, and believe that you understand this information is essential.

Critical Factors in Conducting Clinical Trials

Let's spend the next few minutes, first to identify, and then discuss each of the critical factors necessary to conduct a good clinical study.

Prerequisite Data

First, is there sufficient prerequisite data available from preliminary laboratory studies to justify a commitment to clinical field trials? Is the identity of the test drug adequately defined? Is there sufficient information to establish the dosage form and final formulation? Are there adequate standards for stability and reproducibility to assure that the drug test is essentially the same as that eventually proposed for marketing?

Do you know the physiological and pharmacological profile? The pharmacokinetics? The mechanism of action? Has the probable therapeutic dose and dosage regimen been determined? What are the minimum acute and longer term toxic doses? Are the toxic syndrome and most vulnerable organ systems known? Can the data be correlated to establish the margin of safety in the target species?

Human Health Issues

Before proceeding to clinical trials, all possible human health issues should be thoroughly examined and addressed. If the drug is for food animals, have the issues of tissue residues and withdrawal time been adequately resolved? Is the drug a controlled drug substance? Is there potential for drug abuse, misuse or improper diversion? Is there a potential human health hazard from the possession, handling and administration of the drug? If there is a potential human health hazard, does the nature of the risk prohibit clinical testing, or can it be adequately contained or prevented? What directions, use restrictions, and other safeguards must be followed to prevent a public health hazard? Finally, is there an environmental hazard, and if so, can it be adequately managed?

Animal Welfare

The issue of animal welfare ranks second only to human health in considering the justification for clinical trials. Are conditions of the study humane and compatible with the welfare of the animals involved? Is the risk minimized? Does the possible benefit from the study justify the animal exposure to the test drug?

Selection of Investigators/Commitment to Monitoring

Two early make or break decisions you make are the selection of investigators and the extent of the commitment to monitoring. This determines how well the protocol is followed and may influence how long it takes to complete the study

Clinical studies aren't easily accomplished. The investigator should be given all the assistance possible. This means that the trial sponsor provides all information available on the drug; adequate, clear and concise instructions on the use of the drug; and the advantages of frequent contact by the sponsor.

An Adequate Protocol

If, after all of these considerations, the pre-clinical data is go, the next critical factor is an adequate protocol for the clinical trial.

There are 7 essential elements in a clinical protocol. First, is the objective of the study clearly identified? Is there a well defined disease entity targeted for treatment? What purpose does the drug serve? Is treatment intended for disease prevention, control, elimination, etc?

The next element is proper criteria for selection of patients. In other words, ample diagnostic criteria are needed to assure an accurate diagnosis.

The allocation and/or grouping of patients depends on the number and type of variables. Is the study intended to test more than one dosage form? More than one active ingredient? Several indications? Several levels of severity? Acute vs chronic? Is the disease self limiting? Studies with multiple variables are trouble prone. Limit variables to the extent possible.

The fourth element is acceptable controls. Usually, this means a separate negative, placebo, or positive drug control group. When compatible with humane practices, negative controls are preferable. Owner consent should always be obtained.

The fifth essential element in the protocol is the selection of the best parameters available to evaluate the treatment response. When possible, always use objective, quantifiable parameters. Subjective parameters are used to obtain pivotal data only when there is no other option. Blinding procedures should be used, and are especially needed if there is no alternative to subjective parameters. Graded criteria for evaluation should always be well defined.

Use an adequate number of parameters to conclusively determine whether the drug had the desired effect - but don't over-elaborate. Avoid adding confusion to an already complicated problem at attempting to apply an excessively complex solution. Usually, the pivotal data is best obtained from no more than 2 or 3 parameters while others may be relied on for supportive or backup purposes only. When some parameters are considered more important than others, the relative value of each should be stated before conducting the study.

This leads to the next important element in the protocol, a pre-determined methodology for statistical analysis which will be discussed in detail this afternoon.

The Perennial Issue - How Many Cases Are Required?

In discussing clinical trials the question most frequently asked is how many cases will be required. The answer is determined by considering several factors.

Is the drug for food or non-food animals? More cases are usually obtained for food than non-food animals because of herd vs individual treatment. What is the magnitude of response? A dramatic favorable response required less cases to be convincing than a marginal

response. What type of comparative controls were utilized? Efficacy can usually be demonstrated with fewer cases by comparing the test drug with negative controls than positive drug controls.

What is the incidence of the disease? More cases would be needed to document safety and efficacy for a broad spectrum anthelmintic than for treatment of adrenal disease or hyperthyroidism. What is the nature and extent of the drug's toxic risk: How subtle - how predictable - how discernible is the potential toxicity? If the drug has the inherent potential to cause severe reaction in a uniquely susceptible, small subpopulation of animals, clinical trials involving broad representation and very large numbers of animals may be the only way to identify the problem. A classical example is the organophosphate canine anthelmintics. For some drugs, perhaps we should consider a two phased clinical study: the first phase being a relatively small controlled study to establish data in a large number of animals to confirm the safety.

Format for a Data Summary Analysis

The final job is to assemble, collate, and index the raw data obtained from the trial. As a task for this symposium, I recommend the development of a genetic prototype or format for submitting a data summary analysis of the information obtained from clinical trials. If properly designed, the prototype would achieve a large element of consistency but also be readily adaptable to the specific needs of a given trial. This would not alleviate the need to submit raw data, but could greatly facilitate scientific review of an application.

To be meaningful, the data summary has to provide two things. First, it has to flush out the critical information needed for decision making. Second, it has to do it accurately. All clinical observations should be included, not just those perceived to be drug related.

The concept, if properly developed, may be mutually beneficial. It's something we can accomplish together. I recommend it for your consideration.

Concluding Comments

In closing, permit me a moment for personal reflection. We have made a good beginning. We're ready for the future. Together, there's no limit to what we may accomplish. We will accomplish more because our personal freedoms cause us to care more. I just want to express the pride and appreciation I have for all of us, because we are all part of the most open, diverse, progressive, competitive and socially compassionate system in recorded history - we call it America.