

Clinical Trials: Responsibility of FDA/CVM

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This is the third symposium sponsored by the AAVPT in conjunction with the FDA and pharmaceutical industry to address areas of mutual concerns. The latter conference on dose determination as is this clinical trial session represents a sharper focus on actual problems and not just theoretical concerns. The FDA also sponsored a manufacturing workshop some months ago, which was very favorably received by those in attendance. That workshop grew out of our program analysis on New Drug Evaluation which we conducted in 1983. The evaluation examined our approval records for a 10 year period from 1972 to 1981. Among the data examined we looked at deficiencies in an application and what particular areas constituted the greatest problem. Manufacturing requirements headed the list. However, not far below were deficiencies related to effectiveness. Of 67 total NADA's examined, 78% in the original filing had deficiencies related to effectiveness. The majority, and I quote, "related to providing that the drug will have the effect it purports to, . . . because of inadequate reports of well-controlled investigations including field investigations."

I bring this out simply to reinforce the Center's desires to improve the record with everyone's cooperation. Our sessions here will hopefully aid in the future development of better, more informative clinical studies, an area in the NADA process I believe may have been overlooked in the past. Obviously, the data from our survey would indicate that attention is needed.

The topic I was asked to cover today is that of FDA's responsibilities relative to clinical studies with therapeutic drugs. Others have discussed technical aspects of developing and conducting clinical investigations. I will attempt to focus on my perceptions of those responsibilities.

Years ago when the Bureau of Veterinary Medicine was first beginning the only real responsibility to clinical studies was to the evaluation of the safety and effectiveness data submitted to an application. Even that function was to a large part less significant than it is today because we were still in an era of concern with the historical responsibilities of the Agency. Namely, is the labeling not false or misleading, and is it manufactured properly? Safety and effectiveness was left to the individual reviewers opinion and experience.

Today we have evolved our concerns to cover the entire developmental process of gathering clinical information on drugs. Not only has evaluation become a more exacting science but we are concentrating now on assuring that studies are properly designed and conducted. Of course, these latter responsibilities have led to what some may feel is further regulation over drug research. But, in a way, the Agency has also become consultants to the industry and their investigators through these efforts, and provides daily education based on the many years of experience we have had with the pharmaceutical industry.

Let's examine these expanded responsibilities a bit closer.

Of course, before a study can actually be conducted, it must be conceived and properly designed. This is where a second major responsibility of FDA has taken on greater importance over the years.

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1. The Agency must insure that clinical investigations are adequately designed.

Unlike the human drug regulations the animal drug investigational requirements make no demands on the sponsor to submit a protocol to FDA for prior approval. The Center, though, has encouraged the submission of and face to face discussion on written study protocols. We have the responsibility to take this activity seriously, since this clearly can make the difference between rapid approval and continuing delays in getting the product cleared.

Within this responsibility, I believe several principles can be identified under which reviewers and supervisors need to operate.

- a. Make sure we know what we want from the clinical study.

The criteria for evaluation must be clearly defined for the sponsor. Requested information should be scientifically justified as to what it will provide, and why it is important to the evaluation. The sponsor should be made aware as to how we will likely handle the information. For example, will concurrent therapy seriously compromise the evaluation or are there conditions where other drugs may be used without negating the test drug results. To the extent possible, we should define for the sponsor how various categories of response will be viewed. Will only those animals rated as "excellent" responders be counted in the success column, or will cases rated as "good" also be included? It is important that both the FDA and the drug company have a common understanding of these points before the study is underway.

- b. We need to be flexible and receptive to alternative approaches.

There is no one way of conducting a clinical evaluation. It is frequently easier to advise a company on a study design the Center is comfortable with. An investigator, though, may have an alternative approach to achieving the same end points. As long as the correct scientific decisions can be made on the data, we need to allow such innovation.

- c. Consider the clinical investigators position and potential difficulties.

A realistic approach to study design must take into consideration the limitations of the clinician to provide the information required by the protocol. Are the time frames and frequency of post treatment follow up examinations realistic. How will the investigator deal with failure of the owner to return for followup?

- d. Insure that the results we want are achievable.

The protocol must be carefully thought through step by step as if we were responsible for conducting the study. We shouldn't design studies which require procedures that have a high likelihood for failure or can't practically be performed. A protocol which requires 5 daily IV injections for outpatient treatment for example, is nearly impossible to perform. Can we expect that all animals will be administered a specific required dose and frequency considering the variation in tablet, capsule or other dosage form size?

2. FDA must assure the integrity of clinical investigations and reliability of the test data.

The Bioresearch program has been established to monitor and inspect ongoing and completed safety and efficacy studies. Best known in this program is the Good Laboratory Practice Toxicology inspections. However, FDA also conducts a clinical investigator program under the bioresearch directive. It is generally believed that the GLP conducted studies are far better controlled than our clinical investigations. There are a number of reasons for this. The clinical investigator program operates under a compliance Policy Guide with loose direction given from the INAD regulations under Sec. 511. Most of the studies conducted involve individuals and not tightly run laboratories with quality assurance Boards, etc. Finally, the clinical investigator regulations have not yet been codified which would exact clearer standards for the conduct of these studies.

However, with these shortcomings, the FDA will continue to inspect investigations on an as needed priority basis.

The Center considers all clinical work being performed with either new drug entities or with new combinations to be of high priority for inspection. Therefore, it is policy of New Drug Evaluation to direct inspections within limitations of resources to these type of studies. The data derived from such studies represent the more important type of data the Agency must evaluate; new entities simply by their newness, and drug combinations by their frequent difficulty in analysis. Hence, those of you involved in studies on these kinds of applications should expect a visit from the FDA field offices. The field inspectors operate only through headquarters direction. The inspector is charged with reporting on what he observes and what he believes to be deviations. The inspectors are not scientists though and cannot determine how serious the deficiencies may have compromised the study. He or she is, however, there to assist the investigator with compliance with the regulations, and suggest better ways of recordkeeping when appropriate.

A full clinical inspection is not a trivial matter. The clinical investigator's entire operation with regard to the study is reviewed. Recordkeeping, test article accountability, animal identification, and owner consent are among the items reviewed by the inspector and reported on to headquarters. The inspector will review in some detail the status of an existing protocol for the study. There may be confusion here with this responsibility in view of my previous comments that CVM does not require protocol approval. As far as the FDA inspector is concerned he must ascertain whether a written study plan was provided to the investigator and what, if any, changes have been made since the start of the trial. The regulatory direction for this comes from the new animal drug regulatory requirements within the definition of a well controlled study. Such a study must have a plan, defining, among other things, the objectives method of selection, methods of observation, and type of controls.

The inspector will consider the lack of a protocol addressing these criteria to be a deficiency in the study, regardless of whether or not CVM has reviewed and approved the protocol. No scientific judgments are made though by the inspector as to the validity of the design.

A study may be inspected at any time during the course of the trial or within a certain period upon completion of the study depending on the status of the pending NADA. It is obviously of greater significance to CVM for the review process to inspect a study during or near its completion so as not to delay the eventual review of the data and also to make any necessary mid-course corrections. Assignments for inspections will therefore be attempted at the early INAD phase of the drug development. However, records on a completed study which is considered pivotal to an NADA may be inspected subsequent to FDA review if significant questions are raised with the data.

Now that we have assisted in the design of the study and are assured it was properly conducted, our third responsibility is with the evaluation of the data.

3. FDA must assure that the data was properly evaluated and the correct conclusions were drawn by the sponsor.

The FDA must approach the evaluation of clinical studies in an objective and consistent fashion. If the appropriate criteria have been examined and the data is complete, the job is relatively easy. However, with biologic processes the bottom line in the final analysis will always involve medical judgment. Statistical analysis can serve as a useful tool, but we cannot demand that statistics alone prevail in our final judgment. Many clinical studies may result in a medical conclusion that an efficacious response was observed. Because of what statisticians call the power of the test, though, we may not see statistical significance as the study may not be large enough particularly in non-food animals to satisfy a rigorous statistical examination. Conversely, significance may be satisfied when a comparison is made between the treated and control groups, but the level of efficacy attained is not medically acceptable. This is not to say that we shouldn't try to design studies which can be statistically scrutinized, since an assurance that the findings are not by chance benefits both the company and the FDA. But therapeutic trials can never be handled in the same manner we might review low level growth promotants, for example, where thousands of animals and specific objective measurements are made.

The clinical study will continue to remain the keystone of efficacy testing on therapeutic drugs. We are discussing these days the use of more sophisticated pharmacokinetic techniques to predict efficacy. Of course, models have been in use for some time and in many cases are more important in determining efficacy than are field studies. Such is the case with anthelmintic critical testing. Personally, with my own concern for the use of systemic animal models from an animal welfare standpoint I would like to see more tightly controlled better clinical studies used to support efficacy. Actual experience in the naturally occurring disease cannot be substituted.

I hope that this symposium will improve our techniques in the clinical setting. Thank you. I believe it's now time for discussion.