

Integration of Clinical Trials

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Clinical trials are generally assumed to comprise studies of naturally occurring disease in a normal clinical setting. Dorland (1) defines clinical as that pertaining to or founded on actual observation and treatment as distinguished from theoretical or basic sciences. Recently, in the context of product evaluation, Davis (2) defined clinical trials as follows: "For animal drugs, all studies conducted in the target species of intended use should be within the definition." Davis (2) also indicated that preclinical trials in laboratory animals should provide information essential to the planning of the clinical investigations and that the latter should be conducted in four phases as for human drugs (3). The description of Phases I through IV (2) is indicated in Table I.

TABLE I.

- Phase I: Routes of elimination, pharmacokinetic behavior, dosage range, minimal toxic doses and other essential information in healthy animals of the target species.
- Phase II: Safety and efficacy trials in limited number of animals with target disease or experimentally induced comparable disease.
- Phase III: Trials in appreciable number of patients in variety of settings to confirm the generality of Phase I and II results.
- Phase IV: Long term surveillance of product during widespread clinical use in the field after initial approval.
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Such product approval studies are conducted in a setting of numerous pressures and constraints. There are the ever increasing pressures for safety, humane and ethical care, and product availability on the one hand and the constraints of escalating costs of development and health care on the other. The limitations of design and control of field trials especially have become more and more apparent and the use of induced disease models has increased. The precision and sophistication of diagnosis have improved immensely and the number of disease syndromes escalated. The dial up diagnostic program at Cornell includes over 5,000 diseases. At Mississippi State, 2nd and 3rd year DVM students are exposed (? taught) 1,267 diseases; hospital patients have an average of 2.8 disease problems each; students are required to possess a computer. Escalating clinical

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complexity is demanding additional emphasis upon fundamental or model disease processes rather than specific individual diseases, and the use of the computer for information processing and even diagnostic aid. Nationally there is a continuing trend towards consumption of white meat; product trials in large population units, especially for the alleviation of sub-clinical disease, have become important. Trials in 20 acre ponds of one hundred thousand or more fish are especially challenging (4). In veterinary medicine product approvals have often become increasingly specific (narrow) relative to both dose and target syndrome, with the result that clinical use for other than that specified often predominates.

It is in this above setting that a Task Force of the American Academy of Veterinary Pharmacology and Therapeutics has expressed, among others, the specific concerns that dosage recommendations have become excessively restrictive and that substantial evidence of efficacy should comprise a blend of studies from various sources based upon clinical and scientific judgment (5).

The Task Force states, relative to efficacy, that any one or all studies (retrospective, basic pharmacologic, controlled clinical or model, and clinical trials) may have to provide the bulk of evidence, and that usually a blend or mix will be required.

The blending suggested by the Task Force is appropriate not only for efficacy studies but also for all four phases in the target species. The unnecessary use of animal resources is unacceptable for humane, ethical and economic reasons. Consideration of such a blend or mix of all phases will be illustrated.

An early and continuing experience with drug approval has been with anesthetic drugs. Preclinical data are often comprehensive and may be very beneficial in characterizing the product. Solubility, partition-coefficients, boiling point, and kinetic data amongst other features permit accurate prediction of the nature of drug action inclusive of induction and recovery characteristics (6). Parameters of efficacy (analgesia, sedation, relaxation, immobilization, safety) have been well defined, and recently minimal alveolar values (MAC) have standardized comparisons of inhalation anesthetics (6). Significant studies necessary for approval therefore comprise preclinical data, phase I and II metabolic, elimination, pharmacokinetic, dose range and minimal toxic data in normal healthy animals. While Phase III studies have been conducted, few clinical facilities, other than institutions, have the ability to measure MAC values and to monitor appropriate cardiovascular and respiratory parameters. In addition, observer and prognostic bias are extremely difficult to eliminate. The latter may be partially limited by subjective grading of anesthetic risk (6). The patient however has a broad variation of disease syndromes and intensity with unique supportive therapy regimens prior to, during, and after anesthesia. Unless such a product was of a new class of drug, strong justification could be made for elimination of Phase III field trials in the presence of solid Phase I, II and IV studies. In a recent anesthetic

trial (7, 8, 9) the drug was not of a new class, preclinical retrospective European data was available, analgesia efficacy and dose was evaluated in an equine colic model and a controlled comparison was made with a similar approved product in normal animals. Again valid controlled field studies (Phase III) would impose such a constraint upon the target syndrome and associated regimen that it would have little additional relevance to the real world.

Induced disease models are often used for efficacy and dose response studies. The induced disease may be identical to the target disease, comprise the same fundamental pathologic process, or be a closely related to it. During the past 30 years many drugs have been studied to assess their efficacy for bovine anaplasmosis. A relatively uniform syndrome can be readily induced and measured objectively, and suppression of parasitemia has been shown to be highly correlated with efficacy (10). It is possible that efficacy may now also be assessed in vitro (11). The incidence of the naturally recurring disease varies greatly, clinical disease may not be recognized or its diagnosis may not be timely, and mortality may vary from 0 to catastrophe (10). Having done well controlled-dose response, efficacy and safety studies, are Phase III studies necessary? Is it ethical to delay approval due to annual variations in incidence, when the next outbreak may be catastrophic? Would not Phase IV studies be equally or even more satisfactory? A group such as the anaplasmosis research workers would have been most interested members of this group subsequently reported many such studies. There are a number of other diseases for which a similar case can be made.

During the last 10-15 years there have been numerous studies concerning the efficacy of non-steroidal drugs (12), their mode of action has now been attributed to cyclo-oxygenase inhibition. Potential efficacy has usually been indicated in laboratory animal models of inflammation. These have proven highly predictive. Inflammation models have also proven satisfactory for dose determination and efficacy in the target (equine) species. In one equine inflammation model the inhibition of prostaglandin E_2 has been demonstrated (13). Subsequent to subacute toxicity studies and to well controlled efficacy studies in the inflammation model, equine clinical trials have been conducted in syndromes having the same fundamental pathologic lesion (i.e. inflammation - a lesion or process of which the mediation has been well documented). Clinical trials were conducted under limited conditions of control. They occurred at multiple locations, numerous disease syndromes of varying intensity and duration were treated, criteria for inclusion or exclusion into the study were generally minimal, criteria for evaluation were generally subjective, and circumstances were such that it was difficult to control bias. While there is no laboratory data to indicate that the cyclo-oxygenase inhibitors significantly suppress healing, this process was not considered despite the fact that it is an integral part of the overall inflammatory process. Failure to consider healing adequately as a parameter has had significant implications relative to the use of intraarticular corticosteroids (12).

Intraarticular hyaluronic acid and polysulfated glycosaminoglycan have recently been evaluated for efficacy and dose response in induced carpal joint models (12). The studies were controlled, bias was eliminated, and efficacy was assessed by objective clinical and laboratory parameters. Several of the latter were subsequently used in field trials (Phase III). Joint fluid as well as clinical parameters were used in some studies to determine admission to or exclusion from the trial, and the target syndrome was limited to the carpal joint. Numbers in the trial and coordination between clinical investigators were never such that these could be considered as well controlled clinical trials. They were subject to such variations as lack of positive control, supplemental therapy, lack of compliance, variable duration and degree of syndrome, degree of training, and exercise - parameters over which it is unrealistic to expect appropriate control in the current private clinical setting. Approval was subsequently granted for restricted (limited) disease syndrome(s) and precise dosage, despite the high probability of both efficacy and use in numerous other closely related syndromes.

Having discussed trials in which Phase I and II studies are of major benefit and in which Phase III are at best limited, it is appropriate to mention the other extreme - use of the naturally occurring disease. Uniformity, frequency and predictability of occurrence of the natural disease may permit use of this for Phase II and III studies. The occurrence of diarrhea in recently transported bovine neonates is one such example, although the variability of disease intensity presents problems. Another such example has been described by Brandt (14) in which sulphonamide therapy of bacterial pneumonia of calves was studied. Phase II studies in clinical disease nevertheless are generally difficult due to availability, varying intensity, and to ethical considerations. These problems have also been discussed recently by Gingerich (15).

After consideration of selected drug studies for which emphasis of the various Phases was indicated, it is appropriate to mention briefly the problems of field trials which are often conducted at multiple locations. Problems of such trials have been discussed among others by Meinert (16), Morgan (17) and by Kramer and Shapiro (18). Most trials are too small to answer the questions they are designed to answer - in fact in veterinary medicine not only are the questions too broad (confirm efficacy, dose, safety, establish use data), but they are not well defined. Small trials are of course encouraged by the problems of cost, limited availability of patients, and coordination of multiple study sites. At the same time few clinicians have been trained in the design and conduct of experiments, and the art and science of clinical trials is not yet recognized as a discipline. The biometrician may be viewed as an impediment and if considered at all is thought to be one who conducts analyses at the end of the project. When approached concerning a project, clinicians (and sponsors too) underestimate the necessary time and effort, believing that the study can be "piggybacked" on routine clinical procedures with the result that everything suffers. Patient numbers are usually overestimated forcing extension of the study period, reduction in numbers and/or unequal distribution at

various study sites. Lack of diagnostic precision with consequent uncertainty of patient selection and discrimination may also occur in studies at private locations. In fact other evaluation criteria may similarly suffer. A "shipping fever" field trial is especially likely to have increasing variables due to the difficulty of diagnosing disease subtypes. In equine osteoarthritis, osteoarthritis may be predicted upon radiologic changes which are late to occur (12).

Other problems of the clinical (field) investigation is also confounded variations in compliance and follow-up, in supportive therapeutic, management and nutritional regimens, and disease intensity, duration, and complications. In addition it is often difficult to overcome bias, to select an appropriate positive control, and to comply effectively with randomization. That these problems are not unique to our own experiences has been supported by review of a number of freedom of information summaries.

Having indicated some of the problems and variables it is understandable that uniform treatment of variables by diverse clinical investigators is an extremely difficult task. Increasing the number of trials and locations does little if any to correct the situation. It requires careful planning and design of a protocol of minimal complexity and achievable goals, with thorough communication and input from all concerned, including the biometrician.

- (1) Preclinical and the clinical (Phase I - IV) studies comparable to those of man (3) should be:
 - (a) Defined to focus upon the specific objectives of dose determination, safety, efficacy and post approval product development.
 - (b) Planned to adapt for the variable features of drugs classes and of initial products in a class versus subsequent ones.
 - (c) Should be planned and organized to allow full integration, to avoid unnecessary use of resources including unproductive repetition, to achieve prior approval with a reasonable degree of FDA commitment. The amount of data required should be inversely related to that available for the drug class.
 - (d) Relevant retrospective studies should be given full consideration in the product approval profile developed.
- (2) Clinical studies in naturally occurring disease should be well designed and controlled (i.e. capable of acceptance by review board of a research journal). When conducted at more than one location, the design should reduce inter-investigator variables to a minimum and be acceptable as a multicenter study. (Scientific judgement is rarely if ever improved by addition of more and more poorly controlled cases at more and more locations.)

- (3) The clinical setting of the studies should require:
- (a) An experienced clinical investigator fully cognisant of the requirements of a well controlled clinical study.
 - (b) Diagnostic resources which fully satisfy the needs of the study (e.g. for admission, exclusion and recognition of potential complications).
 - (c) Availability of biometric support.
 - (d) Capable of satisfying GLP requirements for a preclinical study.
- (4) Product approval should reflect the clinical (real world) application of the fundamental disease process used for determination of efficacy. Confining approval to a very specific diagnostic entity is unrealistic.
- (5) A post approval product development plan should be incorporated in the initial product approval strategy. Certain goals currently addressed in preapproval field trials are more appropriate for this stage. They include for example:
- extension of target syndromes
 - adjustment of dosage range relative to disease and other potential modifiers
 - the recognition of low incidence reactions, complications
 - the recognition of favorable and unfavorable drug interactions

"The truth may be reached by different pathways. They are not always straight and true: each may have difficult, even misleading, twists and turns. It is our duty to determine the best we can, the validity of each effort." Schumacker, (19).

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