

THE ISSUES: PERSPECTIVES FROM INDUSTRY

Daniel A. Gingerich, D.V.M., MS*

INTRODUCTION

Perhaps the most significant event that gave rise to the issue of clinical trials in new animal drug development was the passage by Congress of the Harris-Kefauver amendments to the Food Drug and Cosmetic (FD&C) Act in 1962. Prior to 1962, the FD&C Act permitted marketing of new animal drugs if the safety, manufacturing controls and labeling were adequate. The 1962 Harris-Kefauver amendments basically added the requirement that effectiveness be demonstrated as well.

Who could possibly disagree with that? By now probably no one would disagree with Congressional intent in requiring effectiveness data. But back in 1962, how did one obtain effectiveness data on new animal drugs? We all know the answer - in clinical trials, of course.

I don't know what you were doing in 1962, but I was involved in importing Brown Swiss cattle from USA to Bolivia under the auspices of Heifer Project, Inc. (that was before I ever thought about veterinary school). No sooner had those calves gotten off the plane than they were covered with blood sucking ticks, and within weeks were severely affected by life-threatening babesiosis. The veterinarian had us wash the calves with Asuntol (whatever that was) to remove the ticks and give tetracycline injections to eliminate the Babesia. The results were dramatic. I had everything I needed to prove efficacy: sick animal, course of treatment, recovered animal, and most importantly happy client. Clinical trials were all I needed in 1962 to prove efficacy.

But since 1962 there have been tremendous advances in the field of pharmacology and toxicology. In many instances methods of measuring responses to drugs have been developed that are exquisitely more sensitive than what is possible by clinical observation. It would seem rational therefore that drugs should be evaluated by the best possible methods - which often implies studies other than clinical trials.

* Director of Veterinary Research, Bristol Animal Health Care Division, P.O. Box 4755, Syracuse, New York 13221-4755.

In this paper the thesis is developed that, although clinical trials are required and are important in the new animal drug development process, other available pharmacologic methods are also important and should now be given more weight in the overall determination of safety and effectiveness.

FOOD, DRUG and COSMETIC ACT

Did Congress allow for more advanced methods of determining effectiveness or did Congress mean only clinical trials? Let's take a look at the Act as amended:

Congress, 1962: Evidence to Establish Effectiveness

- ... adequate tests
- ... all methods reasonably applicable
- ... substantial evidence

(note that these are judgement words, which seem to call for enough evidence to be convincing, by all available relevant research methods, but no mention of clinical trials thus far)

... adequate and well-controlled investigations

(one might suppose that the term "well-controlled" carried a substantially different meaning in 1962 than it does today in 1985)

... including field investigation

(here at last is the first mention of what we now call clinical trials)

Regarding clinical trials, it would appear that a reasonable interpretation of Congressional intent in the Act would be that a drug product must also be evaluated under actual conditions of proposed use. The Act does not seem to imply that safety and effectiveness must necessarily be proven in clinical studies, but rather that clinical studies must be conducted and that the results must be confirmatory of safety and effectiveness.

It is thus apparent that the FD&C Act requires, but does not emphasize, clinical trials.

REGULATIONS AND GUIDELINES

But apparently judgement words don't work very well in government. For over the years since 1962, the Federal Register has burgeoned with regulations to more accurately define what Congress intended. Beyond the regulations and proposed regulations, which were designed to interpret the FD&C Act, guidelines and proposed guidelines, designed to assist firms in interpreting the regulations, have proliferated as well.

On the whole, the regulations that have emerged since 1962 and which are now published in the Code of Federal Regulations (CFR) have contributed greatly to the new animal drug development and approval process. However, much of the regulatory activity has emphasized clinical investigation, to the exclusion of other methods of obtaining substantial evidence of effectiveness. Likewise, disputes that arise during the review process are, in our experience, more likely to involve clinical trial issues than debates over results of model studies, pharmacokinetics, etc.

Adequate and well-controlled ... CFR section 514.111(a)(5)(ii) spells out the "principles [that] have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical (field) investigations". It is doubtful that any knowledgeable professional would disagree with those principles of good science. It is also doubtful that any good, conscientious clinician could or would ever satisfy all the criteria set forth in that section. The most serious flaw in an "adequate and well-controlled clinical investigation" is that it really is not a clinical investigation at all. Veterinarians do give steroids, do give various drugs in colic, do wash wounds with antibacterial shampoos, do treat mastitic cows with oxytocin, do treat mange in pyoderma cases, do give urinary acidifiers in cystitis cases. Yet it has been our experience that such procedures are not permitted, and we have had clinical cases thrown out of Washington due to all of the above reasons.

I therefore contend that:

THE TERM "WELL-CONTROLLED CLINICAL (FIELD) INVESTIGATION" IS PARADOXICAL. STUDIES CONDUCTED UNDER 514.111 ARE REALLY EXPERIMENTS BEING CONDUCTED IN THE CLINIC.

I would suggest that the issue of whether or not the requirements of 514.111 are in conflict with Congressional intent in requiring field investigation be debated during this symposium.

Controls in clinical studies. A particularly controversial provision in the clinical practice setting, as the group assembled here well knows, is the insistence on a control group. The regulation provides for four types of acceptable controls: (i) no treatment, (ii) placebo control, (iii) active treatment control, and (iv) historical control. In most clinical disease conditions in veterinary medicine it is generally agreed that untreated controls or placebo controls are out of the question on the grounds of professional ethics. Historical controls have never, in our experience, been acceptable to FDA. That leaves active treatment controls as the only realistic option for conducting controlled clinical trials. We have found that active treatment controls do make the lawyers happy in that they satisfy the "well-controlled" provision of the regulation. However, active treatment controls in clinical trials usually contribute very little pharmacologically to knowledge of the effectiveness of a drug product and even less statistically -which of course leaves the statistician unhappy.

It would appear therefore that "well-controlled" clinical trials are conducted largely to satisfy the lawyers. The clinician should be entitled to evaluation under actual practice conditions. Neither the pharmacologist nor the statistician is likely to find substantial evidence of effectiveness from the results of positive control clinical trials alone. This leads to the conclusion that:

Positive controls in Clinical Studies (514.111)
contribute a great deal legally, but
contribute little clinically, pharmacologically or statistically

VALUE AND LIMITATIONS OF CLINICAL TRIALS

The foregoing discussion is not intended to imply that clinical trials are of no value and should be abandoned. Rather the assertion is made that clinical studies should be recognized for what they are, with all their limitations, rather than the only forum in which the effectiveness battle can be won or lost.

There are, of course, some new animal drugs and some disease conditions which are best studied in clinical trials. The economic value of growth promotants, I am told, can only be proven in extensive clinical trials under actual conditions of contemporary animal husbandry. Bovine mastitis and equine metritis are conditions in which new drugs are probably also best evaluated in clinical studies. This is because no really good models are available, the conditions are prevalent (there is no shortage of clinical patients), are readily diagnosed by objective criteria, and response to therapy can be readily verified by accepted criteria.

But many questions are simply not best answered by clinical trial data alone. For example, clinical trial data have long since been abandoned as the sole means of determining safety of drugs, as underscored by the emergence (and subsequent disappearance) of the Target Species Toxicology Guidelines.

Yet despite the proliferation of pharmacologically rational methods of evaluating the effects of new animal drugs, we remain preoccupied with clinical trials. If we aren't, why is this entire symposium devoted to clinical trials?

BIORESEARCH MONITORING PROGRAM

As evidence of FDA's preoccupation with clinical trials, I cite the Bioresearch Monitoring Program initiated by the FDA Commissioner in response to adverse findings during a series of audits of facilities, data, and investigators involved in data collection.

As you know, this program culminated in 1977 and 1978 with proposed regulations covering the Sponsor/Monitor Program and the Clinical Investigator Program, commonly called Good Clinical Practices regulations or GCP's. Basically these programs, which have been implemented although never finalized as regulations, require more complete documentation of all aspects of clinical investigations, from adequacy of facilities to accountability of test drugs to strict adherence to the study protocol.

Who could possibly disagree with the importance of adequate documentation to insure dependable study results? Probably no one would disagree with the importance of the issue, but let us examine the effects of the program.

On the positive side, the GCP proposals have had a beneficial effect on our clinical program at Bristol Myers. This began with an FDA audit of our clinical operation in the late 70's and resulted in the development of the monitoring system we have today. We're proud of our system (which Jim Rourke describes in detail elsewhere in this symposium) and would point out that it is the result of industry and FDA working together and taking each other very seriously.

The negative effect of GCP's, however, is to focus attention away from the "adequate ... reasonably applicable ... substantial evidence" provisions of the Act, to the "adequate and well-controlled investigations" provision of the Act. FDA inspectors are assigned to audit selected clinical studies for compliance with proposed GCP

regulations and adherence to the protocol. We have found that these inspections, although well intentioned, often result in misunderstandings and misinformation, since the inspector usually has no scientific training while the hapless veterinary investigator may have little experience in dealing with government auditors. The net effect of the Bioresearch Monitoring Program, then, is to focus attention not on what was done, what was found, and what was concluded, but rather on whether or not the study was conducted in compliance with every provision of the proposed GCP's.

An example illustrates the above point well. One of our excellent veterinary investigators was evaluating the efficacy of intrauterine infusion of amikacin, an aminoglycoside with activity against Gram-negative pathogens, in brood mares with endometritis. The study design required culture and identification of the organism at an outside microbiology laboratory and selection of amikacin or the reference control drug on the basis of a randomized treatment schedule. This veterinarian's usual practice was to examine and culture each mare prior to initiating therapy. For purposes of this study, therefore, the investigator pre-screened the cultures in his own laboratory to determine which mares were infected with Gram-negative, aminoglycoside susceptible pathogens. Having determined that, he would submit the culture to the official laboratory for identification and susceptibility testing, and refer to the random treatment schedule to determine which of the study drugs should be infused.

During an audit, the FDA inspector noted the veterinarian's pre-screening procedure, made the assumption that the veterinarian was assigning test drugs on the basis of zone size around sensitivity discs and interpreted that as a protocol violation. The inspector's report filed in Washington resulted in the disqualification of all the data from that study.

The inspector's observation was correct (the veterinarian did pre-screen his cultures). His assumption and interpretation, however, were incorrect (the veterinarian did not select study drugs on the basis of zone size). The error went undetected all the way back to Washington and through the compliance system. The consequence of the misunderstanding, having nothing to do with safety or efficacy or science or integrity, was disqualification of the study and delay in approval of the new drug. (As it turned out, we had enough other substantial evidence so that amikacin was eventually approved and the matter subsequently dropped.)

Occasional problems notwithstanding, the Bioresearch Monitoring Program does serve a useful purpose in insuring that the best possible clinical trial data are accumulated. Based on our experience over the

years, I would urge those of you in industry and those of you who serve as veterinary investigators to take very seriously your encounters with FDA inspectors. Respond to them. They are professionals just like you who have a job to do and need your help to do it accurately. Of those of you in FDA who are involved in the Bioresearch Monitoring Program, I would ask that you show restraint and make certain that any actions you take are consistent with good science, not just the jot and tittle of regulation.

SUBSTANTIAL EVIDENCE

The question of when the accumulated evidence of effectiveness is substantial enough to warrant approval of a new animal drug is a challenging one. FDA has understandably found it difficult to establish standards applicable to the broad range of drug types with which they are confronted. At the Symposium on Dose Determination (November 1983) I pointed out that the standard for antibiotics (20 microbiological cures per organism claimed), although it sounds modest, is impossible to achieve in clinical field studies using a dose titration design. Even after the dosage has been established, 20 microbiological cures are difficult to accumulate in clinical studies, as illustrated by our data obtained in clinical trials with an antibiotic in cats with skin infections. Assuming a 95% microbiological cure rate and that only 50% of the cases will be acceptable to FDA, which Dr. Griffith just now acknowledged, and taking into account the requirement that a control group be included, the following numbers of clinical patients must theoretically be treated in order to obtain 20 cases per claim:

<u>ORGANISM (claim)</u>	<u>INCIDENCE IN CAT SKIN INFECTIONS *</u>	<u>THEORETICAL NO. OF PATIENTS REQUIRED</u>
Pasteurella multocida	19%	444
Staphylococcus epidermidis	15%	562
Staphylococcus aureus	9%	936
Klebsiella pneumoniae	3%	2808

* based on 332 clinical cases studied

If microbiologic results were the only criterion of efficacy that mattered and if clinical studies were the only method of studying antibiotics, the above numbers would not be absurd. What most angers our veterinary investigators, however, is what they perceive as FDA's totally ignoring their clinical evaluation and focusing instead solely on microbiological results.

It has not escaped our attention that two recent new antibiotics, clindamycin and ticarcillin, were approved with claims for only a single organism, both apparently having fallen victim to the claim = organism, 20 cases = claim doctrine. I found myself consulting the PDR to read the human package inserts to find out what the drugs really were. I therefore repeat my earlier statement that:

Present CVM policy that links claims for antibiotics to specific organisms is an extraordinarily restrictive policy that denies the practitioner FDA's sanction to use drugs for all pharmacologically and clinically rational purposes.

On one new antibiotic now under development in dogs we have the following data:

- . Pharmacokinetics in dogs: 3 dosages, 3 routes of administration, including urinary excretion.
- . Dosage titration study using a soft tissue infection model in dogs, showing statistically significant microbiological cure as well as other effects.
- . Two urinary tract infection model studies, both showing statistically significant microbiological as well as other effects, at the previously titrated dosage.
- . Complete antimicrobial activity profile in thousands of clinical isolates from animals and humans.
- . Complete toxicology package in laboratory animals as well as in dogs.
- . Over 500 published articles on the safety and effectiveness of the drug in humans as well as animals.

Given even a portion of the above data, there is little doubt that an expert or panel of experts qualified by scientific training and experience would fairly and reasonably conclude that the drug is safe and effective. Furthermore, on the basis of available data, a comprehensive meaningful, authoritative package insert could be written. Why then has FDA not yet approved it? Because we have not yet submitted it, because we are still struggling to accumulate substantial clinical (field) investigation evidence, as required by current regulations. Thus, at this very moment valuable research resources are being expended on studies which are unlikely to give the pharmacologist, statistician, or clinician any additional relevant insight into the safety and effectiveness of a new animal drug.

CONCLUSIONS

In this paper I have tried to establish the points that:

- Laboratory data are often more useful than clinical data in the determination of safety and effectiveness.
- Over - emphasis of clinical trial data as evidence of effectiveness has resulted in the imposition of such restrictive pharmacologic standards on clinical studies that drugs are often never evaluated under true field conditions.

I believe that the new animal drug development process would be greatly improved if industry and FDA, with the support of the practitioner and the academic community, would come to grips with the concept that:

- The FD&C Act does not require that every individual study prove effectiveness, but rather that the sum total of the available data provide substantial evidence of safety and effectiveness.

The pharmacologist, the clinician, the statistician, and the lawyer must all be satisfied in every new animal drug application, but not necessarily in every clinical study. In order to satisfy all interests I would advocate development of a score card on every new drug product consisting of all available evidence: in vitro evidence, in vivo evidence, laboratory animal evidence, toxicologic evidence, human clinical trial evidence, clinical observation evidence, etc., until sooner or later we could all agree that that evidence is substantial (providing of course that enough of it is adequate and well controlled).

Such a score card can only be developed by experienced, qualified, pharmacologically and clinically oriented scientists. It cannot be developed by the statistician or by the lawyer. We in industry, with the support of the clinician and the academic community, can provide substantial evidence of safety and effectiveness. And we can provide it within the framework of current regulations including CFR 514.111.

What is needed is a change of emphasis.