

CLINICAL TRIALS WITH PHYSIOLOGICAL DRUGS

REQUIREMENTS, RESULTS, AND CLAIMS

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Many thanks to the co-sponsors of the AAVPT, CVM, American Association of Industrial Veterinarians, the AVMA, and the Animal Health Institute for making this opportunity available to me. What more could one ask than to be introduced by a George Washington in this historical district!

Let me continue this presentation by stating that it is a real pleasure to be here for one such as I who has spent time within three quarters of the elegant circle of parties involved with the dynamic business of bringing new, safe, and effective drugs to the public. Academia, the Center for Veterinary Medicine, industry, and now principle investigators are commingled here with the expressed intent of improving the existing system through dialogue, debate, and at times, honest differences (Figure 1). As most of you know, I was with CVM, FDA for 14 years and have been with Monsanto for the last 13 months.

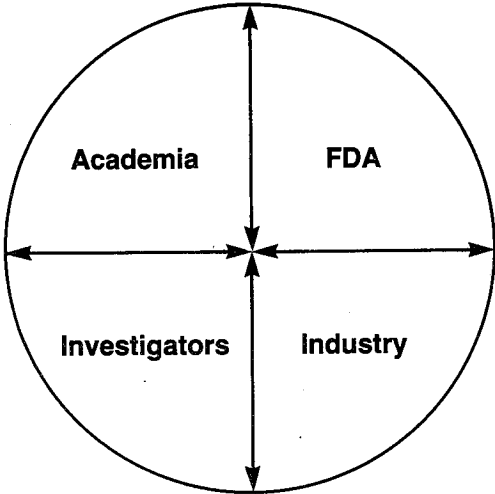
I want to dispel right now any notion that there are significant differences among industrial and regulatory objectives. The differences lie primarily in the methods and means to achieve economically viable results, that is, enhancing the welfare of people worldwide through making available safe and effective animal drugs.

The various categories of drugs established in today's afternoon agenda by Dr. John Paul and others is not accidental. Early on the Program Committees recognized that key clinical trial elements would vary most depending on the bioactivity of specific compounds. However, those elements such as sound control groupings and adherence to the scientific concepts of good scientific practices, must obviously be encompassed in all categories. Physiologically acting drugs represent a broad array of compounds including diuretics, insulin, antispasmodics, analgesics/tranquilizers, anesthetics, hormone-like anabolic agents such as zeralonol and estradiol antihistamines, antidotes and preanesthetics like atropine, muscle relaxants, polypeptides like bovine growth factor known as (somatotropins), and even anti-inflammatories.¹ This category is so large that no one presenter could cover it in the time allotted. Physiological drugs have elegant mechanisms of

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Figure 1

ANIMAL DRUG DEVELOPMENT PARTNERS



action and all affect the structure or function of the body or both. Dr. Bud Dawley will be discussing anti-inflammatory drugs as a separate paper in the next presentation because of their importance to animal health.

The physiological drugs usually benefit from eliciting dramatic biological responses in animals and those responses can be examined under laboratory conditions with clinical trial studies serving primarily as confirmation of effects under real world animal management situations. A potential design challenge with this class is that while possessing these profound physiological effects, it can be difficult to show the influence of these effects on a disease process or for meat, milk, or egg production improvement. I will talk more about this challenge later.

As a primary example of this category of drugs, I have chosen the diuretics for discussion. Furosemide, chlorothiazide, hydrochlorothiazide, and trichlormethiazide are available for animal use. There are a number of other compounds used in human medicine--a gap this symposium will hopefully fill! For a new diuretic, it would be relatively easy to conduct urinary output studies under laboratory conditions to show a dramatic diuresis as compared to another diuretic or against a placebo control. The design and conduct of such physiologically oriented studies are well established and need no discussion here.

Having established that a given compound can promote a desirable response from the kidney, perhaps the more important questions remain. Those include what disease process can be resolved via the nephritic or other responses? What are the extra-renal impacts such as hemodynamic effects that may have therapeutic usefulness or liability? Does the agent have the ability to mobilize extracellular fluid induced by a disease or natural process? Increasing urine volume alone may or may not be sufficient in and of, itself. Unless an acceptable disease model is available, the answer to these and other questions rests in conducting appropriate clinical trials.

The key element of any clinical trial (and perhaps all scientific investigation) is not its conduct! If I can leave you with one idea, it would be that the penultimate issue is clearly defining the objective of the trial. All in this audience, having been duly accepted into the society of scientific pursuit, have pledged allegiance to the scientific method. However, often in our rush to results we pay less homage to stating the hypothesis than to implementing the proving or disproving actions. "Hypothesis management" is still the most important thing we do, particularly as it relates to eventual labeling claims.

To illustrate this important point, let us return to the example of the diuretic drugs. The design of clinical trials would be radically different if the objective was to show that increased urine output occurs as opposed to the reduction of site swelling due to injury or physiological edema. Among other things, the kinds of measurements, animal numbers, animal selection and removal, would be dramatically different between these two objectives. For a pure physiological claim "healthy" animals could be selected whereas for tissue fluid movement, animals experiencing a disease process such as injury or cardiac insufficiency would be necessarily involved. Diseased animals present a significantly more difficult and challenging population for study. Safety considerations become more important in such cases as well as clinical judgement, subjective ratings, humane considerations affecting control selection, and possible statistical unacceptability of results.

Now that contemporary science strategies are progressing away from the whole body and systems levels towards the intracellular and biochemical levels, the challenge of drug claim definition and management prior to the initiation of clinical trials is of increased importance. The recent breakthroughs in recombinant DNA technology are opening up new frontiers for us to investigate. These include heretofore unavailable bioactive proteins, intracellular therapeutic manipulations, dietary engineering, and even specific gene therapy.^{2,3} These advances aligned to attack disease and promote food production will present awesome challenges to the four partners in the circle. For example, what claims are appropriate for an agent which has the effect of slowing the dissemination of cancer cells from the primary site and thereby reduce metastasis of tumors. If such a drug were available now, would the scientific community including FDA accept a claim for such a "physiological" effect at the cellular level in advance of having long term clinical trial data to demonstrate prolongation of life as a result of slowing metastatic activities?

Other examples of therapeutically useful claims for physiological drugs are the alleviation of symptoms such as pain, vomiting, diarrhea, and respiratory distress. Drugs appropriate for these negative physiological states are valuable clinical aids although they do not attack the disease etiological agent itself. Because of the relative difficulty of making objective measurements of symptomatic improvements in a clinical setting, perhaps clinical trials in these instances should focus principally on ease of administration, safety considerations, and the like.

I suggest that the Task Forces meeting after this symposium consider the issue of identifying claims for physiologically beneficial drugs in the absence of specific examination of complex clinical trial data, particularly where a single or specific group of symptoms or effects are being therapeutically managed as opposed to the entire

disease complex itself.

Drugs designed for symptomatic relief present some interesting challenges as to the selection of a control group for comparison. In most instances negative or placebo controls may be the least desirable from the humane or esthetic perspectives. When clinical cases are presented predominately for symptomatic complaints, it is likely the problem is substantial in both terms of duration and severity. The animal usually needs immediate proactive therapy. I, for one, and Dr. Art Aronson for another, wouldn't want to tell Mrs. Jones that her Poodle with extreme watery diarrhea may be sent back home with only shame treatment! Since we practitioners of the healing arts often don't make a specific disease diagnosis, symptomatic claims seem very rational and acceptable.

Although you will likely hear substantial, penetrating discussion about the technical persuasiveness of negative and placebo controls at this symposium, I suggest that active treatment controls are more appropriate in all situations involving serious or life threatening diseases. Perhaps, active controls are the only rational controls in clinical trials except in less serious, stabilized conditions like chronic otitis media. However, in cases where there is no approved animal drug (as currently required by FDA) to serve as the active treatment comparison, I suggest that the animal could well serve as its own control in these special circumstances. It should be recognized that a higher degree of scientific subjectivity is introduced by such a control but we should not fear placing great value on the investigators judgment. However, lacking a better control alternative, the development process should not be impeded for lack of an approved drug substance--quite to the contrary! The breakthrough physiological drugs of the future are likely to be for those claims we haven't even imagined yet, let alone benefit from prior approvals. Another item I suggest the Task Forces consider is recommendations for control groupings in clinical trials for which neither an approved animal drug exists and where humane considerations and good medical practice prohibit shame treatments of the controls.

A final concept I wish to endorse to you for consideration is that of facilitating earlier marketing of new animal drugs under semi-vigorous monitoring conditions. I am not referring to taking reckless technical short cuts. The assumption is that a contemporary package of pre-approval data exists including rigorous but small sized controlled clinical studies. This permission to market would be followed by larger magnitude clinical studies which would be uncontrolled but collect primarily user information which might uncover the so called "idiosyncratic adverse events". For example, a sponsor could commit to supplying the results of these studies within an appropriate time--say 12-18 months following initial marketing. This monitoring concept is

more intense and goes beyond the current drug experience monitoring system now in place. An ancillary gain to industry, the general public, and practitioners would be the identification of things like clinician discoveries for additional claims or enhanced use directions. This proposal for change deserves deeper consideration at this symposium for it could well acceptably and safely reduce the time to initial approval by 25%.

In summary and to paraphrase a page from Roman history: "I came to praise clinical trials and not to condemn them" for they represent a most useful tool which should be interpreted liberally and flexibly; concentrated in initial effort; and followed by broader scales of study immediately post initial marketing authorization.

I appreciate your listening to me today on my maiden presentation before you as a member of industry. As I said at the beginning of this presentation, one thing which I can assure you is that government, industry, academia, and principle investigators share much more in common than they do differences. I am truly excited about what is happening at this symposium and even more enthusiastic about the future of research and development of animal drugs. Thank you.

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