[DA ANIMAL INDUSTRY ADMINISTRATIVE ORDER NO. 9, January 31, 1994]

GUIDELINES GOVERNING THE CONDUCT OF CLINICAL TRIALS OF VETERINARY DRUGS AND PRODUCTS

Pursuant to the provisions of Republic Act No. 3720, as amended by Executive Order No. 175, otherwise known as the "Foods, Drugs and Devises and Cosmetics Act", R.A. No. 6675, otherwise known as the "Generics Act of 1988", R.A. 382 known as the "Pharmacy Act" - R.A. 6425 known as the Dangerous Drug Act of 1972 as Amended", R.A. No. 1556, otherwise known as the "Livestock and Poultry Feeds Act"', R.A. 1071, an Act to regulate the sale of veterinary biologics and medicinal preparation and R.A. 3101, an Act authorizing the Director of the Bureau of Animal Industry, subject to the approval of the Secretary of Agriculture to promulgate regulations for the preparation, sale, traffic in shipment and importation of vaccines, sera, toxin, or analogous products used for the treatment of domestic animals; and the Memorandum of Agreement between the Department of Agriculture and the Department of Health in the delineation of responsibilities regarding registration of veterinary drugs and products the following rules and regulations governing the conduct of clinical trials of veterinary drugs and products are hereby promulgated.

This regulation concerns the general and scientific principles for the demonstration of efficacy and for the conduct, performance and control of clinical trials of veterinary drugs and products, particularly in the context of authorization of new substances.

SECTION 1. Definition of Terms -

1.1 "Veterinary Drugs and Products" - refer to any substance, including biological products, applied or administered to food producing, companion, aquatic, laboratory and exotic animals, whether used for therapeutic, prophylactic or diagnostic purposes or for modification of physiologic functions or behaviors.

1.2 "Established Veterinary Drugs and Products" - refer to veterinary drugs and products the safety and efficacy of which have been demonstrated through long years of general use and can be found in current official USP-NF, and other internationally-recognized pharmacopeias.

1.3 "Clinical Trials" - mean systematic studies in target species or in particular categories of such animals, in order to establish the therapeutic effects, which include confirmation of the pharmacodynamics and/or to monitor any adverse response from the use of veterinary drugs and products. Studies on the metabolism, the pattern of absorption, distribution and excretion of active substances (pharmacokinetics) in target categories of animals in order to support the evaluation of efficacy are also included.

Clinical trials are generally classified into a number of phases but it is not possible to draw distinct lines between them.

Pharmacological-based studies in target species are usually classified as pre-clinical trials.

1.4 "Efficacy" - although the term is not actually defined (or even used) within the relevant directives, it is nevertheless one of the fundamental criteria on which authorization of a veterinary drug and product is based.

It is clear that marketing authorization should be refused where a veterinary drug and product lacks therapeutic effect or where there is insufficient proof of such effect.

It is also made clear that the concept of therapeutic effect must be understood as being the effect promised by the manufacturer. This may be interpreted as meaning the specific claims (for example, to control condition 'X' caused by organism 'Y') made within the product literature and by any promotion.

Therefore, the efficacy of a veterinary drug and product is understood to be degree to which the medicinal claims made by the manufacturer have been justified and are likely to be attained under practical field conditions within the community.

SECTION 2. Community Objective - The primary reason fore recommending a common basis for clinical evaluation of veterinary drug and products in the Philippines community is two-fold:

First, to establish a basis on which effective products, which are also safe, can be developed; and secondly, to facilitate the understanding and the harmonization by all international regions of regulatory and administrative requirements for the conduct, secondly, to facilitate the understanding and the harmonization by all international regions of regulatory and administrative requirements for the conduct of clinical trials.

2.1 Define a general scientific framework, including basic methods and the necessary professional ethical principles for the conduct of clinical trials so that optimal and relevant data are generated and also so that the results can be recognized by the competent authorities of all regions.

2.2 Indicate the regulatory and administrative requirements of the BAI governing the conduct clinical trials, in order to facilitate the task of an applicant wishing carry out multicenter studies in the community.

2.3 Use these concepts as a starting point for the efforts to establish a greater degree of convergence in the various regulatory and administrative requirements governing the conduct of clinical trials to be performed in the regions. Thus, the results of such trials may eventually be enclosed as documentation in applications for marketing authorization filed with the competent authorities of the regional offices.

2.4 Establish that clinical tests should take account of the full range of conditions, animal management systems, disease conditions, etc., throughout the community, even if, testing is performed outside community border.

SECTION 3. Rationale - It is necessary to provide efficacy data by using the product (preferably in the formulation intended for marketing) in controlled clinical trials which have been designed specifically to justify the relevant claims in each on the indicated target categories of animals.

If this is not entirely possible, other means of providing efficacy data should be employed. The manufacturer must fully justify the claims made for the product if these are from inadequately controlled clinical trials. It is expected that at least a proportion of the data provided will emanate from well organized, scientifically based clinical trials. While sound clinical trial data from any source will enhance the application, these should be supported by information from target animals managed under conditions as similar as possible to those existing within the community. In order to demonstrate that the correct dosage or dosage range is recommended, pre-clinical trials involving dose titration studies followed by dose confirmation studies will be a precursor of the clinical studies.

It is important to realize that the demonstration of efficacy may be supplemented by the development of data other than from the clinical trials already indicated. For example, the efficacy of an antimicrobial product against specified bacterial strains may be demonstrated by careful linking of appropriate tissue or plasma pharmacokinetics with data on the in vitro activity of the antimicrobial ingredient against recent and relevant field isolates of target organism. This approach may also be of relevance in the determination of appropriate dosage levels. Clinical efficacy trials with the intended antimicrobial product may demonstrate full efficacy, but the dosage employed could conceivably be in excess of the minimum or optimum necessary.

Because of the wide range and uses of veterinary drugs and products, each situation has to be individually considered to determine which pharmacokinetic parameter is of importance.

In the case of ectoparasiticidal sheep dips for example, data on the systemic absorption of the active ingredient may be of little importance, whereas, the pattern of persistence of the active ingredient in the dip wash, and within the fleece and on the skin, may be of greater relevance to efficacy. Similarly, useful efficacy data on teat dips may be obtained from in vitro tests designed to demonstrate that the recommended dilution of the product will inactivate the relevant bovine mastitis organisms within a reasonable contact time.

SECTION 4. Clinical Trials - It is important for anyone preparing for a clinical trial that specific problems be thoroughly considered and that the chosen solutions are justified on scientific and ethical grounds. It should be emphasized that responsibility lies with the registrant/sponsor of the trials and the overall supervisor, as well as the actual individual investigators. Furthermore, when considering the strategy of clinical evaluation of new active substances, it is highly advisable to plan and design individual trials as part of a logically constructed chain of investigations, from limited numbers of animals in near-experimental-type studies, to substantial number of animals in near-marketing-type field studies.

While in principle the results of clinical trials should be acceptable irrespective of where they are carried out, the BAI may require additional trials to be undertaken where scientifically justified for the assessment of efficacy of the product, e.g., where normal husbandry or environmental conditions differ markedly from reported test conditions.

Care must be taken in designing clinical trials, and in interpreting the results, to distinguish between effect due to the active substance itself and those due to a particular formulation of the substance in question.

For a positive treatment control group it will be preferable to compare the product containing a new active substance with a gully authorized reference product rather than with a special formulation. It is important to use species and precise categories of target animals which relate to the eventual uses of the product. For example, a product intended for juvenile animals or pregnant animals should be tested in that precise circumstance.

A trial design and protocol must be worked out and adhered to, with proper instruction given to all investigatory staff.

The conditions of the physical framework in which the trial is carried out must be carefully prepared and of high quality as regards supervision of the animals, staffing, laboratory facilities (where necessary), emergency instructions, etc. The responsibilities of the registrant/sponsor and the overall supervisor, as well as those of the investigator(s) and all collaborators, must be clearly defined before the start of the clinical trial.

SECTION 5. Qualifications of Investigators - The protection of animals in the trials must be primary concern of every person responsible for the implementation of clinical trials. Furthermore, a high degree of concern must be established for the safety of the environment, for persons administering the veterinary drugs and products and for any consumer of animal products from the trial animals.

All investigators must demonstrate the highest possible degree of professionalism in the observation of animals in the trials and the reporting of such observations. Therefore:

5.1 the clinical investigator ultimately responsible on behalf of the sponsor for the complete range of trials (the 'Overall Supervisor') should hold the veterinary qualifications and be clinically competent. He/she should have sufficient experience in the clinical evaluation of veterinary drugs and products and in the conditions under investigation.

5.2 the 'Overall Supervisor' should have access to competent toxicologists, environmental biologists, (human) medical advice, etc. in order that the safety of trials is maintained;

5.3 the clinical investigators responsible for individual trials at particular locations (site supervisors) must have expertise in the biology and clinical handling of the particular disease or condition under study;

5.4 the ethical standards, independence and professional integrity of all the investigators should be beyond reproach.

SECTION 6. Pre-Clinical Trial Data - Relevant chemical, pharmaceutical, experimental animal pharmacology and toxicological data on the medicinal substance and professionally evaluated before a new veterinary drug and product is the subject of clinical trials in target species. The registrant/sponsor's responsibility (through the Overall Supervisor) for obtaining exhaustive, complete and relevant information is emphasized.

The experimental animal data referred to above should include those from laboratory animal species plus target and other domestic species, examined under experimental conditions. Before clinical trials in food producing animals are