Republic of the Philippines
DEPARTMENT OF AGRICULTURE
Office of the Secretary
Elliptical Road, Diliman, Quezon City

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ANIMAL INDUSTRY
ADMINISTRATIVE ORDER
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SUBJECT : **GUIDELINES GOVERNING THE CONDUCT OF CLINICAL TRIALS OF VETERINARY DRUGS AND PRODUCTS**

Pursuant to the provision of Republic Act No. 3720, as amended by Executive Order No. 175, otherwise known as the "Foods, Drugs and Devices 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 Drugs Act of 1972", as amended, R.A. 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 the 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 for recommending a common basis for the 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 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 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 of clinical trials, in order to facilitate the task of an applicant wishing to 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 of 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 inactive 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 numbers 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 fully 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 investigators (s) and all collaborators, must be clearly defined before the start of the clinical trial.

SECTION 5. QUALIFICATIONS OF INVESTIGATORS

The protection of health and welfare and the interests of all the animal in the trials must be a 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 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/or the pharmaceutical form in question must be available 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 considered, a secure waiting period before slaughter or the taking of any produce must be clearly established and justified by means of pre-clinical trials.

The extent of such pre-clinical trials should be related to the waiting time intended to be employed during the clinical trials. In general, the shorter the waiting time (especially when large numbers of animals are involved) the more detail will be required from the pre-clinical studies.

SECTION 7. TARGET ANIMAL PHARMACOLOGY

When a veterinary drug and product is to be studied in clinical trials, all existing research data in target species and any in target categories must be considered. Apart from the expected effects in tissues, possible effects on other important organ systems should have been studied at the relevant dosage levels.

Consideration should also be given to results from kinetic studies of the active ingredient and the intended formulation, perhaps with several routes of administration. Results from other investigations on which the choice of dosage is based, e.g., studies of dose/response and/or concentration/effect relationships and safety studies must be included. Investigators should be aware of the possibility of interactions with other products which may administered concurrently.

SECTION 8. TRIAL PROTOCOL

A well designed trial relies predominantly on a thoroughly considered, well structured and complete protocol which should be completed before the trial is initiated. The protocol should be drawn up to fit in with already established constraints in the operation of a trial.

The protocol should, where relevant, contain the information given in the following list of items, this list should at least be considered, whenever a trial is contemplated.

8.1 General Information

a) title of the project;

b) the names and contact points of the investigators responsible for the trial; the names other possible participants and their professional background (e.g., veterinarian, biochemist, parasitologist, experimental animal attendant, statistician, etc.) should also be made clear;

c) the name and any contact point of the registrant/sponsor;

d) the identity of the farm/department/group of veterinary practices where the trial will take place (affiliations, addresses).

8.2 Justification and Objectives

a) aim of the trial. The objective in conducting the study must be clearly established;

b) the reason for its execution;

c) the essentials of the problem itself and its background, referring to relevant literature.

8.3 Schedule

a) description of the schedule of the trial, i.e., its date and time of commencement, investigation period, observation period and termination date;

b) justification of the schedule, e.g., in the light of how far the safety of the drug and product has been tested, the time course of the disease in question and expected duration of the treatment;

c) justification of the waiting period before slaughter, etc. Even if the post-medication period of observation of the live animal is in excess of this period, a waiting period must be established for all animals removed from the trial.

8.4 Design

a) specification of the type of trial, e.g., controlled study, pilot study;

b) description of the randomization method, including the procedures to be adopted and practical arrangements to be followed;

c) description of the trial design (e.g., parallel groups, cross-over design) and the blinding technique selected (e.g., double blind, single blind or open);

d) specification of other bias reducing factors to be implemented.

8.5 Subject Selection

a) specification of the type of animal to be used, including species, age, sex, breed, category, prognostic factors, etc.;

b) provision of a clear statement of diagnostic admission criteria;

c) exhaustive listing of the criteria for inclusion, pre-admission exclusions and post-admission withdrawals of animals from the trial.

8.6 Treatment

a) clear, precise and detailed identification of the product(s) to be used. These should be fully formulated products likely to be proposed for marketing and not just “laboratory drugs”. There should be a justification of the doses to be used;

b) description of treatment applied to control group(s) or for control period(s) (placebo, other products, vehicle only, etc.);

c) route of administration, dose, dosing schedules, treatment period(s) for the test products(s) containing the active substance under investigation and for the comparative product(s);

d) rules for the use of concomitant treatment;

e) measures to be implemented to ensure the operator’s safety while handling the test products prior to and during administration;

f) measures to promote and control close adherence to the prescribed instructions/ordinances (compliance monitoring).

8.7 Assessment of Efficacy

a) definition of the effects to be achieved before efficacy can be claimed;

b) description of how such effects are measured and recorded;

c) times and the periods between observation and recording of the effects;

d) description of special analyses and/or tests to be carried out (pharmacokinetic, clinical, laboratory, radiographic, etc.)

8.8 Adverse Reaction/Side Effects, etc.

a) methods of recording suspected adverse reaction/ side effects/untoward reactions;

b) provisions for dealing with such reaction, e.g., treatment, changes to method of administration;

c) information on where the trial code will be kept and how it can be broken in the event of an emergency;

d) details for the reporting of suspected adverse reaction/side effects, in particular the name of the individual designated to receive such reports.

8.9 Operational Matters

a) a meticulous and specified plan should be drawn up of the various steps and procedures necessary to control and monitor the trial most effectively;

b) definition of and instructions for anticipated deviations from the protocol, e.g., therapeutic failure;

c) the duties and responsibilities of the investigation team and their coordination;

d) instruction to staff, including a trial description;

e) addresses, telephone numbers, etc., enabling any staff member to contact responsible members of the investigation team at any hour;

f) consideration should be given to any problems of confidentiality

8.10 Handling of Records

a) procedures for handling and processing the records of various effects, including suspected adverse reactions, to use of the product(s) under study should be defined;

b) procedure for the maintenance of all the records for each individual (or test group) within the trial must be available. These records should, as far as possible, permit the ready identification of the individual animals concerned;

c) a copy of the test animal recording form should be included.

8.11 Evaluation

a) definition of the measure of test animals' response, e.g., a scoring system, in order to evaluate the clinical response;

b) definition of the methods of computation and calculation of the effect of using the veterinary drug and product;

c) description of how to deal with and report on animals withdrawn or otherwise removed from the trial;

d) quality control of evaluation procedures.

8.12 Statistics

a) a thorough description of the statistical methods to be employed;

b) the planned number of animals to be included in the trial(s) and the reasoning for the choice of sample size, including reflections on (or calculations of) the power of the trial and the clinical justification, should be provided. If such a plan is not followed, appropriate justification for any changes should be given;

c) description of the statistical unit;

d) the level of significance to be used;

e) rules for the termination of the trial.

8.13 Summary, Supplements

The protocol should comprise a comprehensive summary and relevant supplements (e.g. information to the owners of animals, instructions to staff, description of special procedures).

8.14 References

A list of relevant literature, referred to in the protocol, must be included.

SECTION 9. REPORTING AND RECORD KEEPING

Reporting the outcome of a clinical trial must be carefully planned and agreed upon by all participants (A policy for publication in scientific journals or elsewhere should similarly be considered as a part of the cooperation between the parties involved).

All suspected adverse reactions/side effects, whether or not serious and/or frequent, should be reported as quickly as possible to the competent authority. This is usually organized by reference to the Overall Supervisor. In cases of serious adverse effects, any investigator or animal owner should report directly. The competent authority should be informed in writing if any major deviation from a previously submitted trial protocol is contemplated. Likewise, if the trial does not begin, or is interrupted before its purpose is achieved, the reason should be conveyed in writing to the BAI.

When a trial is completed, the BAI should be informed of the results, including any suspected adverse reactions/side effects. A formal report is required, and this should also include a short, comprehensive summary of the essential findings of the trial and its methodology. Such a report should be evaluated in conjunction with the final protocol.

All clinical and experimental data, including the records of the complete formulation used in each trial, should be kept safely by the Overall Supervisor and/or the sponsor for a period of five (5) years or more after completion of the trial. Such documentation should be retained in an archive until beyond the time of issue of the relevant marketing authorization. This should be done in order to validate the results later and/or submit the documentation for inspection, if requested.

SECTION 10. LABELLING

The provisions of labelling should be applied by analogy to the labelling of all veterinary drugs and product (s) or placebo (es) etc., used in clinical trials.

Additionally, the labeling should include the words “For Veterinary Clinical Trial Only”, or similar, the identity of the Overall Supervisor responsible for the trial or the manufacturer sponsoring the trial. There should also be included an assessment of safety, on which a waiting time prior to slaughter must be based, as well as any warning statements relevant to the safety of the animal, the operator or the environment.

SECTION 11. SYSTEMS OF NOTIFICATION /APPROVAL OF CLINICAL TRIALS

In conducting clinical trials, due regard must be taken of effect of the product on the environment, of residues in produce of treated animals and the eventual fate of animals used for food production.

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RECOMMENDING APPROVAL:

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