MEDICINES CONTROL COUNCIL

GUIDELINE ON PRECLINICAL SAFETY STUDIES FOR VETERINARY MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data for preclinical studies. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach and does not bind the MCC nor confirm any rights for or on any person. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all studies are conducted in accordance with set standards of good practice. The MCC may make amendments in keeping with the knowledge which is current at the time of consideration of preclinical safety data.

REGISTRAR OF MEDICINES
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1.PRECLINICAL STUDIES

The safety documentation of the dossier shall show:

- the potential toxicity of the veterinary medicine and any dangerous effects which may occur under the proposed conditions of use in animals. These should be evaluated in relation to the severity of the pathological condition concerned;
- the potential harmful effects to man of residues of the veterinary medicine or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuff;
- the potential risks which may result from the exposure of human beings to the medicinal product, for example during manufacture, in feed mixing of or on administration to the animal;
- the potential risks for the environment resulting from the use of the medicinal product.

All results shall be reliable and valid generally. Where ever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally, clinicians shall be given information about the therapeutic potential of the product and about the hazards concerned with its use.

The following preclinical information must be submitted

i. Pharmacology
ii. Pharmacodynamics
iii. Pharmacokinetics
   a Kinetic and metabolism in rats
   b Kinetic and metabolism in primates)

1.1 Toxicity

The study procedures, as found in the latest published guidelines of the following authorities, are acceptable for Preclinical Studies to be performed:

OECD Guidelines for Testing of Chemicals, and/or

EEC Directives, Methods for the Determination of Toxicity, and/or

US EPA Pesticide Assessment Guidelines, and/or

JAPAN/MAFF: Testing Guidelines For Toxicity Studies

1.2 Acute toxicity

1.3 LD_{50}

Single-dose toxicity studies can be used to:

- predict the possible effects of acute overdosing in the target species;
- predict the possible effects of accidental administration to humans;
- predict the doses which may usefully be employed in the repeat dose studies;
- assess the relative toxicity of the compound.

Single dose toxicity studies should reveal the acute toxic effects of the substances and the time course for their onset and remission.

These studies should normally be carried out in both sexes of at least two mammalian species. One species may be replaced, if appropriate, by an animal species for which the medicinal product is intended. Preferably two different routes of administration should be studied. The route selected should be the same as that proposed for the target species. If substantial exposure of the user of the medicinal product is anticipated, for example for inhalation or dermal contact, these routes should be studied.

1.4 Approximate LD

In order to reduce the number and suffering of the animals involved, new protocols for single dose toxicity testing are continually being developed. Studies carried out in accordance with these new procedures when properly validated will be accepted, as well as studies carried out in accordance with established internationally recognized guidelines. The "fixed dose procedure" proposed by the British Toxicological Society could be followed (e.g. Van den Heuvel *et al*. 1990. *Fd. Chem. Toxic.* Vol 28, 469-482).

All studies must be done on the active ingredient. If acute toxicity studies with the formulation are available these should also be submitted.

1.5 Subacute toxicity

Repeat-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

In the case of substances or medicinal products intended solely for use in animals which do not produce food for human consumption, a repeat-dose toxicity study in one species of experimental animal will normally be sufficient. This study may be replaced by a study conducted in the target species. The frequency and route of administration, and the duration of the study should be chosen having regard to the proposed conditions of clinical use. The investigator shall give reasons for the extent and duration of the trials and the dosages chosen.

In the case of substances or medicinal products intended for use in food producing animals, the studies should be conducted in at least two species, one of which should be a non-rodent. The investigator shall give reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The duration of some of the studies shall be at least 90 days. The investigator shall clearly state and give reasons for the method and frequency of administration and the length of the trials.

The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the toxic effects shall be based on observation of behaviour, growth, haematology and physiological tests, especially those relating to the excretory organs, and also autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, the repeated-dose tests may, except where toxicity test have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator, who shall submit his reasons for such modifications.

1.6 Chronic toxicity and carcinogenicity studies

Where applicable long-term toxicity determinations i.e. one year chronic study in dogs or a lifetime chronic study in rats, may be required.

Long-term animal carcinogenicity studies will usually be required for substances to:
- which human beings will be exposed,
- which have a close chemical analogy with known carcinogens,
- which during mutagenicity testing produced results indicate a possibility of carcinogenic effects
- which gave rise to suspect signs during toxicity testing.

The state of scientific knowledge at the time the application is submitted shall be taken into account when designing carcinogenicity studies and evaluating their results.

1.7 Mutagenicity/Clastogenicity

Mutagenicity tests are intended to assess the potential of substances to cause transmissible changes in the genetic material of cells. If there is any indication of mutagenicity, carcinogenicity studies will be required.

Any new substances intended for use in veterinary medicinal products must be assessed for mutagenic properties.

The number and types of tests and the criteria for the evaluation of the results shall depend on the state of scientific knowledge when the application is submitted.

1.8 Reproductive toxicity

Reproductive studies will be required if there is any indication of adverse effects on potential reproduction in the preceding preclinical studies.

The purpose of such studies is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the medicinal products or substance under investigation.

In the case of substances or medicinal products intended for use in food-producing animals, the study of the effects on reproduction shall be carried out in the form of a two-generation study on at least one species, usually a rodent. The substances or product under investigation shall be administered to males and females from an appropriate time prior to mating. Administration should continue until the weaning of the F2 generation. At least three dose levels shall be used. The maximum dose should be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the effects on reproduction shall be based upon fertility, pregnancy and maternal behaviour; suckling growth and development of the F1 offspring from conception to maturity and the development of the F2 offspring to weaning.

1.9 Study of embryotoxic/foetotoxic effects including teratogenicity

Embryotoxic/foetotoxic, including teratogenicity studies will be required :

- In the case of substances or medicinal products intended for use in food-producing animals, studies of embryotoxic/foetotoxic effects, including teratogenicity, shall be carried out. These studies shall be carried out in at least two mammalian species, usually a rodent and the rabbit. The details of the test (number of animals, doses, time at which administered and criteria for the evaluation of results) shall depend on the state of scientific knowledge at the time the application is lodged and the level of statistical significance which the results should attain. The rodent study may be combined with the study of effects on reproductive function.

- In the case of substances or medicinal products which are not intended for use in food-producing animals, to animals which might be used for breeding, a study of embryotoxic/fetotoxic effects, including teratogenicity, shall be required in at least one species, which may be the target species.

1.10 Neurotoxicity

Neurotoxicity studies will be required if there is any indication of such effects in the preceding preclinical studies or if the product is chemically related to a group with such potential.

1.11 Other requirements

1.11.1 Immunotoxicity

Where the effects observed during repeated dose studies in animals reveal specific changes in lymphoid organ weights and/or histology and/or changes in the cellularity of lymphoid tissues, bone marrow or peripheral leukocytes, the investigator shall consider the need for additional studies of the effects of the product on the immune system.

The state of scientific knowledge at the time the application to be is submitted shall be taken into account when designing such studies and evaluating their results.

1.11.2 Microbiological properties of residues

1.11.2a Potential effects on the human gut flora

The microbiological risk presented by residues of anti-microbial compounds for the human intestinal flora shall be investigated in accordance with the state of scientific knowledge at the time the application is submitted.

1.12 Potential effects on the microorganisms used for industrial food processing

In certain cases, it may be necessary to carry out tests to determine whether residues cause difficulties affecting technological processes in industrial foodstuff processing *e.g*. cheese production..

1.11.3 Observations in humans

Information shall be provided showing whether the constituents of the veterinary medicinal product are used as medicinal products in human therapy. If this is so, a report should be compiled on all the effects observed (including side-effects) in humans. This may be important for assessment of the veterinary medicinal product. When constituents of the veterinary medicinal products are no longer used as medicinal products in human therapy, the reasons should be stated.

EXCEPTIONS

Where a medicinal product is intended for topical use, systemic absorption shall be investigated in the target species of animal. If it is proved that systemic absorption is negligible, the repeated dose toxicity tests, the tests for reproductive toxicity and the carcinogenicity tests may be omitted, unless:

- under the conditions of use laid down, oral ingestion of the medicinal products by the animal is to be expected, or
- the medicinal particular may enter foodstuffs obtained from the treated animal (intra-mammary preparations).

2 SAFETY STUDIES IN TARGET SPECIES

2.1 Tolerance studies

In accordance with the guidelines (Evaluation of the safety of veterinary medicinal products for the target animals) provided in terms of Directive 81/851/EEC as amended should be followed. Details should be provided of any signs of intolerance which have been observed during studies conducted in the target species. The studies concerned, the dosages at which the intolerance occurred and the species and breeds concerned should be specified. Details of any unexpected physiological changes should also be provided.

To assess the safety of the compound being applied for the formulation should be tested at multiples of the recommended dose/concentration until signs of intoxication is induced in at least one animal of each sex. A ten fold overdose need not be exceeded. If applicable, the degree of irritation that the formulation causes following administration should also simultaneously be assessed.

2.2 Reproductive safety studies

Reproductive safety studies in the target species will be required if there is any indication of adverse effects on potential reproduction in the preceding trials.

2.3 Field safety studies

In food-producing animals the safety of the formulation should be extensively tested under a wide variety of local field conditions at least double the recommended dose/concentration.

3 ENVIRONMENTAL SAFETY STUDIES

3.1 Ecotoxicity

The purpose of the study of the ecotoxicity of a veterinary medicinal product is to assess the potential harmful effects which the use of the product may cause to the environment and to identify any precautionary measures which may be necessary to reduce such risks.

An assessment of exotoxicity shall be compulsory for any application for marketing authorization for a veterinary medicinal product other than applications submitted in accordance with point 10 of Article 5, second paragraph, of Directive 81/851/EEC.

This assessment shall normally be conducted in two phases.

- In the first phase, the investigator shall assess the potential extent of exposure to the environment of the product, its active ingredients or relevant metabolites, taking into account:
  - the target species, and the proposed pattern of use (for example, mass-medication or individual animal medication),
  - the method of administration, in particular the likely extent to which the product will enter directly into environmental systems.
  - the possible excretion of the product, its active ingredients or relevant metabolites into the environment by treated animals and in particular persistence in such excretia,
  - the disposal of unused or waste product.

- In a second phase, having regard to the extent of exposure of the product to the environment and the available information about the physical/chemical, pharmacological and/or toxicological properties of the compound which has been obtained during the conduct of the other tests and trials required by this Directive, the investigator shall consider whether further specific investigation of the effects of the product on particular eco-systems is necessary.

If appropriate, further investigation may be required of:

- fate and behaviour in soil,
- fate and behaviour in water and air and
- effects on aquatic organisms,