

EVALUATION OF THE SAFETY OF VETERINARY MEDICINAL PRODUCTS FOR THE TARGET ANIMALS

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EVALUATION OF THE SAFETY OF VETERINARY MEDICINAL PRODUCTS FOR THE TARGET ANIMALS

1. GENERAL INTRODUCTION

These guidelines are intended to provide general directions for acquiring essential information pertinent to the evaluation of safety for the target animal species for which the veterinary medicinal product is intended. This information can be acquired by the following three types of approach:

- a) first existing data on pharmacodynamics, especially on secondary pharmacodynamics, but also data on toxicological and pharmacokinetic properties, should be used to focus upon the requirements for tolerance studies of the veterinary medicinal product in the categories of target species and for specific effects to be monitored during clinical trials.
- b) secondly, tolerance studies conducted in the target animal species should document any adverse effects that may occur under the proposed conditions of use for a given veterinary medicinal product. Furthermore, effects associated with over-doses and increased duration of administration of the product should be demonstrated. The margin of safety may be documented if both overdoses/increased treatment period and the therapeutic dose/therapeutic treatment period are included in the tolerance study. The product should normally be tested in each category of target species. Deviations shall be justified. Non-target animal studies cannot be used to replace studies in target animals, but may provide useful supportive information.
- c) thirdly, clinical trials protocols should include the specific monitoring of the potential side-effects on the health and welfare of the animal. These will be identified on the basis of the nature of the substance/product under investigation, the results of pharmacodynamic investigations, toxicology tests, and tolerance studies. The specific monitoring may include physical examination of particular organ systems, special blood chemistry and haematology tests, (FN) AB cytology, behavioural observation and analysis, etc..

2. DOCUMENTATION OF SECONDARY PHARMACODYNAMIC ACTIONS

The purpose of pharmacodynamic investigations is to generate information relative to pharmacodynamic action(s) of a substance beyond (secondary) the clinically desired (primary) physiological effects.

There is a great variety of pharmacodynamic test methods. In addition, new substances may require new and tailored test methods, alternatives to the more classical ones. Furthermore, pharmacodynamics are undergoing fast-track evolution. Therefore, these guidelines do not describe precise test procedures.

The range of secondary pharmacodynamic activities to be documented results from a case-by-case analysis of e.g.:

- the nature of the substance under investigation;

- the basic knowledge of the substance's family;
- the forecasted use of the final product;
- any unexpected side-effect occurring during primary pharmacodynamic evaluation;
- the result of toxicological studies.

Depending on the analysis mentioned above, the testing of secondary pharmacodynamic effects of the test substance shall include the examination of the relevant organ systems, e.g.:

- neuromuscular system: central, motor, and peripheral autonomic;
- cardiovascular system: cardiac function and peripheral circulation;
- respiratory system: upper respiratory tract and lung function;
- gastrointestinal tract;
- renal function and hydro-electrolytic homeostasis;
- hepatic function;
- endocrine organs (e.g. thyroid, adrenals, hypophysis, endocrine pancreas) and metabolism of carbohydrates, lipids, proteins, and minerals;
- blood cells and bone marrow.

2.1 Experimental conditions

In order to cover the entire variety of potential secondary pharmacodynamic actions of a substance screening tests should initially be performed taking into consideration the results of tests on primary pharmacodynamics and on toxicity. The studies should be conducted with negative and possibly positive controls. The positive controls include using substances with known pharmacodynamic actions.

It may be necessary to conduct studies in intact, laboratory animals, ideally the species the primary pharmacodynamic effect had been investigated on. The suitability of test system(s) (organ, cellular, subcellular) should be justified.

When using a metabolic test system, the pharmacodynamic actions of both the active substance and its metabolites should be evaluated. Significant observations should be documented from more than one test system.

Studies in intact laboratory animals should be performed by single administration of at least two or three effect doses. The lowest one may comply with the ED₅₀ of the desired effect in the same species. The route(s) of administration should correspond with the intended one as well as ensure absorption of the agent as complete as possible.

2.2 Analysis of test results

For any kind of pharmacodynamic action, a quantitative dose-response relationship should be documented with respect to the substance under investigation and, if applicable, to a control substance. The physiologic effects should be assessed by comparing the dose-effect relationship to the desired response and the untoward effects as a means of obtaining information on doses that possibly can be tolerated and the possible therapeutic index in the target animal. The dose-responses should be explained in terms of the mechanism(s) by which the substance exerts its physiological effects and the resulting change(s) in vital body functions. Furthermore, observed interactions, including the underlying mechanism(s), and contra-indications should be addressed, if applicable.

3. TOLERANCE STUDIES IN THE TARGET ANIMAL

This part gives the details of investigation of safety in few animals of each target species, where many parameters should be measured under controlled conditions.

For the purpose of these guidelines target animal species are the species for which the product is intended.

The specific information needed for a veterinary medicinal product depends on such factors as classification of the active ingredient(s), type of product, proposed use regimen, species, breed and/or class of animals, claims, dosage and/or previous use history. All data mentioned in these guidelines would not necessarily need to be collected for every product. Omission and deviation should be justified. For certain products (e.g. intramammary, ophthalmic, otic products etc.) information not specified in these guidelines may be required.

Studies on target animal tolerance should be adequately designed, well controlled in order to have relevance to the target population under study.

Investigations of target animal tolerance should, whenever possible, be carried out in a controlled, randomised design, employing an adequate number of animals/experimental units per treatment group. Where prior knowledge is likely to influence allocation to treatment, management of treatment groups, or the assessment of response parameters, blind techniques should be employed.

The appropriate number of animals per treatment and the number of replicates will depend upon such things as the variability of the observations, the size of the difference among the various treatment groups that the experimenter would like to be able to detect, as well as the significance level and power of the statistical tests employed.

3.1 Studies on general tolerance

3.1.1 Experimental conditions

3.1.1.1 Test animals

Unless otherwise justified, the studies should be performed in groups of each category of each target species in comparison with appropriate control groups. A negative control group is recommended. Treated and control animals should be handled identically except for product exposure.

Test animals should be healthy and of the species and representative categories for which the product is intended. Selection of species other than the target animal species may be made in exceptional cases, e.g. in the case of minor species. Justification should be made for non-target animal species.

Appropriate diagnostic tests, vaccinations, prophylactic and therapeutic treatments should be completed prior to the baseline period of the test period. Exceptions should be included in the study protocol. No treatment other than the administration of the test product should be given during the study period.

Sufficient time must be given to acclimate test animals in line, especially if a special diet or feeding regimen is intended.

3.1.1.2 Test product

The product to be evaluated must be identical to the product intended to be marketed, i.e. same chemical, same particle size, and same formulation. Any exception shall be justified.

3.1.1.3 Route of administration

The routes of administration should include at least those proposed by the label. The site of application must be specified. The choice of a different approach should be justified. For products exhibiting a narrow margin of safety it may be necessary to test others than the proposed route of administration: e.g. if significant amounts of the active ingredient(s) of a product intended for external use will be ingested under the proposed use conditions, the oral tolerance should be tested. For products to be administered intramuscularly or subcutaneously it may be necessary to test the intravenous tolerance.

3.1.1.4 Dosage regimen

The studies should be conducted using the recommended dose and multiple dose levels in order to determine the margin of safety for the product for the proposed duration of use.

The choice of dose levels should take into account the proposed use of the product, management conditions etc.. Omission of multiple dose studies should be justified.

3.1.1.5 Duration of administration

It is recommended that the products should be studied for a period of time in excess of the recommended maximum duration of use administering the highest recommended dose level. However, for products intended for long-term administration (15 days or longer) it may be impossible to carry out studies for such a period. If this arises, tolerance studies should be conducted with the product being administered at least for the maximum use duration and using the highest recommended dose level.

3.1.2 Observations

Investigations necessary to evaluate effects of the product depend on the type of action of the active ingredient, potential of toxicity, proposed use of the product, and class to which the target animals belong.

Clinical observations should be recorded at predetermined intervals appropriate for the investigative purpose(s), during the entire study period.

Where relevant, appropriate diagnostic procedures/tests (clinical or otherwise) should be carried out at predetermined intervals, either on all animals, or on a representative sample from each treatment group, as the case may be.

A complete physical examination should be performed, and baseline data should be collected. Data should be obtained prior to the start of the trial and at reasonable, predetermined intervals thereafter.

Evaluation should include:

- daily monitoring of feed and, if possible, water consumption;
- periodic weighing;
- characterisation of all toxic responses;
- appropriate clinical pathologic procedures which should be conducted on all test groups. This is required on all animals in each group or, when appropriate, on a representative number of animals preselected at random of each group at predetermined intervals, as provided in the protocol;

- where appropriate animals which have not shown overt clinical signs of intolerance but which have demonstrated changes in blood chemistry, urinalysis, etc., should be monitored until such parameters return to within the accepted range for normality;
- a necropsy examination with gross pathology and histopathology should be performed on all animals which die or which undergo euthanasia to prevent further suffering. Histopathology should be performed on all grossly affected organs or suspected target organs, identification of the latter will be based on laboratory animal toxicological studies and other pertinent data;
- Necropsy including histopathology should be carried out of all, or a representative sample of animals, from treatment groups which have shown overt clinical signs of intolerance.

For products intended for use in breeding animals reproductive performance should be documented. Omission shall be justified.

3.2 Studies on local tolerance

3.2.1 Tolerance testing of injectables

Testing of injectables includes intravenous, intramuscular, and subcutaneous routes.

3.2.1.1 Dosage regimen

Studies should take into account the proposed dose levels. Where necessary, studies on the product vehicle may be carried out. The applicant should take into consideration the volume of injection of the product necessary for the treatment in relation to the body weight. Particular attention must be paid where heavier animals, e.g. cattle or horses, require large volumes.

3.2.1.2 Observations

3.2.1.2.1 Clinical examination

Repeated observations of the animals and the injection sites should be performed. Examination of injection sites and surrounding tissues should be carried out at regular intervals during the 48-96 hours period after administration. Time intervals should be justified by the nature of the substance/product under investigation. If significant lesions are still present at the end of this period, observations should continue until the lesions have subsided to an insignificant level. The sites should be carefully examined for signs of inflammation (swelling, pain, etc.) by inspection and palpation; the dimensions of (palpable) lesions should be recorded.

3.2.1.2.2 Gross and microscopic pathology

For injectables intended for intramuscular or subcutaneous administration pilot studies on local toxicity may be carried out in laboratory animals, e.g. in rabbits. The concentration and the injection volume of the test product to be administered should be justified. Laboratory-animal testing may suffice, provided that such testing conclusively shows any damage to be negligible. Such studies should consist of three parts, i.e. macroscopic and microscopic examination of the injection site, and determination of the serum activity of the enzyme Creatinine Phosphokinase (CPK) before injection and at appropriate time intervals after injection, until the pre-injection level is reached.

For products where testing in laboratory animals and/or in the target animal species indicate tissue reactions, target animal studies on local tolerance must always include a

comprehensive post mortem examination of the injection sites. All injection sites, or a representative sample from each treatment group should be examined at the end of the trial period, and any lesion revealed should be examined histologically.

In order to document the reversibility of any local lesion, injection sites should be examined at various time intervals after administration of the product, until such time that no significant change is detectable, or until such time that any lesion present is unlikely to show further regression (healing up) within a reasonable period of time.

3.2.2 Tolerance testing of products intended for dermal application

The local toxicity of pour-on products and similarly formulated preparations should be investigated clinically and, where warranted, by post mortem examination. In addition, if the product is intended for use in production animals, in which the hide is normally used for leather manufacturing, the quality of the tanned skin must be documented.

3.2.3 Tolerance testing of certain products intended for oral administration

Bolus-formulated products should be tested with respect to any effect that may arise, either in connection with the administration procedure (e.g. "large" boluses intended for "small" animals may get stuck in the oesophagus), or may be caused by the presence of the product in the gastrointestinal tract for extended periods (e.g. sustained-release or pulse-release boluses intended for ruminants may cause damage to the forestomachs).

4. ASSESSMENT OF RESULTS

Observations shall be documented according to the requirements. All results indicating signs of intolerance, including any adverse effect reported in connection with the use of the product in clinical trials, shall be assessed and their significance in relation to the proposed use of the product shall be evaluated.

5. MONITORING OF POTENTIAL SIDE-EFFECTS IN CLINICAL TRIALS

Efficacy studies and field trials enable to potentially observe side effects in a much larger number of animals, although a more limited number of parameters than in tolerance studies are evaluated. These suspected adverse drug reactions or side effects occurring following the use of the product in clinical trials should be documented and evaluated.

5.1 Experimental conditions

The purpose is here to evaluate the incidence of potential side effects at the intended dose level in a much larger number of animals in the conditions very close to or identical to those in which the product is intended to be.

The protocols for efficacy studies and field trials shall take due consideration of the monitoring of these effects and facilitate their record. Positive findings from pharmacodynamic studies (mostly carried out in laboratory animals) and from tolerance studies, carried out in the target animal(s), shall warrant more specific clinical monitoring of particular organ systems. The following techniques may be relevant for this purpose:

- detailed physical examination of relevant organ systems;
- blood chemistry;

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- haematology;
 - (fine needle) aspiration biopsy cytology;
 - electrodiagnosis (e.g. ECG);
 - imaging techniques (X-rays, scanner, echography);
 - behavioural analysis.

The experimental conditions shall be those required for the efficacy trial in question. The composition of the product, the dose level, the route of administration, treatment duration shall be identical to the product intended to be marketed. Any deviation shall be duly justified.