



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

**GUIDELINE FOR THE CONDUCT OF POST-MARKETING
SURVEILLANCE STUDIES OF VETERINARY MEDICINAL PRODUCTS**

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NOTE FOR GUIDANCE ON THE CONDUCT OF POST-MARKETING SURVEILLANCE STUDIES OF VETERINARY MEDICINAL PRODUCTS

1. Introduction

Before granting of a marketing authorisation for a veterinary medicinal product, aspects of quality, efficacy and safety of the new drug are studied by experts of the regulatory authority with the aim to guarantee a maximum of drug safety.

However in some cases this aim can not be achieved by a scientific evaluation before granting the marketing authorisation. It may be necessary to undertake a continuous surveillance of the veterinary medicinal product under field conditions for a defined period of time after the marketing authorisation is granted.

Although with veterinary medicines there is an advantage over human medicines in that the conduct of pharmaco-toxicological trials can be conducted in animals, not all adverse effects will show in these trials with a limited number of animals. Many adverse reactions can be seen only after the use of the drug in clinical practice in a large population of animals. Sensitive subpopulations such as young animals or specific sensitivities of animal species and breeds can only be discovered by use of the drug on a large scale.

Surveillance of marketed drugs is a shared responsibility of the Regulatory Authorities and Marketing Authorisation Holders (MAH).

Post-marketing surveillance refers to a specific time in the life of a drug: the life span that begins once the drug enters the general market. Post-marketing surveillance is important because at the time a drug is approved for marketing a number of clinically and epidemiologically important questions are unanswered.

Post-marketing surveillance of drugs therefore plays an important role to discover undesirable effects that might present a risk. Post-marketing surveillance studies provide additional information on the benefits and risks of a drug, resulting in possible drug safety hazards being identified which impact on, or may influence the overall benefit/risk ratio of a medicinal product. As a result the competent authority may request, or the holder of the marketing authorisation may propose appropriate measures of risk prevention or propose studies to further investigate the hazard and frequency of its occurrence. Such studies should comply with this guideline.

If the risk is not acceptable compared to the therapeutic value of a drug, regulatory measures might be initiated to keep the benefit risk balance on a positive scale.

Post-marketing surveillance studies should compliment spontaneous Adverse Drug Reaction (ADR) reporting systems, which are very important in the detection of background signals, which might indicate a problem. However spontaneous reporting systems do not provide a quantitative risk assessment i.e. give the incidence of an adverse reaction in a population. Therefore it is difficult to estimate the relevance of a risk described in single case reports, without knowing the number of exposed and treated animals within a given time period. Post-marketing surveillance studies can provide a denominator and give the answer to specific questions, which have been generated by signals from the spontaneous reporting system.

A commitment to post-marketing surveillance studies (PMS) may be required at the time of marketing authorisation. In this case the study should be carried out on the basis of information of the Summary of Product Characteristics (SPC) and in accordance with veterinary Good Clinical Practice (ref.: Volume 7 of The Rules Governing Veterinary Medicinal Products in the European Union).

The basic types of questions to be addressed in PMS studies are:

- long term effects that manifest themselves only after long periods of use, or after long periods of latency,
- low frequency effects-that can only be detected in large populations,
- efficacy in customary practice,
- modifiers of efficacy: concurrent drugs, disease severity, husbandry conditions, feed,
- increase in frequency or severity of known adverse reactions.

In veterinary pharmacovigilance as the scope is set much wider than for human drugs (ref.: CVMP Guidelines for Pharmacovigilance of Veterinary Medicinal Products), monitoring of resistance to veterinary medicinal products or surveillance of ecotoxicity might also be an objective of post-marketing investigation.

In veterinary pharmacovigilance until now, there is little experience on conducting post-marketing surveillance studies. Although the methodology must be sometimes adapted to quite specific aspects of the veterinary field, profit can be gained from the experience in human medicine post-marketing surveillance. As pharmacoepidemiological science and methods are basically the same regardless of the species concerned, similar procedures whenever possible should be used and adapted to the veterinary sector.

2. Scope of the guideline

This guideline applies to the conduct of studies, which evaluate the safety of marketed veterinary medicinal products, whether sponsored by the company or not.

It includes studies where the drug is provided by the sponsoring company and studies where it is prescribed and used in the normal conditions of clinical veterinary practice.

It provides a framework whereby a variety of data collection methods can be used to evaluate the safety of marketed veterinary medicinal products. Though the study design used must be adopted on a case by case basis for particular products and hazards the guideline defines the essential principles to be applied in a variety of situations.

As the study methods in this field continue to develop, there will be a need to regularly review this guideline to ensure that it reflects advances made in the assessment of product safety.

3. Definition of a post- marketing surveillance study

Any study of a marketed veterinary medicinal product, which has the evaluation of clinical safety as an objective, can be considered as such.

However this guideline relates principally to those studies where there is a known safety issue under investigation and/or when the number of animals to be included in the study will add significantly to the existing safety data already provided for the product(s).

If a study, which is not conducted for the purpose of evaluating safety, unexpectedly, identifies a hazard, then the study would be included in the measures laid down in this guideline.

Clinical trials for new indications, new methods of administration or new combinations, are not covered by this guideline.

In cases of doubt as to whether or not a study comes under the scope of this guideline the person responsible for the study should discuss the intended protocol with the relevant regulatory authority of the Member State (s) in which the study is to be conducted.

4. Extent and objectives of post-marketing surveillance studies

Post-marketing surveillance studies may be conducted for the purpose of confirming previously unrecognised safety issues (hypothesis generation), investigating possible hazards (hypothesis testing in order to substantiate a causal association) or confirming the expected safety profile of a veterinary medicinal product under marketed conditions. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Objectives may be

- i) to measure the incidence of an adverse reaction in animals treated with the suspected drug,
- ii) to compare the incidence of an adverse reaction in animals treated and not treated with the drug,
- iii) to identify the risk factors associated with the development of an adverse reaction in animals treated with the suspected drug, such as concurrent drugs, disease severity, husbandry conditions, breeds, age, feed, etc,
- iv) to identify risk factors responsible for an increased frequency or severity,
- v) to further clarify biological effects of adverse reactions due to a suspected drug.

The design to be used will depend on the objectives of the study, which must be defined in the study protocol. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods.

5. Design of studies

5.1. Observational cohort studies

Cohort studies have the advantage to provide information about the incidence of an event in a primarily unaffected population group. It is possible to test a hypothesis defined prior to the start of the study, which could take a prospective or retrospective approach.

The results allow an assessment of risk (relative, absolute and population attributable risk).

Disadvantages could be that they are mainly useful for frequent events, they necessitate large population samples, they are time consuming and costly.

- a) The animal population studied should be as representative as possible of the general population of animals normally treated and be unselected unless specifically targeted by the objectives of the study. Exclusion criteria should be limited to the contra-indications stated in the SPC. In prospective studies the veterinarians involved in the study should be provided with the SPC for all products to be used. Where the product is used outside the indications of the SPC at the discretion of the prescribing veterinarian, such animals should be included in the analysis of the study findings.
- b) Observational cohort studies should normally include appropriate control group(s). These groups will usually include animals with the disease/indication(s) relevant to the primary study product and such animals will usually be treated with alternative therapies.
- c) The protocol should stipulate the minimum and maximum number of animals in each trial supervised by each veterinarian.

5.2. Case control studies

This study type allows hypothesis testing in a relatively short time at low cost. The approach to the research question can be concurrent or historic. It provides information for rare events and the relative risk can be estimated by calculating the odds ratio.

Disadvantages are that this study type is susceptible to bias and confounding factors and it allows no incidence estimate, nor a calculation of the absolute risk. The selection of proper controls is particularly important for this study type.

Case control studies are usually conducted retrospectively. Comparison is made between the product exposure of cases with the disease/event of interest and appropriate controls without the event. The study design should account for known sources of bias and confounding factors.

5.3. Group surveillance

The purpose of group surveillance is to study groups of animals where problems may arise which could be product-related and to ascertain product exposure. Companies who sponsor such studies should liaise particularly closely with the relevant regulatory authority in order to determine the most appropriate arrangements for the reporting of cases. Regulatory agencies may require such surveillance programmes to acquire information on emerging trends in large populations in relation to safety and/or efficacy.

5.4. Clinical trials

Specific clinical trials are sometimes necessary to clarify the mechanisms of adverse reactions and to identify the means of prevention. Large clinical trials may also be useful in the investigation of post-marketing safety issues and these may involve random allocation to treatment. Exclusion criteria should normally be limited to the contra-indications in the SPC unless they are closely related to the particular objectives in the study. Clinical trials should also adhere to Good Clinical Practice.

6. Conduct of studies

Responsibility for the conduct of the study shall be vested in the sponsor.

It shall be supervised by designated monitor(s) sited within the EU, and whose names shall be recorded in the study documents. Consideration should be given to the appointment of an independent advisory group to monitor the data and oversee the study.

7. Liaison with regulatory authorities

Companies or other institutions such as universities, proposing to perform a post-marketing surveillance study are advised to discuss the draft protocol at an early stage with the relevant regulatory authority. Particular consideration should be given to specific safety issues, which may require investigation. National legislative requirements or guidelines should be taken into account where these exist.

Before the study commences a protocol must be finalised which explains the aims and objectives of the study, the methods to be used (including statistical analysis) and the record keeping which is to be maintained. The company should submit the protocol plus any proposed communications to veterinarians participating in the study to the relevant regulatory authorities at least one month before the planned start of the study. The authorities may comment as necessary. The responsibility for the conduct of the study will, however rest with the sponsoring pharmaceutical company.

The company should inform the relevant authorities when the study has commenced and will normally provide a brief report on its progress every six months, or as requested by the authorities.

The usual reporting requirements for reporting of suspected adverse reactions must be fulfilled. Companies should ensure that they are notified of serious suspected adverse reactions and should report these to the relevant regulatory authorities within 15 days of receipt. All non-serious events should not be reported individually, but they should be summarised in the final report.

A final report on the study should be sent to the relevant regulatory authorities within 3 months of follow-up being completed. Ideally this should be a full report but a brief preliminary report within 3 months followed by a full report within 6 months of completion of the study would normally be acceptable.

In the case of products authorised through the centralised procedure, progress reports and final reports should also be sent to the EMEA.

Companies should follow the veterinary Good Clinical Practice guidelines on the content of the protocols, and final reports. For progress reports, an example is given here:

Suggested content of progress report

- i) Tabulation of number of animals identified as suitable for the study, animals entered and followed up
- ii) Estimate of overall exposure to study product(s) in animal-years or months or days
- iii) Status of all animals who have completed the study e.g. on/off treatment, died, lost to follow up
- iv) Tabulation of the reasons for stopping treatment during the study
- v) Individual listing of causes for each death and animals needing care in specialist clinics
- vi) Table of all serious adverse events (numerical form plus a line-listing)

N.B. If there are multiple study products, data should be reported for each product separately.

Generally only the data listed above should be included. Other information should not be included without prior discussion with the regulatory authorities. After review of the report regulatory authorities may request additional information.

They may require adaptation to suit the needs of individual studies.

8. Promotion of veterinary medicinal products

Post-marketing surveillance studies should not be conducted for the purposes of promoting the use of medicines. Company representatives should not be involved in studies in such a way that it could be seen as a promotional exercise.