



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE:

**PHARMACOVIGILANCE OF VETERINARY
MEDICINAL PRODUCTS**

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DRAFT GUIDELINES FOR PHARMACOVIGILANCE OF VETERINARY MEDICINAL PRODUCTS

1. LEGAL BASIS AND PURPOSE

The legal framework for pharmacovigilance of veterinary medicinal products in the Community is given in Council Regulation (EEC) No 2309/93 (Title III, Chapter 3), Commission Regulation (EC No 540/95) and Council Directive 81/851/EEC as amended by Council Directive 93/40/EEC.

Pharmacovigilance activities come within the scope of the criteria of quality, safety and efficacy, as new information is accumulated on the veterinary medicinal product under field conditions of use in the marketing situation. Pharmacovigilance obligations apply to all authorised veterinary medicinal products.

Council Regulation No 2309/93 (Articles 41 to 44), Commission Regulation (EC No 540/95) and Directive 81/851/EEC as amended (Chapter VI articles 42a to 42c) describe the respective obligations of the person responsible for placing the medicinal product on the market (the Marketing Authorisation holder) and of the competent authorities to set up a system for pharmacovigilance in order to collect, evaluate and collate information about suspected adverse reactions. All relevant information should be shared between the competent authorities and the Marketing Authorisation holder, in order to allow the partners in pharmacovigilance activities to assume their obligations and responsibilities. This requires an exchange of information between the Agency, the competent authorities of the Member States, and the Marketing Authorisation holder, as well as procedures to avoid duplications, maintain confidentiality and ensure the quality of the systems.

These guidelines introduce some new concepts for veterinary products such as post authorisation safety studies and reinforce others, such as risk/benefit evaluation, which are used in "human" pharmacovigilance. These concepts should be considered as trends to explore and adapt progressively to veterinary situations. Specific methodological technology and procedures will need to be developed in the near future and these will involve the EMA, national authorities and centres of veterinary pharmacovigilance as well as specialists in epidemiological and veterinary clinical sciences.

In accordance with Article 46 of the Regulation and Article 42g of the Directive, guidance for marketing authorisation holders on the implementation and practical procedures involved in complying with the above legislation, in the interests of protecting public and animal health, has been prepared. The areas covered are set out in the paragraphs that follow:

2 SCOPE

The scope of veterinary pharmacovigilance covers not only clinical safety, but also other aspects of post-authorisation surveillance. These include:

- lack of expected efficacy and misuse (see 2.1.3) of a veterinary medicine;
- human reactions to vet medicines;
- epidemio - surveillance of resistance;

- potential environmental problems;
- reported violations of approved residue limits.

For veterinary medicinal products authorised in the Community (whether through the centralised or national procedures):

- all suspected adverse reactions (serious or otherwise) should be reported when received from veterinarians, other animal health professionals, animal owners or users of the veterinary medicinal product. For the accuracy and usefulness of the information reported, it is recommended for animal owners and users to seek veterinary advice prior to reporting. Suspected adverse reactions should be reported even if the marketing authorisation holder does not agree with the reporter's assessment of a possible causal association. These include spontaneously reported suspected adverse reactions and suspected adverse reactions from post-authorisation surveillance studies.

2.1 Further information on items included within the scope of pharmacovigilance:

2.1.1 Reporting of human reactions to veterinary medicinal products

All suspected adverse reactions occurring in humans following use of veterinary medicinal products should be reported immediately, and in no case later than 15 calendar days following receipt, to the competent authorities of the Member State in whose territory the incident occurred. (See section 7 for details of what to report).

2.1.2 Reporting of lack of expected efficacy

Directive 81/851/EEC as amended cites the lack of therapeutic effect as a reason for refusal or revocation of authorisation. It is incumbent therefore for companies to investigate such reports.

Where the conclusions drawn from the suspected adverse reaction reports differ from those in the dossier on which the authorisation was granted and which might normally be expected, the company should inform the competent authority.

Lack of efficacy in this context means: lack of expected efficacy of a veterinary medicinal product according to the indications claimed for.

2.1.3 Extra-label use (unlicensed use of products)/Misuse¹

Reports of suspected adverse reactions may be obtained on products used outside the terms of the marketing authorisation e.g. use of a product in non-authorised species/indications, use at doses differing from those set out in the summary of product characteristics (SPC) and package insert. (Products with national authorisations should follow the national SPC and products with Community authorisations should follow the unique EU SPC.)

While this practice is neither endorsed nor recommended, such reports can provide useful information on the safety of the product and should be recorded by the person responsible for pharmacovigilance and reported to the competent authorities in the normal way.

The system shall also collate information on serious **abuse**² of veterinary medicinal products.

¹ Misuse: Use of a veterinary medicinal product in a way which is not recommended in the summary of product characteristics, with the exception of those cases referred to in Article 4.4. of Directive 81/851/EEC.

² Abuse: Persistent or sporadic, intentional excessive use or administration of a veterinary medicinal product inconsistent with or unrelated to the recommendations of the summary of product characteristics

2.1.4 Medicated premixes

When medicated premixes which have been incorporated in the finished feed are suspected of causing a reaction in animals or humans, both the premix and the finished feed should be investigated without delay.

Among the factors that have to be examined are the composition of the finished medicated feed, the inclusion levels of active ingredients, the operation of the milling process(es) and, when possible, the actual dosage administered to individual target animals.

2.1.5 Reporting of violations of approved Maximum Residue Limits (MRLs)

Where investigation of drug residues in tissues or produce of treated animals casts doubt on the validity of the withdrawal period in respect of a veterinary medicinal product, it is important that this information is brought to the attention of the competent authority responsible for authorisation of the veterinary medicinal product concerned. Such cases should be reported as suspected adverse reactions in the Periodic Safety Update reports (see 6.3.7iii).

2.1.6 Use of human medicines in animals

Occasionally suspected adverse reaction reports may be obtained on human medicines having been used in animals, where legislative circumstances allow. Such reports can provide useful information on the safety or otherwise of the product ingredients and should be recorded by the veterinary surgeon who used the product and, if appropriate, the veterinary representative of the company who holds the Marketing Authorisation for the human medicine concerned.

3. RESPONSIBILITIES OF MARKETING AUTHORISATION HOLDERS

The responsibilities of the qualified person responsible for pharmacovigilance are as follows:

- 3.1** the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, including representatives, is collected and collated so that it may be accessed at least one point within the Community, as indicated by the holder of the authorisation;
 - 3.2** the preparation and submission of the following documents for the European Medicines Evaluation Agency (EMA) and/or competent authorities of Member States where the medicinal product is authorised as referred to in the Regulation and Directive and further detailed in this document:
 - Serious suspected adverse reaction reports
 - Periodic safety update reports to include:
 - ongoing risk/benefit evaluation during the post-authorisation period;
 - all (serious and non-serious) spontaneous reports involving animals or humans, including reports of lack of expected efficacy or misuse;
 - reports on epidemic - surveillance of resistance;
 - potential environmental problems;
 - reported violations of approved residue limits;
 - ongoing risk/benefit evaluation during the post-authorisation period.
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- Reports of suspected adverse reactions in humans

3.3 Ensuring that any request from the competent authorities in any of the 15 Member States of the EU, for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product, is answered fully and promptly. This includes the provision of information about the volume of sales of the medicinal product concerned;

3.4 Products licensed under article 5.10(a)(i) of Council Directive 81/851 (EEC) as amended:

The MA holders for both the original reference product (Product A) and the essentially similar product (Product B, authorised according to article 5.10(a)(i) of Directive 81/851) assume full responsibility for the pharmacovigilance relating to their respective products.

Nevertheless they should maintain close liaison, and in particular suspected adverse reactions to Product B must be communicated to the MA holder for Product A. Where identical products are co-marketed by more than one company any report of a serious suspected adverse reaction must be communicated by one company to another. Any regulatory action resulting from pharmacovigilance information related to the products involved in the above scenarios would need to be applied as appropriate to both products.

3.5 If the marketing authorisation holder is aware that a reporter has reported a reaction to one of its products directly to the authority of a Member State, the marketing authorisation holder should still report the reaction, informing the authority that the report is likely to be a duplicate of a previous report. In this situation it is essential for the marketing authorisation holder to provide all the available details, including any reference number provided to the reporter by the authority, in order to aid identification of the duplicate.

4. SUSPECTED ADVERSE REACTION REPORTING

Adverse Drug Reaction (ADR)/Adverse Reaction: A reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

4.1 The marketing authorisation holder is responsible for reporting suspected adverse reactions to the authorities of the Member States and EMEA for their veterinary medicinal products authorised under the centralised procedures and to the appropriate authorities of the Member States for their medicinal products authorised through the national procedures. (For details of the reporting requirements see sections 5-7)

4.2 Minimum requirements for any suspected adverse reaction (serious/non-serious/human) report to be recorded by the Marketing Authorisation holder, and reported to the Member State (and EMEA for Community authorisations):

A case report will be considered as a suspected adverse reaction report provided that at least the following data are available:

- (i) An identifiable source, wherever possible this should include the name and address of the reporter (e.g. veterinarian, pharmacist, animal owner)
- (ii) animal details : species, sex, age / human details: sex, age or adult/child
- (iii) suspect product. - (name and marketing authorisation number)
- (iv) reaction details

The reference point for deadlines for submission of reports is the time of receipt of the minimum information. It should be stressed that these are minimum requirements and that companies should endeavour to provide all the information necessary for a full evaluation. (See sections 5.3 and 6.3 for details of information required).

4.3 Suspected adverse reaction reports can be divided into the following:

- **Serious Suspected Adverse Reaction Reports** (see section 5)
- **Periodic Safety Update Reports** (see section 6)
- **Human Suspected Adverse Reaction Reports** (see section 7)

4.4 Reports from post-authorisation studies

During the post-authorisation period the product will be used in a different setting from clinical trials and larger populations are likely to be exposed. Much new information will be generated which may impact on the risk/benefit ratio and an evaluation of this needs to be an on-going process, both within pharmaceutical companies and regulatory authorities.

Compared to human medicine, the tolerance of veterinary drugs is more predictable since it is studied in the target species at supra-therapeutic doses, which allows for the evaluation of a margin of safety. Therefore the need for post authorisation surveillance studies is certainly not so stringent in the veterinary field. Spontaneous reporting schemes are expected to provide the complementary information concerning adverse drug reactions, especially those which are unexpected. However, for specific cases concerning suspected adverse reactions occurring for products used on a large scale such as post-vaccinal reactions, post authorisation studies should be encouraged.

The methodology for such studies is obviously quite specific to the veterinary field and should be considered as an area for investigation in veterinary pharmacovigilance, and will be the subject of further guidelines. Serious suspected adverse reactions for post-authorisation studies should be reported to all Member States where the product is authorised. (See section 5 for reporting requirements.) Non-serious reactions should be reported in summary at the end of each study and included in the PSU report (see section 6).

5. SERIOUS SUSPECTED ADVERSE REACTION REPORTING REQUIREMENTS

Serious Adverse Reaction: An adverse reaction which is fatal, life threatening, disabling, incapacitating, or which results in permanent or prolonged signs in the animals treated.

In veterinary medicine the existence of a variety of animal species and husbandry conditions require a modified approach to the classification of a 'serious ADR'. For example in intensive animal production with species such as poultry, fish or bees, a certain level of mortality rate is considered as 'normal' or 'expected'. These species are usually treated as a group and only an increased incidence of mortality, or severe signs, or variations of animal production levels exceeding the rates normally expected should be considered as a 'serious ADR'.

However, in species like dogs, cats or horses a single death constitutes a 'serious ADR'. This also applies to cases of individual deaths in cattle, sheep, pigs, goats and rabbits even if they are kept in herds or flocks in intensive animal production because treatment is often performed on the individual animal and therefore a single death or severe symptoms have to be considered on an individual basis.

Note: For all species if they are kept as individual companion animals a single death constitutes a 'serious ADR'.

5.1 ADR reports occurring in the EC

Council Regulation (EEC) 2309/93 Article 44
Council Directive 81/851 (EEC) Article 42d

The marketing authorisation holder should record and report all suspected serious adverse reactions occurring within the Community which are brought to its attention. These should be reported immediately, and in no case later than 15 calendar days from receipt, to the Member State in whose territory the incident occurred. (See section 5.3 for details of what information is required).

For centrally approved products, the responsibility for ensuring that all serious suspected adverse reactions to such products occurring within their territory are further reported to the EMEA, rests with the member states concerned. Such reports must be submitted to the Agency immediately, and in no case later than 15 days following receipt of the information

In addition, serious reactions together with all other reactions should be reported as line listings in the Periodic Safety Update (PSU) report (see section 6).

5.2 ADR reports occurring outside the EC

Council Regulation (EEC) 2309/93 Article 44

The marketing authorisation holder should report all suspected serious and unexpected³ adverse reactions occurring in the territory of a third country and brought to its attention. These should be reported to the EMEA immediately for all centrally approved products and to all Member States immediately, and in no case later than 15 calendar days following receipt, where the product is authorised nationally.

In addition, all unexpected adverse reactions from third countries should be reported as line listings in the PSU (see section 6).

5.3 Content/Required information for suspected serious adverse reactions (Single) reports

Marketing Authorisation holders are expected to fully validate and follow-up all serious reactions reported by them to the authorities. It is essential for marketing authorisation holders to provide as complete as possible details, including all relevant clinical information for cases of suspected serious adverse reactions in order to facilitate assessment. The report of a suspected adverse reaction should as far as possible include the information below. The original words used by the reporter should be provided even if they are also classified or coded according to Marketing Authorisation holder or competent authority accepted terminology.

5.3.1 Marketing Authorisation (MA) holder details and original reporter's details

- i) The name of the qualified person responsible for pharmacovigilance employed by the marketing authorisation holder.
- ii) Address, telephone and fax number of the qualified person.
- iii) MA holder case reference number.
- iv) Date of receipt of report by MA holder (in country of qualified person responsible for pharmacovigilance).
- v) Source of report e.g. spontaneous, clinical trial, post-authorisation study.

³ Unexpected Adverse Reaction: This relates to an adverse reaction which is not mentioned in the EC summary of product characteristics (SPC).

- vi) Details of the original reporter - name (if acceptable under national law), address, profession and speciality (if available).
- vii) Reporting country (country where the incident occurred).
- viii) Purchase country (where suspect product was purchased if different from that above).

5.3.2 Animal Details

- i) Number treated
- ii) Characteristics of animals showing signs:
 - Species
 - Breed
 - Sex
 - Age (in days/weeks/months/years)
 - Weight (in kilograms)

5.3.3 Suspect Product details

- i) Product name(s)/brand names(s)
- ii) Approved Scientific Name(s) (INN - International Non-proprietary Name)
- iii) Marketing Authorisation Number
- iv) ATCvet Code (Therapeutic Group)
- v) Pharmaceutical form
- vi) Batch number
- vii) Expiry date of batch - if relevant
- viii) Storage details - if relevant

5.3.4 Treatment details

- i) The person who administered the product (e.g. animal owner, veterinary surgeon etc.)
Include identifier (name/initials) and relevant occupation/qualification of person
- ii) Reason for treatment including diagnosis
- iii) Dose (and frequency if relevant) of treatment given
- iv) Route and site of administration used
- v) Start date
- vi) Stop date and/or duration of treatment
- vii) Time between administration and reaction to the product
- viii) Action taken after reaction (e.g. drug withdrawn, dose reduced)

- ix) Previous reaction(s) to the product if occurred/reported, (re-challenge information) to include:
- Approximate date animal(s) previously treated with product
 - Description of reaction including - were previous reaction signs similar to the present reaction signs
 - Outcome including any treatment given

5.3.5 Other products used concurrently

All medicinal treatment over at least a one week period preceding the suspected reaction should be provided when available. This should also include non-prescription medicines, magistral preparations⁴ and medicated feedstuffs if appropriate.

For each medication:

- i) Product name(s)/brand names(s)
- ii) Approved Scientific Name(s) (INN - International Non-proprietary Name)
- iii) Marketing Authorisation Number
- iv) ATCvet Code (Therapeutic Group)
- v) Pharmaceutical form
- vi) Batch number if relevant
- vii) Expiry date of batch if relevant
- viii) Storage details - if relevant

(Treatment details for other product(s) used concurrently)

- ix) The person who administered the product (e.g. animal owner, veterinary surgeon etc.) Include identifier (name/initials) and relevant occupation/qualification of person
- x) Dose (and frequency if relevant) of treatment given
- xi) Route and site of administration used
- xii) Start date
- xiii) Stop date and/or duration of treatment
- xiv) Other relevant information

5.3.6 Details of the animal suspected adverse reaction(s)

- i) Description of reactions(s) including site and severity (intensity of the reaction). (The initial reporter's words and/or phrases to be used where possible (with explanations if appropriate))

⁴ In the case of magistral products, details of individual constituents of the formula should be indicated

- ii) Start date or onset of reaction
 - iii) Stop date or duration of reaction
 - iv) Specific treatments adopted against the observed adverse reaction
 - v) Number of animals showing signs
 - vi) Number of animals dead
 - vii) De-challenge information (e.g. any obvious effect of removal of treatment)
 - viii) If available the following information should be provided:
 - Number of treated animals alive with sequelae
 - Number of treated animals recovered
- Any previous reactions to the product should be recorded under 5.3.4 xviii)

5.3.7 Other information

Any other relevant information available to facilitate assessment of the case should be provided, for example: disposition to allergy or changes in feeding habits, and/or production levels.

5.3.8 Investigation

- In a case of fatal outcome the cause of death should be provided and its relationship to the suspected reaction commented upon. Post-mortem examination findings or laboratory findings, if carried out, should be provided.
- Summary of product sample investigation (if relevant)
- Nature of MA holder investigation (if relevant)

5.3.9 Causality assessment

Marketing authorisation holders may comment on whether they consider there is a causal association between the suspect product(s) and reactions(s) reported and should provide the criteria on which they have made the assessment.

The causality assessment should be done using the ABON-system if possible. According to this system, four categories of causality can be made:

- category "A" : probable
- category "B" : possible
- category "O" : unclassified (cases where insufficient information was available to draw any conclusion)
- category "N" : unlikely to be drug related

In assessing causality the following factors should be taken into account:

- i) associative connection, in time - including dechallenge and rechallenge following repeated administration (in clinical history) - or in anatomic sites;

- ii) pharmacological explanation, blood levels, previous knowledge of the drug;
- iii) presence of characteristic clinical or pathological phenomena;
- iv) exclusion of other causes;
- v) completeness and reliability of the data in the case reports;
- vi) quantitative measurement of the degree of contribution of a drug to the development of a reaction (dose-effect relationship).

For inclusion in category "A" (probable), it is recommended that **all** the following minimum criteria should be complied with:

- There should be a reasonable association **in time** between the administration of the drug and onset and duration of the reported event.
- The description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology of the drug.
- There should be no other equally plausible explanation(s) of the case. (If such are suggested - are they validated? What is their degree of certainty?) In particular, concurrent use of other drugs (and possible drug interactions) or intercurrent disease should be taken into account in the assessment.

Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information) then such reports can only be classified as "B" (possible), "N" (unlikely) or "O" (unclassifiable/unassessable).

For inclusion in category "B" (possible), it is recommended that this be applied when drug causality is one (of other) possible and plausible causes for the described event but where the data does not meet the criteria for inclusion in category "A".

For inclusion in category "N" (unlikely), cases where sufficient information exists to establish beyond reasonable doubt that drug causality was not likely to be the cause of the event.

For inclusion in category "O" (unclassifiable/unassessable), all cases where reliable data concerning a SAR is unavailable or is insufficient to make an assessment of causality.

5.3.10 Reporting forms

Until a standardised reporting form is agreed, reporting forms acceptable to the competent authorities of the Member State should be used. An example of a reporting form is attached at Table A. Computer-generated forms are acceptable provided they are legible and follow the accepted content and layout. Reports should be in the national language(s), or in English if this is acceptable to the appropriate competent authorities.

6. PERIODIC SAFETY UPDATE REPORTS/ PERIODIC SAFETY UPDATES (PSU)

A Periodic Safety Update is intended to provide competent authorities with an update of the world-wide safety experience of a veterinary medicinal product at defined times post-authorisation. At these times marketing authorisation holders are expected to provide succinct summary information together with a critical evaluation of the risk/benefit of the product in the light of any new or changing post-authorisation information. This is in order to ascertain whether further investigations need to be carried out and/or whether changes should be made to

the SPC, labelling or product promotion. In compliance with the requirements laid down in Commission Regulation (EC No 540/95), holders of marketing authorisations must include in the periodic safety updates details of all suspected unexpected adverse reactions arising in the Community or in a third country

6.1 Where to send Periodic Safety Updates

Periodic Safety Updates for veterinary medicinal products authorised under the centralised procedure should be submitted to all the competent authorities of Member States and the EMEA in accordance with Regulation (EEC) No 2309/93 Articles 43 and 44 and for veterinary medicinal products authorised nationally to the competent authorities of the Member States in accordance with Directive 81/851/EEC Articles 42a and 42d.

6.2 Scope and frequency of reports

Unless otherwise required by the licensing authority, a periodic safety update summary report, in the specified format (see Table B), should be prepared for all authorised medicines at the following intervals:

- 6-monthly for the first 2 years after authorisation
- annually for the subsequent 3 years
- thereafter 5-yearly at the time of renewal.

Each safety update report should cover the period of time since the last update report and should be submitted within 60 days of the Data Lock Point (DLP)⁵

Each medicinal product will have an EC birth date, which will be the date on which the product was first authorised in the EC. The year of the EC birth date determines the start of submission of periodic safety updates and the DLP (6 monthly, annually and 5 yearly). However, some flexibility may be used in order to harmonise periodic safety updates internationally. Thus the month for data lock may be +/- six months within the EC birth date, provided that the first periodic safety update is submitted not later than 6 months after the EC birth date e.g.

International birth date	EC birth date	Periodic Safety Updates
	May 1995	
	Sept 1993	Sept 95, March 96 etc.

The DLP in subsequent Member States shall be co-ordinated so that they all fall on the same day as those in the first Member State. In effect the first DLP is likely to be at less than 6 months in the second and subsequent Member States.

For the purpose of the PSU the marketing authorisation holder's database should be frozen in relation to the product at the DLPs defined below. Up-to-date safety data, i.e. data that becomes known to the marketing authorisation holder after the DLP and which may influence the evaluation should also be included in the report in the final section (see 6.3.10). Data relating to serious adverse reactions must also be reported separately, see 5.3, as well as in the periodic safety update report.

⁵ Data Lock Point (DLP): The date designated as the cut-off date for data to be incorporated into a particular safety update. On this date the data available to the author of the safety report is extracted for review and stored.

The report should include a cross reference to combination products, where appropriate, with reference to the active substance. This will only be possible where the MA for a single and combination product are held by the same Marketing Authorisation holder. It will be necessary, in a given report, to separate different formulations, routes of administration, and indications, if this information is available. When relevant, the safety update should also differentiate data associated with salient pharmaceutical aspects, including the active moiety or moieties, excipients, strength(s) and dosage form(s), etc.

6.3 Content of Periodic Safety Updates

A PSU for a Community authorised product should be written in English. For nationally authorised products the PSU should be written in the national language(s), or in English if this is acceptable to the appropriate competent authorities. All PSUs should fulfil the following format and content:

6.3.1 SPC (Article 5 Council Directive 81/851 (EEC))

The EC SPC must be included for reference in the report. If no SPC is available, e.g. in cases of old non-reviewed/renewed products, an explanation should be given and the package insert should be provided.

6.3.2 Update of regulatory or marketing authorisation holder actions taken for safety reasons

An update should be presented if any significant regulator-initiated or marketing authorisation holder - initiated actions have been taken, or are to be taken, for safety reasons during the report period anywhere in the world.

The format should be a brief narrative stating the reasons for significant regulatory or marketing authorisation holder action, with documentation appended when appropriate.

6.3.3 Sales volume

A safety update must address the relationship of sales volume of a product related to numbers of suspected adverse reactions reported.

For nationally authorised products, each PSU report should contain the number of doses/amount of product sold in the relevant member state. These should be expressed in an appropriate form. For Community authorised products, each PSU report should contain the number of doses/amount sold in each Member State.

The following forms are suggested:

- Vaccines to be expressed in numbers of booster doses;
- Liquid to be expressed in litres;
- Powder to be expressed in kilograms;
- Tablets to be expressed in numbers of tablets;
- Sprays to be expressed in litres or kilograms;
- Flea collars to be expressed in numbers of collars;
- Paste to be expressed in kilograms

For nationally authorised products the incidence of reactions in each Member State, should be calculated by dividing the total number of animals reacting during the period by the number of doses sold (in appropriate units) in that Member State during the period of the report and multiplying by 100. For Community authorised products incidence should be calculated for each country and presented accordingly.

$$\text{Incidence} = \frac{\text{No of animals reacting during period} \times 100}{\text{No of doses sold during period}}$$

A proportion of veterinary medicines are indicated for more than one species. Where such a situation pertains it is clearly not possible to calculate individual species incidence of reactions. Theoretical calculations for single species are sometimes of value, but should always be treated as arbitrary. A significant number of PSUs will show no reports of suspected adverse incidents. In these cases it is not possible to calculate an incidence of reactions.

6.3.4 Marketing Authorisation (MA) holder and product details

Each PSU should include:

- i) The name of the MA holder
- ii) The product name(s)
- iii) The marketing authorisation number

6.3.5 Individual case histories

The minimum information constituting a reportable individual case is listed at 4.2

The standard information required for an individual case (line listing) includes:

- i) Company case reference number (+ country where incident reaction/occurred if different to the country of the Member States concerned, or if Community approved product)
- ii) Date(s) of treatment(s)/Date(s) of vaccination(s)
- iii) Was the product used as recommended?
- vi) Date of reaction
- v) Number of animals treated
- vi) Species
- vii) Age(s)
- viii) Number reacting (approximate)
- ix) Number dying
- x) Other products, including authorised medicated premixes, used concurrently
- xi) Presenting signs/diagnosis
- xii) MA comments and causality assessment

6.3.6 Reporting forms

All the individual case information listed above should be presented in the line-listing format given in Table B.

6.3.7 Suspected adverse reaction reports to be included in the PSU

The appropriate individual suspected adverse reaction reports/case histories defined below should be included only if received during the period of review.

i) Spontaneous reports (serious and non-serious)

All individual case reports (including reactions in humans and reports involving lack of expected efficacy) sent spontaneously to the MA holder and attributed to the drug which relate to all reactions, including interactions and extra-label use/misuse should be included, as well as suspected unexpected adverse reactions classified as non-serious as required under Commission Regulation (EC No 540/95)

The line listing should also include all serious reactions that qualified for reporting by MA holders as full 15 day reports under the guidelines on adverse reaction reporting by MA holders. These cases should be identified (e.g. asterisked) in the comments section of the line listing (where MA holders have received reports from the regulatory authorities these should also be included in the line listing and identified in the comments section accordingly).

ii) Serious case reports from other sources

Marketing authorisation holders sometimes receive ADR information on individual incidents from other sources, including regulatory authorities; those from regulatory authorities should also be listed, identifying their source. A signal generated on the basis of these case reports should be reported in the narrative with sufficient case information. The aim is to be comprehensive but to avoid duplication of reporting.

iii) Other reports to be included

Information on violations of approved residue limits, emerging trends of resistance to the product in question, or any environmental problems should be provided as fully as possible in this section.

iv) Reports from post-authorisation studies

Serious and non-serious ADR reports from post-authorisation studies should be included as line listings in the PSU report (see section 4.4).

v) Narrative review of the individual case histories

The report should include a brief narrative based on the marketing authorisation holder's analysis of the cases presented in the line listing. This should include a comment on any increase in frequency.

6.3.8 Published ADR reports

A brief narrative overview with a bibliography of published ADR reports should be attached to the copies of the full report, if relevant.

6.3.9 Overall safety evaluation

The safety update should include a concise critical analysis and opinion on the risk/benefit profile of the product written by a suitably qualified expert for pharmacovigilance. Any new important information on the following should be explicitly included:

i) evidence of previously unidentified toxicity

- ii) increased frequency of known toxicity
- iii) drug interactions
- iv) overdose and its treatment
- v) suspected adverse reactions associated with extra-label use/misuse.
- vi) human reactions associated with the use of the product.

For each of these points, lack of significant information should be reported.

The evaluation should indicate in particular whether the safety data remain in line with the cumulative experience to date and the SPC, and should specify any action recommended and the reasons why.

In the event of any new or changing information becoming available which impacts on, or may influence the overall benefit/risk evaluation of a veterinary medicinal product, the marketing authorisation holder should immediately inform all the competent authorities in countries in which the product is authorised and in addition, for products which have Community authorisation to the EMEA. A comprehensive report evaluating the issue and the risks in the context of the benefits should be submitted at the earliest opportunity and no later than 4 weeks of being requested, to all competent authorities of the Member States in which the medicine has been authorised and in addition, for products which are authorised centrally, the Commission and the EMEA.

6.3.10 Important information received after data lock point

This section is for reporting any important new information received by the marketing authorisation holder since the database was frozen for review. It may include significant new cases or follow-up data that affect the interpretation or evaluation of existing reports. The impact of this information on the overall safety evaluation should be discussed.

7. HUMAN REACTIONS TO VETERINARY MEDICINAL PRODUCTS

Information about any suspected adverse reactions (serious or non-serious) in humans, as a result of administering veterinary medicinal products, should be given with the following details:

- i) Patient identification (as appropriate according to national laws)
- ii) Sex
- iii) Age or adult/child
- iv) Occupation - if relevant to exposure to product
- v) Nature of exposure (e.g. inhalation, injection, ingestion or dermal exposure)
- vi) Nature of reaction including signs and symptoms
- vii) Date product used
- viii) Date of reaction

- ix) Outcome of reaction (e.g. extent of recovery, specific treatment required)
- x) Name, address, telephone number of medical doctor/physician (or Poison Centre) if consulted

Suspected adverse reactions, to nationally authorised products, occurring in humans should be reported immediately, and in no case later than 15 days following receipt, to the competent authorities of the Member State in whose territory the incident occurred. The same timescale applies for products with Community authorisations. Where not all the information is available at the time of sending the report the minimum information may be sent (see section 4.2) with a follow-up report to be sent later.

TABLE A

INDIVIDUAL REPORT FORMAT FOR SUBMISSION OF REPORTS OF SERIOUS SUSPECTED ADVERSE REACTIONS TO COMPETENT AUTHORITIES/EMA

(Please use 1 form per suspected adverse reaction report)

MA HOLDER DETAILS

Sender identifier (*name of qualified person for pharmacovigilance*):

Sender address, telephone and fax number:

Date report sent by MA holder to competent authority/EMA:/ /

REPORT IDENTIFICATION

MA holder case reference number:

Date report received by MA holder:/ /

(*in country of qualified person for pharmacovigilance*)

Reporting country (*country where the incident occurred*):

Purchase country (*country where the suspect drug was obtained*):

Report source (*e.g. spontaneous, clinical trial, post-authorisation study*):

.....

REPORT ORIGIN/PRIMARY SOURCE (*e.g. veterinary surgeon, pharmacist, animal owner*)

Reporter identifier (*name and address*):

Reporter qualification/occupation:

ANIMAL DETAILS

- Number treated:
- Number with signs:
- Details of animals with signs: Species -
Breed -
Sex -
Age (*in days, weeks, months, years*) -
Weight (*in kgs*) -

SUSPECT PRODUCT DETAILS (*Medicinal Product*)

- Product name(s)/brand name(s):
- Approved Scientific Name/Active substance:
- MA Number:
- ATCvet Code (*Therapeutic Group*):
- Pharmaceutical form:
- Batch number:
- Expiry date of batch (*if relevant*):
- Storage details (*if relevant*):

Treatment Details

- Administrating person identifier:
(*Name/initials and qualifications/occupation*)
- Reason for treatment (*include diagnosis*):
- Dose (*and frequency if relevant*) of treatment given:
- Route and site of administration used:

- Start date of treatment:/ /
- Stop date and/or duration of treatment:/ /
- Time between administration and reaction to product:
- Action taken after reaction (*e.g. drug withdrawn, dose reduced*):

Previous reaction(s) to the product (*if occurred/reported*)

- Approximate date animal(s) treated:
- Description of reaction(s):
- Outcome (*including any treatment given*):

OTHER PRODUCTS USED CONCURRENTLY

For each medication/product

- Product name(s)/brand name(s):
- Approved Scientific Name (INN)/Active substance:
- MA Number:
- ATCvet Code (*Therapeutic Group*):
- Pharmaceutical form:
- Batch number:
- Expiry date of batch (*if relevant*):
- Storage details (*if relevant*):

Treatment with other products used concurrently

- Administrating person identifier:
(Name, initials and occupation)
- Dose (and frequency if relevant) of treatment given:
- Route and site of administration used:
- Start date:/ /
- Stop date and/or duration of treatment:/ /
- Other relevant information:

DETAILS OF THE ANIMAL REACTION(S)

- Reaction description (*describe the sequence of events, all clinical signs and other relevant observations including site and severity and original reporters words where possible*):
.....
.....
.....
- Start date:/ /
- End date/duration of reaction:/ /
- Treatment of reaction (*if any*):
- Number of animals showing signs:
- Number of animals dead:
- De-challenge information:
- If available the following information should be provided:

No. of treated animals with sequelae:

No. of treated animals recovered:

Investigation

- Post mortem and/or laboratory findings (*if relevant*):
- Summary of product sample investigation (*if relevant*):
- Nature of MA holder investigation (*if relevant*):

CAUSALITY ASSESSMENT

- MA holder comments and conclusions (*including the appropriate A, B, O, N category*):
.....
.....

DETAILS OF THE HUMAN REACTION(S)

- Patient identification (*as appropriate according to national laws*):
- Sex: Age or adult/child:
- Occupation (*if relevant to exposure to product*):
- Date product used:/ / Date of reaction:/ /
- Duration of reaction:
- Description of reaction (*including signs and symptoms*):
.....
- Nature of exposure (*e.g. inhalation, injection, ingestion or dermal*):
- Outcome of reaction (*e.g. extent of recovery, specific treatment required etc*):

- Name and address of physician and/or Poison Centre, if consulted:
.....

Name and signature of MA holder investigator: _____

Date:/ /

IN CONFIDENCE

TABLE B

VETERINARY PHARMACOVIGILANCE SCHEME - PERIODIC SAFETY UPDATE REPORT
MARKETING AUTHORISATION HOLDER FORM FOR MULTIPLE REPORTS OF ANIMAL SUSPECTED ADVERSE REACTIONS

MARKETING AUTHORISATION HOLDER

PRODUCT:

AUTHORISATION NO:

PERIOD OF REPORT FROM/../.. TO/../..

No. OF DOSES DURING PERIOD OF REPORT:

INCIDENCE:

MA HOLDER CASE REF	DATE(S) OF TREATMENT(S)/ VACCINATION(S)	DATE OF REACTION	NO. TREATED	SPECIES AND AGE (Juv/Adult)	NO. REACTED	NO. DIED	WAS PRODUCT USED AS RECOMMENDED YES/NO	OTHER PRODUCTS USED CONCURRENTLY	PRESENTING SIGNS/ DIAGNOSIS	MA HOLDER COMMENTS & CAUSALITY ASSESSMENT
TOTAL										

FOR NATIONAL PHARMACOVIGILANCE USE ONLY

REFERENCE:

DATE OF RECEIPT:

NUMBER OF INCIDENTS: