



The European Agency for the Evaluation of Medicinal Products  
*Veterinary Medicines and Inspections*

EMEA/CVMP/183/96- Rev.1-CONSULTATION

**COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS**

**GUIDELINE ON  
PHARMACOVIGILANCE FOR VETERINARY MEDICINAL PRODUCTS  
– GUIDANCE ON PROCEDURES FOR MARKETING AUTHORISATION HOLDERS**

ADOPTION BY CVMP	15-17 July 1997
DATE FOR COMING INTO OPERATION	1 January 1998
REVISED BY PHARMACOVIGILANCE WORKING PARTY	12-13 January 2004
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	17 March 2004
START OF CONSULTATION	18 March 2004
END OF CONSULTATION	17 September 2004

Public

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# **GUIDELINE ON PHARMACOVIGILANCE FOR VETERINARY MEDICINAL PRODUCTS – GUIDANCE ON PROCEDURES FOR MARKETING AUTHORISATION HOLDERS**

## **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 Directive 2001/82/EC of the European Parliament and of the Council (Title VII).

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 (EEC) No 2309/93 (Articles 41 to 44), Commission Regulation (EC) No 540/95 and Directive 2001/82/EC (Title 1 Definitions, Article 1 and Title VII Pharmacovigilance, Articles 72 to 79) describe the respective obligations of the person responsible for placing the veterinary medicinal product on the market (the Marketing Authorisation Holder, MAH), 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 MAH, in order to allow the partners in pharmacovigilance activities to assume their obligations and responsibilities. This requires an exchange of information between the EMEA, hereafter referred to as the Agency, the competent authorities of the Member States, and the MAH, as well as procedures to avoid duplications, maintain confidentiality and ensure the quality of the systems.

Norway, Iceland and Liechtenstein are part of the EEA (European Economic Area) together with the Member States of the European Union. The EFTA (European Free Trade Association) States Norway, Iceland and Liechtenstein have, through the EEA-agreement, adopted the complete Community acquis on medicinal products and are consequently parties to the Community procedures.

Where in this Guideline reference is made to Member States of the Community, this should therefore be read to include these EFTA states.

The only exemption from this is that legally binding acts from the Community (e.g. Commission decisions) do not directly confer rights and obligations but have first to be transposed into legally binding acts in these EFTA states. According to Decision No 74/1999 of the EEA Joint Committee when decisions on approval of medicinal products are taken by the Community, these EFTA states will take corresponding decisions on the basis of relevant acts. Consequently, these EFTA states are concerned by the single European market for medicinal products.

In accordance with Article 46 of the Regulation and Article 77 of the Directive, guidance on the implementation and practical procedures involved in complying with the above legislation, in the interests of protecting public and animal health, shall be prepared and published by the European Commission, in Volume 9 of The Rules Governing Medicinal Products in the European Union, based on guidelines drafted by the CVMP and any other international harmonisation work carried out in the field of pharmacovigilance.

The areas covered are set out in the paragraphs that follow:

## 2 SCOPE

The scope of veterinary pharmacovigilance as defined in Article 73 of Directive 2001/82/EC covers not only safety aspects in animals and in humans related to veterinary medicinal products, but also other aspects of post-authorisation surveillance. The system also takes into account any available information arising from the use of veterinary medicinal products, such as:

- lack of expected efficacy of a veterinary medicinal products;
- adverse reaction reports related to off-label use;
- reported violations of approved residue limits, possibly leading to investigations of the validity of the withdrawal period;
- potential environmental problems;

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

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 MAH 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.

In the following this guideline will not include the word 'suspected' when making reference to adverse reactions, serious adverse reactions, human adverse reactions, or lack of expected efficacy, however these terms should be understood to address suspected adverse reactions or events. When making reference to adverse reactions by acronym this guideline will use 'SAR' as in 'Suspected Adverse Reaction', in preference to the previously used acronym 'ADR' (adverse drug reaction).

### 2.1 Reporting of human adverse reactions to veterinary medicinal products

All adverse reactions occurring in humans following use of veterinary medicinal products whether occurring in conjunction with the treatment of animals, the handling of a veterinary medicinal product or following exposure through the environment should be reported immediately by the MAH, 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).

### 2.2 Reporting of lack of expected efficacy

Directive 2001/82/EC cites the lack of efficacy as a reason for refusal or revocation of authorisation.

It may be defined as the apparent inability of an authorised product to have the recognised efficacy in an animal, according to the claims of the SPC and following use of the product in accordance with the SPC. Report of lack of expected efficacy should not normally be expedited (i.e. report within 15 days after receipt), but should be discussed in the relevant Periodic Safety Update Report (PSUR) (see section 6). However, in certain specific circumstances, e.g. where a change to a condition of use of a marketing authorisation might be necessary in order to safeguard the continuing efficacy of the product, reports of lack of expected efficacy of veterinary medicinal product may be recorded and reported promptly to the competent authorities. The "European Veterinary Pharmacovigilance reporting form" attached in Table A should be completed, as appropriate (see section 5.3.10).

It is also important to identify if the lack of expected efficacy is a due to a possible quality batch problem. However, quality-related issues must be reported according to the relevant requirements (see Revised Compilation of Community Procedures on Administrative Collaboration and Harmonisation

of Inspections, Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects (<http://www.emea.eu.int/Inspections/docs/335103en.pdf>).

### 2.3 Off-label use

**Off-label use: the use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product<sup>1</sup>**

Reports of 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.)
- on products used outside the terms of the marketing authorisation but in conformity with the provisions of Article 10 of Directive 2001/82/EC.

Such reports can provide useful information on the safety of the given medicinal product and should be recorded by the person responsible for pharmacovigilance and reported to the competent authorities in the same way as for all adverse reactions. The “European Veterinary Pharmacovigilance reporting form” attached in Table A should be used, as appropriate (see section 5.3.10).

### 2.4 Premixes for medicated feedingstuffs<sup>2</sup>

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

Among the factors that have to be examined and reported, if appropriate, are the composition of the medicated feedingstuffs, the inclusion levels of active substances of the premix, the operation of the milling process(es) and, when possible, the estimated dosage administered to individual target animals.

### 2.5 Investigation of the validity of the withdrawal period

Reports of such cases may arise from different sources including:

- Farmers or veterinarians detecting residues of veterinary medicinal product when testing bulk milk for antibiotics
- Analytical laboratories or food producers who routinely monitor foodstuffs for residues for instance in slaughterhouses or dairies
- State or regional veterinary authorities conducting statutory or other residue surveillance on food for food producing animals.

The report should contain details about the source of the report, the veterinary medicinal product and active substance, including marketing authorisation number and batch number if available, date of use and date of detection of the residues, the location of the case, the species and details of the residues detected. The report should also contain details about the steps taken by the MAH. The “European Veterinary Pharmacovigilance reporting form” attached in Table A should be completed as appropriate (see section 5.3.10).

Where veterinary medicinal product residues in tissues or food products of treated food producing animals cast doubt on the validity of the withdrawal period of the given veterinary medicinal product,

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<sup>1</sup> as defined in Article 1(16) of Dir. 2001/82/EC

<sup>2</sup> as defined in Article 1(5) of Dir. 2001/82/EC

this information should be reported to the relevant competent authority responsible for authorisation of the veterinary medicinal product concerned. Reports which cast doubts on the validity of withdrawal periods should not normally be expedited (i.e. reported within 15 days after receipt), but should be discussed in the relevant PSUR (section 6). However, in certain specific circumstances, reports regarding the validity of the withdrawal period of the veterinary medicinal product should be recorded and reported promptly to the competent authorities.

## **2.6 Potential environmental problems**

A potential environmental problem is a situation where animals (non-target), humans or plants may be adversely affected through exposure to a veterinary medicinal product present in the environment.

Any suspected environmental problem related to its veterinary medicinal products should be recorded by the MAH as soon as it comes to his knowledge. The minimum requirements for any potential environmental problem to be recorded by the MAH and reported to the concerned competent authorities are: the location, the animal species involved, the nature of the suspected environmental problem and the suspected product(s). The “European Veterinary Pharmacovigilance reporting form” attached in Table A should be completed as appropriate (see section 5.3.10) and used for reporting to the competent authorities.

Reports of potential environmental problems should not normally be expedited (i.e. report within 15 days after receipt), but should be discussed in the relevant PSUR (section 6). However, in certain specific circumstances, in order to limit further environmental damage, reports of potential environmental problems related to the veterinary medicinal product, should be recorded and reported promptly to the competent authorities.

## **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 adverse reactions which are reported to the personnel of the MAH, including representatives, is collected and collated so that it may be accessed at least one point within the Community, as indicated by the MAH;

**3.2** the preparation and submission of the following documents for Agency and/or competent authorities of Member States where the veterinary medicinal product is authorised as referred to in the Regulation and Directive and further detailed in this document:

- **Serious** adverse reaction reports **in animals**
- Reports of adverse reactions **in humans**
- Periodic safety update reports (PSURs) to include:
  - risk/benefit evaluation during the post-authorisation period, covered by the PSUR;
  - all (serious and non-serious) spontaneous adverse reaction reports **in animals**
  - all adverse reactions reports **in humans**
  - any available information on;
    - lack of expected efficacy
    - adverse reactions reports related to off-label use
    - potential environmental problems
    - investigations of the validity of the withdrawal period due to reported violations of

approved Maximum Residue Limits (laid down in Council Regulation (EEC) No 2377/90 as amended).

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

**3.4** Products authorised under Article 13(1)(a)(i) of Directive 2001/82/EC:

The MAHs for both the original reference product (Product A) and the essentially similar product (Product B, authorised according to Article 13(1)(a)(i) of Directive 2001/82/EC) assume full responsibility for the pharmacovigilance relating to their respective veterinary medicinal products.

Nevertheless they should maintain close liaison, and in particular adverse reactions to Product B must be communicated to the MAH for Product A. Where identical products are co-marketed by more than one company any report of a serious adverse reaction must be communicated by one company to the other one. 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 MAH is aware that a reporter has reported an adverse reaction to one of its products directly to the competent authority of a Member State, the MAH should still report the adverse reaction, informing the competent authority that the report is likely to be a duplicate of a previous report. In this situation it is essential for the MAH 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. Adverse Reaction Reporting**

**Adverse Reaction<sup>3</sup>: 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 MAH is responsible for reporting adverse reactions to the competent authorities of the Member States and EMEA for their veterinary medicinal products authorised under the centralised procedures and to the appropriate competent authorities of the Member States for their medicinal products authorised through the national procedures (for details of the reporting requirements see sections 5 to 7).

**4.2** **Minimum requirements for any adverse reaction (serious/non-serious/human) report** to be recorded by the MAH, and reported to the competent authorities in the Member State and/or the Agency as appropriate, see event charts in Annex I for details:

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

- (i) an identifiable source, wherever possible this should include 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) veterinary medicinal product concerned - (name and marketing authorisation number)

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<sup>3</sup> Also referred to as suspected adverse reaction (SAR)

(iv) adverse 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). Follow-up reports on incomplete adverse reaction reports should be submitted by the MAH, in particular in cases where only the minimum information was submitted within 15 days, however in general whenever relevant further information becomes available, or at least when the investigation of the adverse reaction is completed.

### 4.3 Reports from post-authorisation studies

During the post-authorisation period the veterinary medicinal 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 medicinal products 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 reactions, especially those that are unexpected. However, for specific cases concerning adverse reactions occurring for products used on a large scale such as post-vaccinal adverse 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 adverse reactions from post-authorisation studies should be reported to all Member States where the product is authorised (see section 5 for reporting requirements). Non-serious adverse reactions should be reported in summary at the end of each post-authorisation study and included in the PSUR (see section 6).

## 5. Serious Adverse Reaction Reporting Requirements

**Serious Adverse Reaction: An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect or which results in permanent or prolonged signs in the animals treated.**

In veterinary medicine the existence of a large diversity of animal species and husbandry conditions require a modified approach to the classification of a 'serious adverse reaction' ('serious SAR'). 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 of mortality rate, or severe signs, or variations of animal production levels exceeding the rates normally expected should be considered as a 'serious SAR'.

However, in species like dogs, cats or horses a single death constitutes a 'serious SAR'. 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 kept as an individual animal, a single death constitutes a 'serious SAR'.

## 5.1 Adverse reaction reports occurring in the EU

Article 44 of Council Regulation (EEC) No 2309/93 and Article 75 of Directive 2001/82/EC provide the Community requirements for adverse reactions reporting.

The MAH should record and report all 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 serious SAR occurred (see section 5.3 for details of what information is required).

For centrally authorised products, the responsibility for ensuring that all serious adverse reactions to such products occurring within their territory are further reported to the Agency, 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 adverse reactions together with all other adverse reactions should be reported as line listings in the PSUR (see section 6).

## 5.2 Adverse Reaction reports occurring outside the EU

Article 44 of Council Regulation (EEC) No 2309/93 and Article 75 of Directive 2001/82/EC provide the Community requirements for adverse reactions reporting.

The MAH should report all serious and unexpected<sup>4</sup> adverse reactions occurring in the territory of a third country and brought to its attention. These should be reported immediately, and in no case later than 15 calendar days following receipt to the Agency and to all Member States for all centrally authorised products, and to the concerned Member States for nationally authorised products.

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

A general overview on the reporting of adverse reactions (Serious/non-serious/human; Unexpected/expected) in relation to the type of authorisation (centrally or nationally authorised, including mutually recognised) is presented in the Event Charts in Annex I.

## 5.3 Content/Required information for serious adverse reactions (single) reports

MAHs are expected to fully validate and follow-up all **serious** adverse reactions reported by them to the authorities. It is essential for MAHs to provide as complete as possible details, including all relevant clinical information for cases of serious adverse reactions in order to facilitate assessment. The report of a serious 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 MAH or competent authority accepted terminology.

### 5.3.1 Marketing Authorisation Holder (MAH) details and original reporter's details

- i) The name of the qualified person responsible for pharmacovigilance employed by the MAH.
- ii) Address, telephone and fax number of the qualified person.
- iii) MAH case reference number.

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<sup>4</sup> Unexpected Adverse Reaction: This means an adverse reaction the nature, severity or outcome of which is not consistent with the summary of the product characteristics, as defined in Article 1.13. of Dir. 2001/82/EC

- iv) Date of receipt of report by MAH (in country of qualified person responsible for pharmacovigilance).
- v) Source of report e.g. spontaneous, clinical trial, post-authorisation study.
- 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 veterinary medicinal 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 veterinary medicinal 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 adverse reaction to the product

- viii) Action taken after reaction (e.g. product withdrawn, dose reduced)
- ix) Previous adverse reaction(s) to the product if occurred/reported, (re-challenge information) to include:
  - Approximate date animal(s) previously treated with product
  - Description of adverse 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 adverse reaction should be provided when available. This should also include non-prescription medicines, magistral preparations<sup>5</sup> and medicated feedingstuffs if applicable.

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 adverse reaction(s)**

- i) Description of adverse 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).
- ii) Start date or onset of reaction
- iii) Stop date or duration of reaction

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<sup>5</sup> In the case of magistral products, details of individual constituents of the formula should be indicated.

- 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 adverse reactions to the given product should be recorded under 5.3.4 ix).

### 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 rates.

### 5.3.8 Investigation

- In a case of fatal outcome the cause of death should be provided and its relationship to the serious adverse 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 MAH investigation (if relevant)

### 5.3.9 Causality assessment

MAHs may comment on whether they consider there is a causal association between the suspected veterinary medicinal product(s) and adverse 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"<sup>6</sup>:             unclassifiable/unassessable (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;

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<sup>6</sup> Where there is a possibility that an SAR could be related to treatment but present data is not enough to draw a conclusion, it has proved to be useful to create working subcategories for O: O1 – inconclusive (cases where other factors prevent a conclusion being drawn, but a product association cannot be discounted) and O-2 unclassified (cases where insufficient or unreliable information did not allow to draw any conclusion).

- 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 veterinary medicinal product 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 product.
- 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 products (and possible 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 veterinary medicinal product 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 veterinary medicinal product 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.

Further guidance on how to carry out causality assessment will be published in a separate guideline.

### 5.3.10 Reporting forms

For the reporting of adverse reaction (in animals or in humans) by the MAH to competent authorities and for the reporting of any available information as lack of expected efficacy, adverse reactions related to off-label use, investigations of the validity of the withdrawal period or potential environmental issue, the "European Veterinary Pharmacovigilance reporting form" attached at Table A should be used. 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.

The EudraVigilance Veterinary project, which is a system for electronic exchange of pharmacovigilance data has been released for testing in July 2003 and will gradually replace the need for paper reporting. MAHs are encouraged to register to EudraVigilance Veterinary (see <http://erstest.emea.eu.int/vet>).

## **6. Periodic Safety Update Reports (PSURs)**

A Periodic Safety Update Report (PSUR) 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 MAHs 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.

For centrally authorised veterinary medicinal products, PSURs should be submitted to all Member States competent authorities and the Agency in accordance with Article 44 of Regulation (EEC) No 2309/93.

For other veterinary medicinal products;

- authorised within the scope of Directive 87/22/EEC (ex-concertation procedure) or;
- that have benefited from the mutual recognition procedure in accordance with Directive 2001/82/EC or;
- that have been subject to referrals under Article 36, 37 and 38 of Directive 2001/82/EC or;
- other nationally authorised,

PSURs should be submitted to the competent authorities of the concerned member states in accordance with Article 75 of Directive 2001/82/EC.

The requirement for the submission of a PSUR applies irrespective of whether the veterinary medicinal product is marketed or not.

### **6.1 Scope**

In compliance with the requirements laid down in Directive 2001/82/EC holders of marketing authorisations must include in the PSURs of all veterinary medicinal products, whether authorised nationally or through the centralised procedure, details of all adverse reactions arising in the Community or in a third country.

The PSUR should include information on the following types of adverse reaction reports/case histories received during the period of review:

- All adverse reactions in animals and in humans, sent spontaneously to the MAH
- All adverse reactions forwarded to the MAH by the Competent Authority.
- Serious and non-serious SAR reports from post-authorisation studies (see section 4.4).
- Any available information on investigation of insufficient withdrawal period, lack of expected efficacy, adverse reactions related to off-label use or any potential environmental problems, caused by the product under the normal conditions of use.

### **6.2 Frequency and timing of reports**

Unless other requirements have been laid down as condition of the granting of authorisation, a PSUR should be prepared for all authorised veterinary medicinal products at the following intervals:

- immediately upon request
- 6-monthly for the first 2 years after authorisation
- annually for the subsequent 2 years
- at the time of the first renewal (4.5 years after first authorisation)

- thereafter 5-yearly at the time of further renewal.

If in accordance with Article 75(6) of Directive 2001/82/EC a MAH seeks to amend the frequency with which PSURs for a veterinary medicinal product authorised in accordance with the directive are submitted to the relevant Competent Authority(ies), such an application should be supported by reasoned argument.

Each PSUR should cover the period of time since the last update report and should be submitted within 60 days after the Data Lock Point (DLP)<sup>7</sup>.

Data lock points may be set according to the EU Birth Date (date of the first marketing authorisation within the European Union) of a medicinal product or its International Birth Date.

#### Preparation of PSURs according to the International Birth Date:

Veterinary medicinal products, which are also authorised outside the EU, will have an International Birth Date (IBD). This is the date of the first marketing authorisation for the product granted to the MAH in any country in the world. For veterinary medicinal products first authorised in the EU, the EU Birth Date is the IBD. For administrative convenience, if desired by the MAH, the IBD may be designated as the last day of the same month.

In order to harmonise PSURs internationally, the MAH may use the IBD to determine the data-lock points in the EU rather than the EU Birth Date. If the IBD is used, the first data lock point must be within 6 months of the EU Marketing Authorisation Date, unless other requirements have been laid down at the time of granting the authorisation. Regardless of whether the IBD or EU Birth Date is used, the PSUR must always be submitted within the 60 days following the data lock point.

The MAH should submit the renewal application at least three months before the expiry date of the marketing authorisation in the EU. This may be submitted earlier in order to facilitate co-ordination with the regular cycle of the PSUR, but should not be more than 6 months before expiry of the authorisation. At the time of the renewal application the MAH should submit a PSUR no more than 60 days after the data lock point, which should cover the intervening time period since the last PSUR. For centrally authorised veterinary medicinal products further guidance is given in the CVMP Guideline on the processing of renewals in the centralised procedure (EMEA/CVMP/695/01).

For the purpose of the PSUR the MAHs database should be frozen in relation to the product at the DLPs. Up-to-date safety data, i.e. data that becomes known to the MAH after the DLP and which may influence the evaluation should also be included in the report in the final section (see section 6.4.7).

For veterinary medicinal products authorised under the centralised procedure in accordance with Council Regulation (EEC) No 2309/93 the PSUR should cover all authorised presentations covering all pharmaceutical forms and target species, whether authorised with the original marketing authorisation or at a later time point, e.g. through an extension of the marketing authorisation. For each subsequent variation to the original marketing authorisation it will be decided on a case-by-case basis whether the submission cycle for the PSUR needs to be changed. The data lock points remain based on the date of the original marketing authorisation.

### **6.3 Content of Periodic Safety Update Reports**

For a Community authorised product, the PSUR should be written in English. For nationally authorised products, the PSUR should be written in the national language(s), or in English if this is acceptable to the appropriate competent authorities.

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<sup>7</sup> Data Lock Point (DLP): The date designated as the cut-off date for data to be incorporated into a particular PSUR. On this date the data available to the author of the PSUR is extracted for review and stored.

For marketed products, PSUR should fulfil the following format and content:

### **6.3.1 Marketing Authorisation Holder (MAH) and product details**

Each PSUR should include:

- i) The name of the MAH
- ii) The product name(s)
- iii) The marketing authorisation number(s)
- iv) The period covered by the PSUR

### **6.3.2 SPC (Articles 12 and 14 of Directive 2001/82/EC)**

The latest version of the relevant SPC must be included for reference in the report.

- For products authorised through the Centralised or Mutual Recognition procedures, this will be the centrally or mutually accepted SPC in English.
- For products authorised nationally, the specific national SPC in the language of the Member State concerned should be included.

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.

### **6.3.3 Narrative review of individual case histories**

The report should include a narrative based on the MAHs analysis of the cases reported during the period concerned by the PSUR. Information on the individual adverse reaction reports should be presented as a line listing. The line listing should be provided as an appendix (see section 6.4.8).

It will be necessary, in a given report, to separate data relating to different formulations (dosage form(s) and strength(s)). Within formulation, the safety data should be further differentiated based on target species (if the veterinary medicinal product is authorised for use in more than one species), reaction type (that is, serious, non-serious, human reaction, etc.), and then country where the report originated.

### **6.3.4 Incidence of Adverse Reactions**

A PSUR must address the relationship between the sales volume of a product and the numbers of adverse reactions reported.

#### **6.3.4.1 Sales volume**

For nationally authorised products, each PSUR should contain the number of doses/amount of product sold in the relevant Member State(s). For Community authorised products, each PSUR should contain the number of doses/amount sold in each Member State. The sales information should be expressed in an appropriate form.

The following forms are suggested:

- Vaccines to be expressed in numbers of 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

#### 6.3.4.2 *Calculation of Incidence of adverse reactions*

It is suggested that MAHs adopt a two-tier approach to calculation of incidence of adverse reactions.

##### STEP 1:

In the first instance, the ratio of the number of animals reacting during a period to the amount of product sold during that period should be computed:

$$\text{No of animals reacting during period} : \text{No of doses sold during period}$$

This calculation is based on data that tends to be accurate and can be used reliably to monitor trends from one PSUR to the next. Any increase in this ratio relative to previous PSURs may signal a problem and the need for more detailed evaluation of the pharmacovigilance data. For PSURs submitted with applications for product authorisation renewal (beginning with the second renewal), sales volume should be broken down by calendar year and the ratio of the number of animals adversely reacting to the amount of product sold should be computed for each of the years concerned by the report.

##### STEP 2:

The incidence (%) of adverse reactions should be calculated by dividing the total number of animals reacting during the period by an estimate of the number of animals treated during the period of the report and multiplying by 100.

$$\% \text{ Incidence} = \frac{\text{No of animals reacting during period} \times 100}{\text{Estimated No of animals treated during the period}}$$

For both national and community authorised products, incidence should be calculated individually for each country. In the first instance, it is expected that % incidence will be calculated based on the total number of animals reacting during a period derived from all A, B and O coded reports. This calculation may then be revised to exclude O coded reports (that is, this final calculation focuses on A-probable- and B-possible- coded reports only).

The values included in the calculation of incidence must be justified. It is expected that the values used for estimation of the number of animals treated would be representative of the conditions of use of the veterinary medicinal product. When calculating the number of animals treated during a period, the following points should be taken into consideration:

- For some veterinary medicinal products, the number of doses (individual units) sold is equivalent to the number of animals treated (e.g. anthelmintic boli, flea collars). For veterinary medicinal products formulated as pastes, aerosols, eye/ear preparations or other formulations where it is likely that each unit of product (for example, syringe, single dose pipettes) will be dispensed for the treatment of an individual animal, the number of individual units sold should be considered equivalent to the number of animals treated.
- For the majority of pharmaceutical veterinary medicinal products, the number of animals treated will be a function of:
  - Recommended treatment regimen (daily RTD (mg/kg) x duration of treatment (days)), as detailed on the authorised SPC. Where a range for dose or duration of therapy is indicated on the SPC, it is appropriate to calculate incidence based on a 'worst case' scenario (that is, use

the upper limit of the dose range and/or duration of therapy). Following from the worst case calculation, it is acceptable to propose alternative assessments of incidence based on known conditions of use of the product. Any such alternative calculations should be justified.

- Average weight of target population (kg).<sup>8</sup>
- Amount of product sold
- For immunological veterinary medicinal products, the number of animals treated may be considered equivalent to the total number of doses sold. Any calculations relating to lack of expected efficacy should take into account the recommended treatment regimen (initial course plus booster doses).

A proportion of veterinary medicines are indicated for more than one target animal species. Where this situation pertains it is recognised that it is difficult to calculate individual species incidence of adverse reactions. However, it is suggested that the ratio be computed for each species based on the estimated conditions of use of the product (sales/species). This information is of importance to competent authorities although the arbitrary nature of such theoretical calculation is recognised.

A number of PSURs will show no reports of adverse reactions. In these cases it is not possible to calculate any incidence of adverse reactions.

### **6.3.5 Reports from other sources**

A narrative overview of available data from other sources (e.g. post authorisation studies, published adverse reaction reports) should be included in this section. Where appropriate, the MAH should cross-refer to available safety information concerning related products (for example, for single active products it would be considered appropriate to cross-refer to available safety information on a combination product containing the same active substance(s).

Published reports relating to adverse reactions or other relevant safety information should be included as an appendix (Appendix II).

### **6.3.6 Overall safety evaluation**

The PSUR should include a concise critical analysis and opinion on the risk/benefit profile of the product written by a suitably qualified expert for pharmacovigilance. This section should include:

- information on any previous action taken by either regulatory authorities or the MAH as a result of safety issues, and
- any new important information on the following:
  - i) evidence of previously unidentified toxicity
  - ii) increased frequency of known toxicity
  - iii) drug interactions
  - iv) overdose and its treatment
  - v) adverse reactions associated with off-label use.
  - vi) adverse reactions in humans related to the use of the product.

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

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<sup>8</sup> The following 'standard' weights are proposed: horse – 550 kg; dog – 20 kg; cat – 5 kg; cow – 550 kg; beef calf – 150 kg; newborn calf – 50 kg; sow/boar – 160 kg; finishing pig – 60 kg; weaner – 25 kg; sheep – 60 kg; lamb – 10 kg. For other species, the weight used in the calculation should be justified.

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.

### **6.3.7 Important information received after data lock point**

This section is for reporting any important new information received by the MAH 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.

MAH are reminded that data relating to serious adverse reactions must also be reported to the relevant Competent Authority as expedited reports, see section 5.3.

### **6.3.8 Individual case histories (PSUR line listings)**

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

The individual case histories of all reports (A, B, O and N coded reports) should be presented as a line listing. The line listing should be included as an appendix to the PSUR. It will be necessary, in a given report, to separate data relating to different formulations (dosage form(s) and strength(s)). Within formulation, the safety data should be further differentiated based on target species (if the veterinary medicinal product is authorised for use in more than one species), reaction type (that is, serious, non-serious, human reaction, etc.), and then country where the report originated.

For adverse reactions in animals, the standard information required in the PSUR, for an individual case includes:

- i) MAH case reference number (+ country where adverse reaction occurred if the PSUR relates to more than one country)
- ii) Competent Authority case reference number, if relevant
- iii) Date(s) of treatment(s)/Date(s) of vaccination(s)
- iv) Was the product used as recommended?
- v) Date of reaction
- iv) Number of animals treated
- vii) Species
- viii) Age(s)
- ix) Number reacted (approximate)
- x) Number dead
- xi) Other products, including authorised medicated premixes, used concurrently (Trade name and active substances)
- xii) Presenting signs/diagnosis (to include VEDDRA terminology), including timing and duration
- xiii) MA comments – brief, informative narrative
- xiv) Causality assessment (A, B, O, N code)

All the individual case information listed above should be presented in the line-listing format given in Table B(1).

For adverse reactions in humans involving veterinary medicinal product, the standard information required in the PSUR, for an individual case includes:

- i) MAH case reference number (+ country where incident reaction occurred if the PSUR relates to more than one country)
- ii) Competent Authority case reference number, if relevant
- iii) Date(s) of exposure
- iv) Date(s) of reaction
- v) Name(s) and region of address (for cross-reference to avoid duplication)
- vi) Occupation
- vii) Nature of accident/exposure
- viii) Nature of reaction/symptoms
- ix) Outcome of reaction) and medical consultation, if applicable
- x) MAH comments – brief, informative narrative

Case information relating to adverse reactions to humans involving veterinary medicines should be presented in the format given in Table B(2).

## **6.5 Content of Periodic Safety Update Reports – Non-marketed products**

For authorised veterinary medicinal products that are not marketed or distributed anywhere and for which no adverse reactions (either in animals or humans) were observed in any additional trial (e.g. clinical trial, post authorisation study) abridged PSURs are considered sufficient, which must contain the following elements only:

- trade name of the product
- marketing authorisation number(s) of the product,
- name and address of the MAH,
- a declaration of the MAH's Qualified Person for pharmacovigilance, that as the veterinary medicinal product was not marketed or distributed anywhere in the world during the reporting period and as no adverse reaction (either in animals or in humans) was observed in any additional trial (e.g. clinical trial, post authorisation study), the risk/benefit balance afforded by the veterinary medicinal product has not changed since the date of the Marketing Authorisation.

## **6.6 Urgent Safety Information**

In accordance with Article 27(3) of Directive 2001/82/EC, any new or changing information that becomes available which impacts on, or may influence the overall benefit/risk evaluation of a veterinary medicinal product, should be communicated to all relevant competent authorities by the MAH immediately upon receipt. A comprehensive report evaluating the issue and the risks in the context of the benefits should be submitted at the earliest opportunity to all relevant competent authorities.

## **7. HUMAN REACTIONS TO VETERINARY MEDICINAL PRODUCTS**

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

- i) Patient identification (as appropriate according to national laws). A name or unique identifier shall be given to allow further information to be requested/collected and to avoid any duplication of reports
- ii) Sex
- iii) Age, date of birth or adult/child
- iv) Occupation - if relevant to exposure to product for example: veterinary surgeon, farm worker, pet owner
- v) Date product used or date exposed to veterinary medicinal product(s)
- vi) Date of reaction
- vii) Nature of exposure (Details of type of exposure e.g. inhalation, injection, ingestion or dermal, how much exposure occurred e.g. volume injected or splashed etc and how it occurred e.g. was it an accident or routine use? And how long did the exposure last (duration). See also xiv) below for details of animals being treated.)
- viii) Nature of reaction including signs and symptoms
- 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
- xi) Marketing Authorisation conclusions/comments on the adverse reaction

Additional information to be provided on the report form to the competent authority:

- xii) Status (e.g. veterinarian, pharmacist, other...); name and contact details of the person who reported the reaction to the MAH, if other than the patient, and if acceptable under national law for follow-up /further information
- xiv) If relevant to incident: Animal data (e.g. way of administration, administration site, number of animals being treated, species and breed)
- xv) Product details: trade name, MA number, active substance and ATCvet code(s). This should be provided for each of the veterinary medicines that the 'patient' has been exposed to in this incident

Any other information on human adverse reactions to veterinary medicinal products available to the MAH should be reported if relevant to the case.

All adverse reactions in humans, to veterinary medicinal products, authorised nationally, mutually recognised or centrally 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. 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.

## Event Chart of Industry Reporting Procedures

### *Serious* Adverse Reactions in *ANIMALS* to Veterinary Medicinal Products

Where the serious SAR occurred	Type of Authorisation	Unexpected/ Expected	Where to report	When to report
In EU	National including mutual recognition	Unexpected and Expected	To MS where the reaction occurred	Within 15 days of receipt
			To MS(s) where the product is authorised	In the relevant PSUR
	Community	Unexpected and Expected	To MS where the reaction occurred	Within 15 days of receipt
			To EMEA and all MS	In the relevant PSUR
<ul style="list-style-type: none"> <li>• Mutual recognition</li> <li>• Products considered within the scope of Directive 87/22/EEC (ex-concertation)</li> <li>• Products that have been subject to a referral</li> </ul>	Unexpected and Expected	In addition to reporting to the MS where the reaction occurred, ensure that serious SARs are reported in such a way as to be accessible by the Reference Member State (RMS) or a competent authority designated as RMS	In addition to reporting within 15 days and in the PSUR, submit reports at intervals and in format to be agreed with RMS or a competent authority designated as RMS	
Outside EU	National including mutual recognition	Unexpected	To EMEA and MS where the product is authorised	Within 15 days of receipt
			To MS(s) where the product is authorised	In the relevant PSUR
	Community	Expected	To MS(s) where the product is authorised	In the relevant PSUR
			To EMEA and to all MS	Within 15 days of receipt and later in the relevant PSUR
Community	Expected	To EMEA and to all MS	In the relevant PSUR	

## Event Chart of Industry Reporting Procedures

### *Non-Serious* Adverse Reactions in *ANIMALS* to Veterinary Medicinal Products

Where the SAR occurred	Type of Authorisation	Unexpected/ Expected	Where to report	When to report
In EU	National including mutual recognition	Unexpected and Expected	To MS(s) where authorised	In the relevant PSUR
	Community	Unexpected and Expected	To EMEA and to all MS	In the relevant PSUR
Outside EU	National including mutual recognition	Unexpected and Expected	To MS(s) where authorised	In the relevant PSUR
	Community	Unexpected	To EMEA and to all MS	In the relevant PSUR in a distinct and clearly identified section
		Expected	To EMEA and to all MS	In the relevant PSUR

# Event Chart of Industry Reporting Procedures

## Adverse Reactions in *HUMANS* to Veterinary Medicinal Products

Where the SAR occurred	Type of Authorisation	Unexpected/Expected	Where to report	When to report
In EU	National including mutual recognition	Unexpected and Expected	To MS where the reaction occurred	Within 15 days of receipt
			To MS(s) where the product is authorised	In the relevant PSUR
	Community*	Unexpected and Expected	To MS where the reaction occurred	Within 15 days of receipt
			To EMEA and all MS	In the relevant PSUR
<ul style="list-style-type: none"> <li>• Mutual recognition</li> <li>• Products considered within the scope of Directive 87/22/EEC (ex-concertation)</li> <li>• Products that have been subject to a referral</li> </ul>	Unexpected and Expected	In addition to reporting to the MS where the reaction occurred, ensure that serious SARs are reported in such a way as to be accessible by the Reference Member State (RMS) or a competent authority designated as RMS	In addition to reporting within 15 days and in the PSUR, submit reports at intervals and in format to be agreed with RMS or a competent authority designated as RMS	
Outside EU	National including mutual recognition	Unexpected and Expected	To EMEA and MS(s) where the product is authorised	Within 15 days of receipt
			To MS(s) where the product is authorised	In the relevant PSUR
	Community*	Unexpected and Expected	To EMEA and to all MS	Within 15 days of receipt and later in the relevant PSUR

\* Directive 2001/82/EC specifically lays down requirements for the reporting of adverse reactions in human beings, which apply to nationally authorised and mutually recognised veterinary medicinal products. The more dated Council Regulation (EEC) No 2309/93 does not yet make a distinction between adverse reactions to veterinary medicines in human beings and in animals. However the guidance drafted in accordance with Article 46 of this Regulation defines that all adverse reactions in human beings should be reported within 15 days (see sections 2.1.1 and 7 of this guideline) in addition to the required reporting in the relevant PSUR.



**7. REACTION DATA** (applicable for all types of adverse reaction(s) reported following administration of veterinary product(s))

Date of onset of signs:

Duration of reaction:

Describe the sequence or events including administration of product(s), all clinical signs, site of reaction, severity, pertinent lab tests, necropsy results, possible contributing factors (if necessary use extra sheet): Include details of treatment given to address this adverse reaction.

Were the signs treated?

No Yes 

Outcome of reaction to date:

	Killed/euthanised	died	under treatment	alive with sequelae	recovered	unknown
No. of animals:						
Date when:						

**8. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT PRODUCT #1 CAUSED REACTION**possible unlikely no attending vet **9. PREVIOUS EXPOSURE AND REACTION(S) TO PRODUCT #1**Previous exposure to this product? no  yes  Date(s):Previous reaction to this product? no  yes  Describe:

De-challenge information:

**10. DETAILS OF SUSPECTED ADVERSE REACTION(S) IN HUMANS**

Patient details Sex: Age/date of birth: Occupation (with relevance to exposure):

Date of exposure: Date of reaction:

Nature and duration of exposure, reaction details (including symptoms) and outcome:

**11. CAUSALITY ASSESSMENT RELATED TO PRODUCT #1**Classification: A (probable)  B (possible)  O (unclassified)  N (unlikely) 

Reason for classification:

**12. OVERALL CAUSALITY ASSESSMENT RELATED TO ALL SUSPECTED PRODUCTS****FOR COMPETENT AUTHORITY USE ONLY**

Name and title of person responsible for the accuracy of the information

Signature

Date

**6. DATA FOR PRODUCTS ADMINISTERED CONCURRENTLY – PRODUCT # <Enter sequential number; 2 or higher>**

<b>Trade name</b> (include dosage form and strength):		<b>M.A. number:</b>	
<b>Active substance(s) (INN):</b>		<b>ATC vet code(s):</b>	
<b>Batch No.:</b>	<b>Expiry date:</b>	<b>Storage details:</b>	
<b>Treatment details:</b>			
Dose/frequency:		Route/site of administration:	
Start date of treatment:	Stop date or duration:	Who administered the product:	
		veterinarian <input type="checkbox"/> owner <input type="checkbox"/> other <input type="checkbox"/>	
<b>Use according to label:</b>	yes <input type="checkbox"/> unknown <input type="checkbox"/>	no <input type="checkbox"/> explain:	
<b>Action taken after reaction:</b>		<i>drug withdrawn</i> <input type="checkbox"/>	<i>dose reduced</i> <input type="checkbox"/>
		<i>other</i> <input type="checkbox"/>	
<b>Did reaction abate after stopping drug?</b>	yes <input type="checkbox"/> no <input type="checkbox"/>	not applicable <input type="checkbox"/>	
<b>Did reaction reappear after reintroduction?</b>	yes <input type="checkbox"/> no <input type="checkbox"/>	not applicable <input type="checkbox"/>	

**8. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT REACTION WAS CAUSED BY PRODUCT #**

possible  unlikely  no attending vet

**9. PREVIOUS EXPOSURE AND REACTION(S) TO PRODUCT #**

Previous exposure to this product? no  yes  Date(s):

Previous reaction to this product? no  yes  Describe:

De-challenge information:

**11. CAUSALITY ASSESSMENT RELATED TO PRODUCT #**

**Classification:** A (probable)  B (possible)  O (unclassified)  N (unlikely)

**Reason for classification:**

IN CONFIDENCE

**VETERINARY PHARMACOVIGILANCE SCHEME - PERIODIC SAFETY UPDATE REPORT**  
**MARKETING AUTHORISATION HOLDER FORM FOR REPORTS OF ANIMAL ADVERSE REACTIONS**  
**TO A VETERINARY MEDICINAL PRODUCT**

MARKETING AUTHORISATION HOLDER:

PRODUCT:

MARKETING AUTHORISATION NO:

PERIOD OF REPORT FROM .../.../... TO .../.../... NO. OF DOSES SOLD IN THE EU DURING PERIOD OF REPORT= ..... DOSE UNITS = % INCIDENCE =

MAH CASE REF	CA CASE REF	DATE OF TREATMENT/ VACCINATION	DATE OF REACTION	NO. TREATED	SPECIES AND AGE (Juv/Adult)	NO. REACTED (a)	NO. DIED (b)	WAS PRODUCT USED AS RECOMMENDED YES/NO	OTHER PRODUCTS USED CONCURRENTLY	PRESENTING SIGNS/ DIAGNOSIS	MAH CONCLUSIONS AND COMMENTS	ABON CODE
EU REPORTS  (REF + NAME & COUNTRY)				<i>(Please ensure that this total is put in)</i>							<i>(Please ensure these sections are completed)</i>	
OVERALL TOTAL OF ALL (EU) PAGES												
Total no of (reports):				Total no of animal reactions (a):				Total no of animals died (b):				
THIRD COUNTRY REPORTS  (REF + COUNTRY)												
OVERALL TOTAL OF ALL (3rd Country) PAGES												
Total no of incidents (reports):				Total no of animal reactions (a):				Total no of animals died (b):				

**FOR COMPETENT AUTHORITY USE ONLY: REFERENCE:****DATE OF RECEIPT:**

IN CONFIDENCE

**VETERINARY PHARMACOVIGILANCE SCHEME – PERIODIC SAFETY UPDATE REPORT**  
**MARKETING AUTHORISATION HOLDER FORM FOR REPORTS OF ADVERSE REACTIONS IN HUMANS INVOLVING A**  
**VETERINARY MEDICINAL PRODUCT**

MARKETING AUTHORISATION HOLDER

PRODUCT:

MARKETING AUTHORISATION NO:

PERIOD OF REPORT FROM ----/----/---- TO ----/----/----

MAH CASE REF	CA CASE REF	NAME(S) + REGION OF ADDRESS OF 'PATIENT'/PERSON AFFECTED	OCCUPATION	DATE OF EXPOSURE	DATE OF REACTION	NATURE OF ACCIDENT/ EXPOSURE	NATURE OF REACTION/ SYMPTOMS	DOCTOR CONSULTED? & OUTCOME OF REACTION	MAH CONCLUSIONS AND COMMENTS
(REF + NAME & COUNTRY)									

**FOR COMPETENT AUTHORITY USE ONLY**

REFERENCE:

DATE OF RECEIPT:

NUMBER OF INCIDENTS: