COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

RECOMMENDATION ON MANAGEMENT AND ASSESSMENT OF PERIODIC SAFETY UPDATE REPORTS (PSURs) OF VETERINARY MEDICINAL PRODUCTS

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# RECOMMENDATION ON MANAGEMENT AND ASSESSMENT OF PERIODIC SAFETY UPDATE REPORTS (PSURs) OF VETERINARY MEDICINAL PRODUCTS

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EXECUTIVE SUMMARY

Periodic Safety Update Reports (PSURs) are submitted by the Marketing Authorisation Holder (MAH) of a Veterinary Medicinal Product (VMP) at defined intervals for assessment by the European Medicines Agency (EMEA, the Agency) or a National Competent Authority of a Member State in the EU (NCA\(^1\)), as further specified. PSURs contribute to the continuous safety surveillance of VMPs once these have been authorised for placing on the market (pharmacovigilance).

This document is a recommendation for the management and assessment of PSURs to facilitate assessors in their scientific and regulatory assessment of PSURs, and aims at standardization of the format of PSUR Assessment Reports (AR) across the EU whatever the marketing authorisation procedure. The objective of this harmonisation is to ensure that PSUR ARs are of high quality and contain necessary information in a well-organised format.

This recommendation facilitates:

- harmonisation of the assessment of PSURs, contributing to consistency in the benefit/risk assessment across all VMPs independent of the authorisation procedure, thereby increasing transparency towards industry;
- increasing consistency in the assessment of PSURs in view of public and animal health;
- more efficient use of the resources available;
- more efficient communication of information related to the assessment of PSURs between all concerned parties.

Given the variability of resources available for and approaches across the EU Member States on PSUR assessments, work-sharing between Member States is currently being considered by Member States. These considerations on how to avoid duplication of work and how to circulate PSUR ARs for nationally authorised VMPs are excluded from this recommendation.

1. INTRODUCTION

PSURs are intended to provide an update of the worldwide safety experience of all clinical and non-clinical safety data received during a specific period. The value of the PSUR depends on the availability and quality of data from different sources. Guidance for MAHs on the content and structure of a PSUR is provided in Volume 9B\(^2\) (See glossary).

This document provides guidance for the Agency and the NCA for rational and harmonised assessment of PSURs based on legal requirements and existing guidance on scientific data, background information and existing assessment procedures in place in the EU. The aim of this recommendation is also to support harmonised preparation of PSUR ARs.

Spontaneous suspected adverse reaction (SAR\(^3\)) reports usually form the substantial part of the data in PSURs. Although data from other, non-spontaneous sources may be less frequently included, these data represent an important component of the PSUR. Any available data obtained from non-spontaneous sources, such as post-marketing surveillance studies and clinical trials, should always be carefully considered as these data are produced in controlled environments and therefore may produce more rigorous evidence. This recommendation emphasises on situations where data may be limited and as a result a complete assessment is difficult to perform, which reflects the current status in veterinary pharmacovigilance concerning availability of different types of pharmacovigilance data.

In case of centrally authorised products (CAP), the CVMP Rapporteur is responsible for assessing the submitted PSUR and drafting a preliminary AR in accordance with the agreed template (Annex I) and agreed timetables, whilst for products authorised using the mutual recognition procedure (MRP) or

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1 The term “NCA” refers also to countries Iceland, Norway and Liechtenstein in this recommendation.
2 Volume 9B of the Rules governing Medicinal Products in the European Union is under development. Until Volume 9B is available, Volume 9 of 2004 will be applied as far as it does not contradict current legislation.
3 The term “SAR” as in ‘Suspected Adverse Reaction’ is preferred to the previously used acronym ‘ADR’ (adverse drug reaction).
decentralised procedure (DCP) this responsibility lies with the Reference Member State (RMS). The remaining CVMP Members or Concerned Member States (CMS) are invited to comment on this draft for the finalisation of the AR. PSURs for products authorised using purely national procedures (NAP), i.e. excluding MRP and DCP, will be assessed by the relevant NCA.

In addition and when there is such a change in the benefit/risk balance of a VMP that is considered to require changes in the status of the marketing authorisation, final conclusions should be communicated to relevant NCAs and the Agency in accordance with relevant guidance on Rapid Alerts.

For products that are not marketed or distributed anywhere in the world and for which no adverse events have been recorded during the reporting period, an abridged PSUR is sufficient. The assessment of abridged PSURs should be limited to regulatory compliance.

2. SCOPE
This recommendation is addressed to assessors of PSURs. It applies, in general, to all veterinary medicinal products, regardless of authorisation procedure.

3. LEGAL BASIS
As described in Article 73 of Directive 2001/82/EC as amended, each MS shall have in place a pharmacovigilance system for collection of information useful in the surveillance of veterinary medicinal products. This pharmacovigilance information includes PSURs. MS shall communicate information to other MS and the Agency in accordance with Articles 73 and 76(2) of Directive 2001/82/EC and Article 47 of Regulation (EC) 726/2004, as relevant. MAHs are required to systematically collect and evaluate information on safety data relating to their medicinal products in accordance with Article 74 of Directive 2001/82/EC, as amended, and Article 48 of Regulation (EC) 726/2004.

In accordance with Article 75(5) of Directive 2001/82/EC, as amended, and Article 49(3) of Regulation (EC) 726/2004 MAHs shall submit PSURs at defined times post authorisation. PSURs are normally required at least every six months after authorisation until the initial placing on the Community market. Thereafter, PSURs shall also be submitted at least every six months during the first two years following the initial placement on the Community market, once a year for the following two years and thereafter at 3-yearly intervals. Additional requirements to PSUR reporting and frequency may be applied.

For the renewal of marketing authorisations, MAHs shall submit a consolidated list in respect of quality, safety and efficacy, at least 6 months before the marketing authorisation ceases to be valid, in accordance with Article 28 of Directive 2001/82, as amended, and Article 39(2) of Regulation (EC) 726/2004. In addition to routine information, PSURs should also contain information on any commitment made in the detailed description of the risk management system (Risk Management Plan (RMP)) that may have been provided in accordance with Article 12(3)(k) of Directive 2001/82/EC, as amended.

4. ASSESSMENT OF A PSUR
4.1 General principles
A basic assumption for the assessment of a PSUR is that its structure and contents are in compliance with the requirements of Volume 9B. Therefore, validation of and feedback to the MAH on the contents of the PSUR against the current requirements is important.

Significant lack of documentation, mainly concerning SAR reports, or lack of other safety-related information should generally be considered as insufficient, thus preventing completion of the assessment. The MAH may be required to provide additional information for finalisation of the assessment.

The content and the quality of the data presented in the PSUR are evaluated and, where necessary, summarised and commented upon. Any comments made by the assessor should be clearly delineated from any necessary descriptive summaries of MAH data.

The assessment should identify the issues of concern: safety concerns, potential signals, follow-up of previously identified signals, and issues that require specific, e.g. cumulative, analysis.

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4 See footnote 2.
If applicable, the assessment may also reflect on other data, experience and policies used for reference (e.g. other recommendations, guidelines, common and scientific knowledge, previous agreements, previous PSURs, internal inconsistency, literature). The assessment may also address non-compliance with regulatory requirements in relation to the MAH’s pharmacovigilance system, commitments laid down in an RMP, inconsistencies within the PSUR, and obvious omissions. References to such relevant other sources should be noted in accordance with good scientific practice.

Tools developed for analysing data in EudraVigilance Veterinary (EVVet) may be used to facilitate signal detection.

Past, ongoing or intended regulatory procedures may be relevant for the assessment in special circumstances, such as referral or mutual recognition procedures, or amendments of product literature or other actions taken for safety reasons. Various dates, such as dates of authorisation in the EU (EU birth date) or the international birth date (IBD), the date of initial placing on the Community market or any other date representing the start of the PSUR submission cycle may also be relevant background information.

It may be of interest to cross-check the world-wide marketing authorisation status against reports from third countries, for an understanding of the use of the product outside the Community.

As a conclusion of the assessment, clear recommendations should be made on the need for any regulatory action or action required from the MAH in order to maintain the benefit/risk balance in favour of the product. The MAH should be promptly informed and invited to comment on these recommendations.

A template for assessment of full CAP, MRP and DCP PSURs is provided in Annex I. Minimum administrative information should be given on the Title Page of the AR. Further details may be given within the report as relevant for the assessment. The latest approved Summary of Product Characteristics (SPC) should be used for reference during assessment and should be attached to the AR in an appendix.

4.2 Data review

The data review should consider the following types of reports:

- All spontaneous SARs in animals and all humans reactions, originating in the Community or in a third country, including all those that the MAH can reasonably be expected to have knowledge of, including also all SARs forwarded to the MAH by the Agency or NCA as well as adverse reactions published in the literature.
- Serious and non-serious SAR reports from post-marketing surveillance studies or clinical studies;
- Any available information on any suspected transmission of an infectious agent via a VMP 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;

Line-listings may be checked against the data available in the national database or in EVVet in order to confirm that relevant SARs have been considered by the MAH in the PSUR in order to ensure that all relevant pharmacovigilance data have been reported in compliance with regulatory requirements. The importance of this analysis increases when the number of SARs is limited in a PSUR.

The assessor should assess the data by the different pharmacovigilance fields: safety issues after recommended and non-recommended (off-label) use, lack of efficacy, potential environmental problems, reported investigations of the validity of withdrawal periods, and transmission of any infectious agent via a VMP. Classification of the SARs according to these pharmacovigilance fields is important for an overview of the distribution. A table may be helpful, but is not mandatory, to facilitate the assessment and to highlight pharmacovigilance fields that need to be studied in depth. Table templates are available in Annex II, for use as necessary.

4.2.1 Estimations of exposure

Estimations of exposure are dependent on sales data that are included in the PSUR. Each PSUR should contain the number of doses/amount of VMP sold within the reporting period in the relevant Member State(s) and third countries (all countries outside EU and EEA5), if applicable. The global sales volume

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5 Third countries are all countries outside the Member States and the EEA countries Iceland, Norway and Liechtenstein.
including those for third countries, if applicable, is necessary for estimating global incidences. It may be useful to consider the sales volume per presentation if several presentations exist. Sales data need generally not be recalculated, unless discrepancies are apparent and likely to affect the assessment. In such a situation the assessor may need to explain the discrepancies in the AR, for which one of the tables in Annex II may be helpful. The assessor would, in practice, be limited to national data for any check of the MAH sales data.

Exposure data is used e.g. for an overall view of the number of treated animals and for calculating the incidence. It is expected that any values used for estimation of animal exposure (e.g. dose range, frequency of dosing and duration) are representative of the conditions of use of the product. The sales data is converted into exposure data by estimating the number of treated animals based on an assumption for the use of the product, e.g. dosage: 1 ml/ 10 kg bodyweight administered to a cow of 400 kg, i.e. 40 ml is equal to one treated cow.

The animal exposure is normally, when data are sufficient, assessed by target species or other appropriate categories (e.g. cattle and calves) depending on the approved dosage. Advice on standardized bodyweights is available for different animal species in Volume 9B\(^6\). The assessor should validate the MAH approach for estimating exposure, in particular for products which are used for several days in one treatment course, or continuously for a chronic condition. It is important that the chosen, and justified, approach is maintained by the MAH in subsequent PSURs, because this will influence the incidence rate. Any different approach should be justified, which may lead to specific questions to be addressed to the MAH.

4.2.2 Assessment of incidence

The incidence will indicate whether a certain number of reports of adverse reactions received during a specific period is high or low. It usually changes with the life-cycle of the VMP. An overall incidence should be calculated separately for all spontaneous adverse reactions (A,B,O, including O1) that occur after recommended or non-recommended (off-label) use in the target species. For clarity, adverse reactions from post-marketing studies should be excluded. In addition, an incidence for lack of efficacy in target species after recommended use should be calculated, when relevant.

In the first instance, however, the ratio of the number of animals expressing an adverse event (reports assigned a causality code of A, B or O, including O1, N) during a period to the amount of VMP sold during that period should be computed to give a rough world-wide overview of the ratio of animals reacting per dose.

Thereafter, the number of animals with reported adverse reactions divided by the calculated number of treated animals will give the incidence rate. Numbers of animals with reactions that are probably (A) or possibly (B) related to the product, as well as reactions for which the causal relationship is unassessable (O) should be included in the incidence calculation. Reports where the suspected adverse reaction has been categorised as unlikely (N) related to the product should be reviewed, while not included in the incidence calculations. An unusually high proportional number of reports coded as unlikely related (N) or unassessable (O) may point at a systematically biased approach to causality assessment, or to a signal on an adverse reaction.

A sample of MAH causality assessments of individual reports may be considered for agreement. Deviations may be noted, when these are likely to affect the overall assessment and conclusions, or when the approach deviates from agreed principles on causality assessment. Additional information from the MAH, for instance regarding the number of reacting animals (target species) for SARs assessed A (probable), B (possible) and O (unassessable), or N (unlikely) may be useful. Source reports may need to be requested from the MAH for a complete overview of the MAH justification.

It may be helpful to present data in the AR, should the assessor disagree with the MAHs causality assessments. It may become relevant to present the MAHs calculation and the assessor's calculation in parallel. Different approaches may, nevertheless, lead to similar incidence values.

The incidence rate is a rough estimate of the occurrence of SARs. Therefore, regulatory decisions should be taken only after evaluation of the SAR reports. For VMPs authorised in multiple MS, incidence should be

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\(^6\) See footnote 2.

\(^7\) The incidence is calculated by the MAH, and this guidance is included in Volume 9B (see footnote 2).
calculated individually for each MS where sales have occurred. Overall incidence rates are calculated for the EEA\(^8\) in total and on world-wide basis, if necessary.

**4.2.3 Assessment of adverse reactions in target species – signal detection**

The purpose of this assessment is to address the following parts of overall safety evaluation:

- a change in characteristics of clinical signs [increase in previously unidentified clinical signs (unexpected reactions) e.g. evidence of previously unidentified toxicity or safety concerns];
- an increase in the reporting rate of known adverse effects, frequency of known toxicity or expected adverse reactions.

Safety signals may be detected from reported SARs. Serious unexpected (unlisted) SARs should be investigated in particular to facilitate identification of possible signals. The focus of assessment should be on the causal relationship between a clinical sign, or a group of closely linked signs, and the product.

The analysis should search for unexpected SARs as well as an increase in the incidence of expected SARs occurring in target species after recommended use (as per SPC), or non-recommended (off-label) use (e.g. overdosing, use of a non-recommended route). It is important to consider data on serious SARs separate from data on non-serious SARs especially after recommended use in target species. Non-serious unexpected adverse reactions will not often provide a safety concern, but should be considered for inclusion in the product literature since they may provide relevant information to health professionals and patients. Signals for unexpected adverse reactions usually appear from SARs assessed B (possible) or O (unassessable). For PSURs with few reports, the information recorded in individual reports become more important. Depending on the seriousness of the reaction, in the context of the global incidence of all reactions, updates of the product literature in line with the current requirements of SPC guidelines for pharmaceuticals and immunologicals may be necessary. For other adverse reactions, more cases will generally be required.

Product characteristics such as the recommended routes of administration, the number of target species, and the dosage may vary during the life cycle of a VMP. Therefore, some SARs could be identified as off-label at the beginning of the period covered by the PSUR and later as recommended use. Such SARs may be highlighted and commented upon by the assessor.

However, if several target species have been approved, it may be useful to assess a full set of data per species. For instance, the target species characteristics, such as the metabolism, may lead to different adverse reaction patterns. However, the underlying condition treated may also lead to a different adverse reaction pattern.

The assessor should comment on drug interactions, if apparent or suspected.

The internationally agreed standard terminology VeDDRA should be used at a feasible level to group SARs (System Organ Classes (SOC) and Preferred Term (PT) level) in the standardised sequence, to facilitate the identification of unexpected adverse reactions. The choice of terms for SAR descriptions should be based on the most suitable option in the terminology.

Especially for PSURs which contain a large number of adverse reactions, the review may be facilitated by summary tabulations and separate tables e.g. for serious reaction, serious unexpected reactions, non-serious unlisted reactions (not mentioned in the SPC) and organ classes. Such tables should be available in the PSUR or may need to be requested from the MAH (see examples in Annex II).

At the end of this assessment - taking into consideration conclusions on previous PSURs and possible MAH commitments - some safety concerns may have been identified that would need to be addressed with the MAH. The Agency or NCA assessment may differ from the MAH overall analysis or the narrative review of individual reports.

Based on the data, the assessor should evaluate if the information in the SPC is sufficient mainly concerning adverse reactions, contraindications, overdosing and precautions for use in the target species.

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\(^8\) EU Member States and countries Iceland, Norway and Liechtenstein
4.2.4 Adverse reactions reported in humans

Human adverse reactions are in general assessed in accordance with similar principles as those described above. Particular attention should be paid to the route and type of exposure (e.g. self-injection, dermal exposure, contact with treated animals) and the related clinical symptoms. In some occasions, it might be relevant to summarise the clinical signs described according to the VEDDRA List of Clinical Terms for Reporting Suspected Adverse Reactions in Human Beings to Veterinary Medicinal Products, and to the nature of the exposure. Tables in Annex II may be helpful in presenting concerns that require action.

Based on these data, the assessor should evaluate if the user safety information in the SPC is sufficient.

4.2.5 Other pharmacovigilance fields

Other fields of pharmacovigilance are lack of efficacy, SARs after use in non-target species, potential environmental problems, investigations of the validity of withdrawal periods and transmission of infectious agents. The assessor should assess any observed events and conclude on any need for action. The efforts of the assessment of the reported events should be focused on proof of the link between the event and the product. An approach similar to that followed for the safety part may be useful in order to ensure consistency in assessment and concerning recommended actions.

Based on the data, the assessor should evaluate if the relevant safety information in the SPC is sufficient.

Lack of efficacy

The assessor should evaluate reports of lack of efficacy and any clinically relevant reports should be considered. Lack of efficacy may be defined as the apparent inability of a VMP to have the recognised efficacy in an animal following use as recommended in the SPC. Therefore, if the use deviates from recommendations given in the SPC, these events (suspected lack of efficacy recorded after off-label use) should not be considered as lack of efficacy. However, for some products, e.g. antibiotics, where an overdose has been administered and lack of efficacy has been observed, it is more correct to assess these as true lack of efficacy reports despite that they have been used outside the SPC recommendation, because it is not reasonable that reduced efficacy will be seen after an overdose.

SARs after use in non-target species

Important information may emerge from SARs recorded in non-target species. The number of SARs, their seriousness and the most relevant clinical signs recorded as well as comments on causality assessments and on the clinical signs (undesirable effects) may be included. If relevant for the veterinary practitioner, information on non-target animal safety may be included in the SPC.

Potential environmental problems

A potential environmental problem is a situation where animals, humans, plants or ecosystems may be adversely affected through exposure from a VMP in the environment.

The nature of the suspected environmental problem, the suspected product(s), the animal species involved, and the location should be clearly identified.

The assessor should check:

- if the VMP has been used in accordance with the SPC recommendations,
- if such effects have been identified when the marketing authorisation was granted,
- if there is relevant information available to prove that the environmental problem results from animal treatments such as persistence of residues in the terrestrial and aquatic compartments. The MAH should provide any relevant information available to assist the CA in the assessment, especially the methods for identification of the contaminant, regardless of the route of reporting (as part of PSUR or separate). Without an identification of the contaminant, it is impossible to thoroughly evaluate and confirm a link between the environmental problems and a specific product and place/time of use.

For immunological veterinary medicinal products, it should be considered whether potential hazards for the environment are known, such as infection of non-target species by a vaccine or infection from organisms excreted by the vaccinated animals.
Investigations of the validity of the withdrawal period

The following factors need to be assessed when considering reports on investigations of the validity of the withdrawal period:

- whether the VMP was used in accordance with the SPC recommendations,
- whether the recommended withdrawal period for the feedingstuffs (meat and offal, eggs, milk, honey) was respected. Analysis results of samples collected after the end of withdrawal period may be available and should then be considered.
- whether the problem relates to a subgroup of animals and/or an administration site or route.
- which analytical method was used to analyse the samples for residues. A validated analytical method is in general preferrable as it is more reliable. The most reliable results are produced by the method for monitoring the marker residue.

Transmission of any infectious agent via a veterinary medicinal product

Particular attention should be paid to events of suspected transmission of any infectious agent via a VMP, as the available information must be sufficient to establish a link between the infectious agent transmitted and the VMP administered. This is mainly related to live organisms present in immunological VMPs. The CVMP Guideline for Environmental Risk Assessment of Immunological Veterinary Medicinal Products (EMEA/70067/2007) may be useful. Transmission of an infectious agent with the equipment used (syringe, needle) is excluded as this is considered as contamination during the administration of the veterinary medicinal product.

4.2.6 Reports from other than spontaneous sources

Reports with relevant pharmacovigilance information could also come from clinical trials sponsored by the MAH, from post-marketing surveillance studies, published literature or other sources.

An assessment of pharmacovigilance data from these studies should be included if the studies contain relevant information for the safe use of the product. If applicable, studies requested as a post-authorisation safety commitment, should be carefully assessed as the data is of high value.

Consistency of reported ongoing studies may need to be checked over consecutive PSURs, due to the fact that interim reports may have been provided.

For completeness, the total number of SARs obtained from studies should also be reviewed and commented upon in accordance with the procedure for SARs from spontaneous sources.

4.2.7 Other Information

Adverse events arising from prescription errors or medication errors, including those due to invented names of VMPs or similar appearance (e.g. mix-up with another VMP) should be commented on, if relevant.

4.2.8. Evaluation of the adverse reactions in view of the information included in the SPC

The assessor should summarise the issues identified in relation to the current information in the SPC and provide an opinion on the matter, including justification in support of the conclusions or opinion whenever an action is required. In particular, the following issues need to be addressed:

- Evidence of previously unidentified toxicity or safety concerns,
- Changes in frequency of known toxicity or expected undesirable effects,
- Drug interactions if relevant,
- Undesirable effects associated with off-label use, including overdose
- Human clinical symptoms associated with the use of the VMP,
- Lack of efficacy

Discussion on the other pharmacovigilance fields, such as environmental problems, investigations of the validity of withdrawal periods and suspected transmission of infectious agents should be included, if suspected or apparent.
The assessor should comment on any increase in the incidence relative to previous PSURs as this may detect a signal and may trigger the need for more detailed evaluation of the pharmacovigilance data.

The assessor should also review and evaluate the MAH benefit/risk analysis.

4.3 Overall conclusion
Considering the data analysed, a short overall conclusion is to be formulated on the benefit/risk balance of the product and whether actions are necessary to maintain a balance. The assessor should clearly describe any change to the benefit/risk balance.

The assessor should conclude on and justify any need to modify some specific sections of the SPC.

The preliminary AR should be circulated to CVMP members or CMSs for comments, which are considered in a revision of the preliminary AR. The PhVWP-V is available for advice on any PSUR for any product, regardless of the procedure used for the authorisation of the product, whenever there are major issues raised during the consultation on which there is no consensus. The advice is given upon request from the Rapporteur, CVMP, or any MS, including RMS or CMS for MRP and DCP products.

4.4 Questions or comments to be addressed to the MAH
The assessor should summarise the additional information that needs to be requested from the MAH before drawing a final conclusion on the PSUR. The draft Assessment Report (AR) should be sent to the MAH, when relevant, for consideration.

4.6 Recommended action
Any recommendations for monitoring of specific signals or safety concerns, post-marketing surveillance studies or other investigational actions should be clearly expressed to the MAH. Changes to the marketing authorisation or to the status of it may be requested, or recommended to the MAH. Amendments of the SPC may be recommended to the MAH in line with guidance on SPC9. Such recommendations should be clear on the nature, frequency and seriousness of the adverse reaction or contraindication or other information to include or amend.

9 Volume 6C (See glossary).
5. DEFINITIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Adverse reaction</td>
<td>A reaction to a veterinary medicinal product which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function.</td>
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<tr>
<td>Adverse event</td>
<td>Any observation in animals, whether or not considered to be product-related, that is unfavorable and unintended and that occurs after any use of VMP (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy according to approved labeling or noxious reactions in humans after being exposed to VMP(s). Ref. VICH Topic GL24 in Volume 9B[^10] and on the VICH homepage <a href="http://www.vichsec.org/en/topics.htm#6">http://www.vichsec.org/en/topics.htm#6</a>.</td>
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<tr>
<td>Agency</td>
<td>The European Medicines Agency. The Agency is an abbreviation used in the legislation.</td>
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<tr>
<td>AR</td>
<td>Assessment report</td>
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<tr>
<td>CAP</td>
<td>Centrally authorised products; Product authorised in accordance with Regulation (EC) 726/2004</td>
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<tr>
<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>CVMP</td>
<td>Committee for Medicinal Products for Veterinary Use</td>
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<tr>
<td>DCP</td>
<td>Products authorised in accordance with the decentralised procedure, in accordance with Directive 2001/82/EC, as amended</td>
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<td>EMEA</td>
<td>the European Medicines Agency</td>
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<tr>
<td>EU Birth date</td>
<td>The date of the first marketing authorisation within the European Union</td>
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<tr>
<td>EVVet</td>
<td>EudraVigilance Veterinary; a central database for reports on suspected adverse reactions in relation to exposure to a veterinary medicinal product</td>
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<tr>
<td>Human adverse reaction</td>
<td>A reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine</td>
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<tr>
<td>IBD</td>
<td>International Birth Date, the date of the first marketing authorisation for the product granted to the MAH in any country in the world</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MRP</td>
<td>Products authorised in accordance with Directive 2001/82/EC, as amended, that have benefited from the mutual recognition procedure</td>
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<td>MS</td>
<td>Member State</td>
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<tr>
<td>NAP</td>
<td>Nationally authorised products: products that have not benefited from the mutual recognition procedure nor have been authorised via the decentralised procedure</td>
</tr>
<tr>
<td>NCA</td>
<td>National Competent (Regulatory) Authority</td>
</tr>
<tr>
<td>Off-label use</td>
<td>The use of a veterinary medicinal product that is not in accordance with the SPC, including the misuse and serious abuse of the product</td>
</tr>
<tr>
<td>Post-marketing surveillance study</td>
<td>Pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorized veterinary medicinal product</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report, a periodical scientific report on suspected adverse reactions and other pharmacovigilance concerns that have been reported to a MAH during a specific period</td>
</tr>
</tbody>
</table>

[^10]: See footnote 2.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSUR, full</td>
<td>A PSUR which is prepared in accordance with Volume 9</td>
</tr>
<tr>
<td>PSUR, abridged</td>
<td>A PSUR that contains less information than a full PSUR and that contains only administrative data, and which has been prepared for a non-marketed product for which no SARs have been reported during the reporting period</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan: a detailed description of a MAH risk management system for a specific product, where applicable.</td>
</tr>
<tr>
<td>RMS</td>
<td>Reference Member State</td>
</tr>
<tr>
<td>SAR</td>
<td>Suspected Adverse Reaction</td>
</tr>
<tr>
<td>Serious adverse reaction</td>
<td>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</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>Unexpected adverse reaction</td>
<td>An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics</td>
</tr>
<tr>
<td>VEDDRA</td>
<td>List of standard clinical terms to be used in reporting suspected adverse reactions in animals or humans after exposure to veterinary medicinal products</td>
</tr>
<tr>
<td>VICH</td>
<td>International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products</td>
</tr>
<tr>
<td>VMP</td>
<td>Veterinary Medicinal Product</td>
</tr>
</tbody>
</table>
6. REFERENCES

EMEA. PSURs for centrally authorised veterinary medicinal products. Procedure on PSUR submission and evaluation of non-marketed products. (EMEA/CVMP/227/01)

EMEA. VICH GL29 on Pharmacovigilance of Veterinary Medicinal Products: Management of Periodic Summary Update Reports (PSUs). (EMEA/CVMP/VICH/646/01)

EMEA. VeDDRA List of Clinical Terms for Reporting Suspected Adverse Reactions in Animals. (EMEA/CVMP/413/99-Rev.5 )

EMEA. VeDDRA List of Clinical Terms for Reporting Suspected Adverse Reactions in Human Beings. (EMEA/CVMP/891/04-Rev.3)

European Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State.


European Commission Regulation (EC) No 540/95 of 10 March 1995 laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorized in accordance with provisions of Council Regulation (EC) No 2309/93.


ANNEX I: Template for Assessment Report on Periodic Safety Update Reports (PSURs)
RAPPORTEUR/CVMP/RMS/Member State ASSESSMENT REPORT

<PSUR type - choose from drop down list>

for

Medicinal Product for Veterinary Use

<PRODUCT NAME>

Active substance(s) / International Non-proprietary Name(s):

<Insert INN>

Marketing Authorisation Holder(s):

<NAME>

Authorisation type:

<Choose from drop down list>

<Concerned Member States :>

MA number(s):

<INSERT NUMBER>

Time period covered in the PSUR:

DD-MM-YYYY - DD-MM-YYYY

Author:

<NAME>

<Date of Assessment Report>

Attachment: Latest approved Summary of Product Characteristics
ASSESSMENT

Data review

Adverse events in target species: (including events of lack of efficacy and those events occurring after off-label use in target species)
After recommended use
After non-recommended use (off-label, including overdose)

Adverse events in humans:

Other pharmacovigilance fields:

Adverse events in non-target species
Potential environmental problems
Investigations of the validity of withdrawal periods
Transmission of infectious agents

Non-spontaneous Reports (overview of available data from other sources e.g. pre-authorisation studies, post authorisation safety studies, published adverse event reports),

Other Information (Adverse events arising from prescription errors or medication errors, including those due to invented names of VMPs or similar appearance (e.g. mix-up with another VMP)

Exposure:

Incidence:

Evaluation of the adverse reactions in view of the warnings included in the SPC

< There is <no concern to be addressed via amendment of the product literature>

• evidence of previously unidentified toxicity or safety concerns,
• <a> change in frequency of known toxicity or expected undesirable effects,
• evidence of drug Interactions,
• evidence of new undesirable effects associated with off-label use, including aspects of overdose
• evidence of clinical human symptoms associated with the use of the product,
• evidence of lack of efficacy,

and therefore the following sections of the SPC need to be amended as follows:

>

Overall conclusion

<As no adverse effect was observed so far, there are no changes to the evaluation of the risks and benefits afforded by the product.

The MAH has concluded that the benefit/risk balance <remains unchanged, has changed and that <the following, no> actions are necessary<: insert actions>. The conclusion of this assessment is <not> in agreement with the conclusion of the MAH < and actions are recommended as listed below>.>

>
Questions or comments to be addressed to the MAH
<There are no questions/comments to be addressed to the MAH.>

Recommended action
<No changes to the product literature or other regulatory actions are necessary.>
ANNEX II: Templates for tables for use as necessary in assessment (optional)

The table templates below are included as examples for those situations when the assessor feels some of the MAH data from the PSUR needs to be presented in the assessment report. Data should be presented only when it is necessary to explain or clarify an issue that is likely to lead to a question or recommendation to the MAH or would require some other specific action. In such circumstances any suitable template can be inserted in the text of the assessment report, or the assessor may create other, more suitable tables. Data should not be routinely presented in the assessment report, but reference to data in the PSUR should be sufficient in most circumstances.

Whenever information in any table below is expressed as <…>, the appropriate option should be chosen.

Template Table 1: Comparison over time of the ratio of animals reported for <SARs, Lack of Efficacy> during a period to the amount of product sold by period <and by year, if data is available>

<table>
<thead>
<tr>
<th>Period</th>
<th>PSUR 1</th>
<th>PSUR 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;Year&gt;</td>
<td>&lt;Year&gt;</td>
</tr>
<tr>
<td>Number of animals <strong>reacting, experiencing lack of efficacy</strong> during the period</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of doses sold during period, sales volume</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;insert sort e.g. Litres, Doses&gt;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio (number of animal:number of doses)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Sales volume only where it is not feasible to estimate the number of doses. Every attempt should be made to estimate the doses sold.

Template Table 2: Sales volume and animal counts on estimated number of treated animals, number and incidence of suspected adverse reactions during the reporting period by country and region

<table>
<thead>
<tr>
<th>Country*</th>
<th>Total sales volume</th>
<th>Number of animals treated **</th>
<th>Number of animals reacted in SARs assessed A, B or O</th>
<th>Incidence***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Luxembourg        
Malta          
Netherlands    
Poland         
Portugal       
Romania        
Slovakia       
Slovenia       
Spain          
Sweden         
United Kingdom 

Iceland        
Liechtenstein  
Norway         

TOTAL EU/EEA   

Third countries

TOTAL

* This table includes details only on those countries of the Community where the product has been sold during the reporting period. Countries with zero (0) sales have been deleted.

** <please explain here assumptions underlying the estimated number of treated animals>

*** <please explain here the assumptions underlying the incidence calculation– see also Volume 9 of the Rules governing medicinal products in the European Union, Part II. 1. Pharmacovigilance of Veterinary Medicinal Products – Notice to Marketing Authorisation Holders>

Template Table 3: Report, animal and outcome counts of all reports received on any suspected adverse reaction during the reporting period in any species, including human beings. All categories expressing the causal (A,B,O,N) between the product and the suspected adverse reaction are included.

<table>
<thead>
<tr>
<th>Reports Community (EU/EEA)</th>
<th>Third Countries (Non EU/EEA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targets specie</td>
<td></td>
</tr>
<tr>
<td>Non-target specie</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

Template Table 4. Report count of serious and non-serious suspected adverse reactions reports received during the period. All categories expressing the causal (A,B,O,N) between the product and the suspected adverse reaction are included. This table excludes reports of lack of efficacy.

<table>
<thead>
<tr>
<th>Use of product</th>
<th>Category of species</th>
<th>Number of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>As recommended in SPC</td>
<td>Target species</td>
<td></td>
</tr>
<tr>
<td>Off label use</td>
<td>Target species</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Target species</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>All</td>
<td></td>
</tr>
</tbody>
</table>

Template Table 5: Number and nature of reports by causality category in <non->target species received during the reporting period (animal count)

<table>
<thead>
<tr>
<th>Reports</th>
<th>A (probable) + B (possible) + O (unclassifiable)</th>
<th>N (unlikely)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected adverse reactions</td>
<td>Number of reported animals (N)</td>
<td>Deaths (N)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Template Table 6: Number and nature of suspected adverse reactions in any species received during the reporting period (report and animal counts)

<table>
<thead>
<tr>
<th>Reports</th>
<th>Community (EU/EEA)</th>
<th>Third Countries (Non EU/EEA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reports (N)</td>
<td>Number of reported animals (N)</td>
</tr>
<tr>
<td>Target species</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used as recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off label use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-target species</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Template Table 7: Event count of clinical signs reported as <Serious, Serious unexpected, Non-serious unexpected (unlisted)> adverse reactions (animal count) by species and VEDDRA terminology

<table>
<thead>
<tr>
<th>Species</th>
<th>Clinical sign</th>
<th>Number of events*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Veddra terms, &lt;SOC, HLT, PT &gt; level</td>
<td></td>
</tr>
</tbody>
</table>

* Number of number of times the clinical sign was reported (i.e. occurrences, citations, occasions)