Instructions on Periodic Safety Update Reports

1 Introduction

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a VMP to Competent Authorities at defined time points post-authorisation. At these times, MAHs are expected to provide succinct summary information on all adverse events together with a critical evaluation of the benefit-risk balance of the VMP in the light of any new or changing pharmacovigilance information. This evaluation is necessary to ascertain whether further investigations need to be carried out and/or whether changes should be made to the SPC or other product information.

For VMPs:

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

PSURs should be submitted to DGV in accordance with point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October.

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

2 General Principles

2.1 General Scope of Information

MAHs must include in the PSURs of all VMPs, details of all adverse events arising in the EEA and in a third country.

The main focus of the PSUR should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR, providing a basis for conclusion whether further investigations or changes in the SPC will be necessary.

For this purpose the PSUR should include information on the following types of adverse event reports/case histories received during the period of review:

- All adverse events in animals and in human beings, sent spontaneously to the MAH and occurring in the EEA and in a third country, including information from literature.
- All adverse events forwarded to the MAH by an NCA;
- Any suspected transmission of an infectious agent via a VMP;

- Serious and non-serious adverse event reports from post-authorisation safety studies;
- Any available information on investigation of the validity of a withdrawal period or any potential environmental problems, caused by the product under the normal conditions of use;
- Any available information on investigation of adverse events related to off-label use;
- Any available information on lack of expected efficacy, as specifically for VMPs used in the treatment of life-threatening conditions and for certain other VMPs, e.g. antibiotics or vaccines, lack of expected efficacy may represent a significant hazard and in that sense may give rise to a safety concern;
- Any data from previously requested close monitoring.

2.2 Frequency and timing of Periodic Safety Update Reports

2.2.1 Submission of PSURs

The periodicity for submission of PSURs is established in point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October. Unless other requirements have been laid down as a condition of the granting of the MA, a PSUR should be prepared immediately upon request or at least every six months after authorisation until the placing on the market.

Following the initial placing on the market, PSURs shall be submitted

- Immediately upon request, or at the following intervals:
  - 6-monthly for the first 2 years
  - Annually for the subsequent 2 years, and
  - Thereafter, at three-yearly intervals.

For products authorised through the MRP or DCP, the PSUR submission schedule should be agreed on and be the same for all involved NCAs.

The PSUR cycle should be based on the EU Birth Date (EBD, date of the first marketing authorisation within the European Union) of a VMP or its International Birth Date (IBD, date of the first marketing authorisation for the product granted to the MAH in any country in the world), or the EU HBD (EU Harmonised Birth Date for VMPs included in the work sharing initiative on PSUR assessments, provided it is not against National Legislation).

Once a VMP is authorised in the EU, even if it is not marketed, the MAH is required to submit PSURs at 6-monthly intervals, until initial placing of the VMP on the market. When launch dates are planned, this information should be reflected in the forthcoming PSUR.

The PSUR covering this period during which the product is launched is considered the last of the six-month PSURs to be submitted before 'initial placing on the EEA market'.

After this initial placing of the product on the EEA market, the MAH should submit at least four PSURs covering 6 months each, in order to ensure that two full years of experience with the product on the EEA market are covered through provision of 6-monthly PSURs, while keeping the DLP according to the EBD, EU HBD or IBD.

2.2.2. PSUR Reporting Period

Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the DLP. Gaps are not allowed. Overlapping should be avoided.

DLPs should be set according to the EU Birth Date (EBD, date of the first marketing authorisation within the European Union) of a VMP or its International Birth Date (IBD, date of the first marketing authorisation for the product granted to the MAH in any country in the world), or the EU HBD (EU Harmonised Birth Date for VMPs included in the work sharing initiative on PSUR assessments).

Preparation of PSURs according to the International Birth Date:

VMPs, which are also authorised outside the EU, will have an IBD. This is the date of the first marketing authorisation for the product granted to the MAH in any country in the world. For VMPs first authorised in the EU, the EBD 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 DLPs in the EEA rather than the EBD. If the IBD is used, the first DLP must be within 6 months of the EBD, unless other requirements have been laid down at the time of granting the MA. Regardless of whether the IBD or EBD is used, the PSUR should be submitted within the 60 days following the DLP, taking into account that the date of submission of the PSUR is in compliance with the stipulated submission schedule.

For the purpose of the PSUR the relevant dataset should be locked at the DLPs and, as relevant, extracted from the database for analysis (frozen) in relation to the product. 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 PSUR (see section 3.1.10).

For purely nationally authorised VMPs that are marketed, the MAH may wish to synchronise national birth dates with the IBD. Such a step may be feasible and should be discussed with DGV.

For nationally authorised VMPs, including those authorised through the MRP or DCP, where national birth dates are used to determine the submissions of PSURs, the MAHs and NCAs voluntarily may agree on an EU HBD which may be the IBD. Thus the first PSUR to be submitted in the EU should be based on the EU HBD and should cover a period in accordance with the life cycle of the VMP in the EU (6 months, 1 year or 3 years). When PSURs have previously been submitted in MS based on different national birth dates, DGV accept that there may be an overlap between the last PSUR based on a national birth date and the first PSUR based on the EU HBD.

3. Content of Periodic Safety Update Reports

The reaction terms used in the PSUR should be in accordance with the VeDDRA terminology.

The structure of a PSUR should follow the guidance given in section 3.1 Content of Periodic Safety Update Reports – Marketed Products.

For non-marketed products without any reports of adverse events an abridged PSUR is considered sufficient (see section 3.2 – Content of Periodic Safety Update Reports – Non-marketed products).

For the presentation of data within the PSUR it is strongly recommended to use the templates, tabulations and tables given in Annex.

3.1 Content of Periodic Safety Update Reports – Marketed Products

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

3.1.1 MAH and product details

Each PSUR should include:

i) The VMP name(s)

ii) The name of the MAH

iii) The MA number(s)

iv) Procedure number, if applicable

v) **EBD** / Start date for PSUR-submission cycle

vi) The period covered by the PSUR

vii) The date of initial placing of the product on the EEA market, understood as the date when the first presentation of the product was first placed on the market in any MS.

viii) Chronological order of PSUR (e.g. 1st 6 month PSUR after initial placing on the market)

3.1.2 Update on regulatory or MAH actions taken for safety reasons

An overview of regulatory and MAH actions taken for safety reasons (e.g. follow-up measures, specific obligations and variations) since the last period covered in the PSUR indicating scope, status and date should be given.

Significant changes in the wording of the SPC should be explained, where of relevance to safety.

3.1.3 Summary of Product Characteristics (SPC)

The latest version of the relevant SPC must be included for reference in the report. It is recommended that when the SPC changed significantly in matters relevant to safety during the covered period, the nature of the change(s) should be succinctly explained in

the PSUR. If evaluation of safety data leads to any proposed changes in the SPC, these should be described, see Part I Section 3.1.9.

- For VMPs authorised through MRP or DCP, this will be the mutually accepted SPC in English.
- For nationally authorised VMPs, the specific national SPC in Portuguese language should be included.

If no SPC is available, e.g. in cases of old non-reviewed/renewed VMPs, an explanation should be given and the package leaflet should be provided.

It is preferable that the SPC(s) are included in an annex.

3.1.4 Estimations of exposure

Sales volume

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, if applicable. The sales information should be expressed per presentation 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
- Pipettes for spot-on solution - to be expressed in numbers of pipettes.

Number of animals treated

The number of animals treated should be calculated independently of reported adverse events. When calculating the number of animals treated during a period, the following points should be taken into consideration:

- For some VMPs, the number of doses (individual units) sold is equivalent to the number of animals treated (e.g. anthelmintic boli, flea collars). For VMPs formulated as pastes, aerosols, eye/ear preparations or other formulations where it is likely that each unit of VMP (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 VMPs, the number of animals treated will be a function of:
  - Authorised treatment regimen (daily dose (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 maximum recommended exposure (that is, use the upper limit of the dose range **and/or** longest duration of treatment). Following from the calculation of maximum exposure, 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. For VMPs indicated for continuous (life-long) treatment, it is advisable to use 6-month standard duration period (this period take in consideration the specific condition of this kind of treatments on the veterinary sector). Any alternative period should justified by the MAH;

- Amount of VMP sold;
- Average weight of target population (kg). The chosen average weight is to be justified.

  Standard weights are recommended in the table below and use of any other standard weight, including for those species not listed below, should be justified in the PSUR.

  Exposure in pigeons is recommended to be calculated on basis of 30 pigeons/litre of drinking water.

Species and subpopulations	**Standard weight (kg)**
horse	550
dog	20
cat	5
cow	550
beef calf	150
newborn calf	50
sow/boar	160
finishing pig	60
weaner pig	25
sheep	60
lamb	10
Poultry, broiler	1
Poultry, layer hen	2
Poultry, turkey	10
Rabbit	1.5

- 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 VMP. For VMPs authorised for more than one species it is difficult to calculate individual species' exposure. However, it is suggested to estimate the number of animals treated for all authorised species individually using the estimated conditions of use of the VMP

(sales/species). Additional information to explain how the distribution of proportional use in different species is estimated should be provided.

- For immunological VMP, the number of animals treated may be considered equivalent to the total number of doses sold. Any calculations should take into account the recommended treatment regimen (initial course plus booster doses).

3.1.5 Incidence of Adverse Events

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

An overall incidence should be calculated 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-authorisation safety studies should be excluded.

In this respect the use of a VMP in non-authorised species under specific conditions laid down in Article 78.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, is regarded as off-label use.

In addition, an incidence for lack of efficacy in target species after recommended use should be calculated, when relevant.

When a VMPs is indicated for more than one target animal species, it is suggested that in addition to the ratio of all animals expressing an event the ratio be computed for each species based on the estimated conditions of use of the VMP (sales/species) (see 3.1.4). This information is of importance to NCAs although the arbitrary nature of such calculation based on assumptions is recognised.

For the calculation of incidence of adverse reactions it is suggested that MAHs adopt the following two-tier approach:

Calculation 1 – Ratio of animals expressing an adverse event

In the first instance, the ratio of the number of animals expressing an adverse event (reports assigned a causality code of **A, B, O, including O1, N**) during a period to the amount of VMP sold during that period should be computed:

$$\text{Ratio of animals with adverse event} = \frac{\text{No of animals with adverse event during period}}{\textbf{No of doses} \text{ sold during the period}}$$

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.

Calculation 2 – Incidence

The incidence (%) of adverse reactions (reports of adverse events assigned a causality code of **A, B or O, including O1**) 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.

$$\% \text{ Incidence} = \frac{\text{No of animals reacting during period (coded A. B or O and O1) x 100}}{\text{Estimated } \mathbf{No\ of\ animals\ treated} \text{ during the period}}$$

For VMPs authorised in multiple MS, incidence should be calculated individually for each MS where sales have occurred.

This calculation may then be revised to exclude O and O1 coded reports (that is, this calculation would focus 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 VMP. All assumptions used for calculation should explicitly be stated.

Overall incidences are calculated for the EEA in total, regardless of the route of authorisation of the VMP.

3.1.6 Data review

The report should include a data review based on the MAHs analysis (including causality assessment) of the individual adverse events reported during the period concerned by the PSUR.

The analysis of the adverse events reported should be supported by tables or tabulations summarising the main findings. It may be helpful, especially for PSURs which contain a large number of adverse events, to introduce summary tabulations and prepare separate tables e.g. for serious expected reactions, serious unexpected reactions, non-serious unlisted reactions (not mentioned in the SPC), or on basis of VEDDRA categories on organ level (e.g. System Organ Class (SOC) or Preferred Term (PT) level).

The data review should be structured as follows:

- Adverse events in target species, including events of lack of efficacy and those events occurring after off-label use in target species;
- Adverse events reported in humans;
- Other pharmacovigilance fields:
  Adverse events after use in non-target species;
  Investigations of the validity of the withdrawal period;
  Transmission of any infectious agent via a veterinary medicinal product;
  Potential environmental problems arising from the use of the VMP.

Information on the individual adverse event reports should be presented as line listings (see section 3.1.12 and Annex).

The main focus in the data review should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR (e.g.

evidence of previously unidentified toxicity or safety concerns, increased frequency of expected undesirable effects or known toxicity).

It is necessary to structure the data review further in relation to e.g. different formulations (dosage form(s) and strength(s)), target species (if the veterinary medicinal product is authorised for use in more than one species), event type (that is, serious, non-serious, human adverse event, etc.), and country where the event occurred.
Aspects relevant to different batches of immunological products should be considered in the PSUR when relevant, and batch numbers should be identified in the review and the line listings, as available.

3.1.7 Non-spontaneous Reports

A narrative overview of available data from other sources (e.g. post-authorisation safety studies, published adverse event reports, user experience studies) should be included in this section. The data should be analysed and discussed as part of the benefit-risk assessment.

The overview should include a review of all adverse event reports eligible for expedited reporting that were received during the PSUR period from post-authorisation safety studies.

Summaries from post-authorisation safety studies should be included once final results become available, and should consider all adverse events reported from the study.

A bibliographic listing of the scientific articles that address adverse events and which are found in a widely accepted search engine published during the PSUR period that pertains to the VMP should be included as an appendix. Information on databases used should be provided. The literature search should primarily be product-based.

Additionally, a bibliographic line listing of the studies that address adverse events and for which the MAH is the sponsor, should be included as an appendix.

3.1.8 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 reported in PSURs.

Where names convey misleading therapeutic connotations, there may be a risk for misuse or abuse of the product. Adverse events arising from such misuse or abuse should be reported in PSURs.

A summary report on medication errors, including those due to name confusion, occurring with the VMP should be submitted as an annex to the PSUR.

3.1.9 Overall safety evaluation

Together with concise summary information on all adverse events, the PSUR should include a scientific analysis of the data presented and a critical evaluation of the benefit-risk balance of the product in light of any new or changing pharmacovigilance information, written by a suitably qualified expert for pharmacovigilance. It should

clearly be stated, whether further investigations will be necessary and whether the wording of the SPC needs to be changed.

This section should include (lack of significant new information should be mentioned for each):

- 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 or safety concerns
  ii) increased frequency of known toxicity or expected undesirable effects
  iii) drug interactions
  iv) adverse events in animals associated with off-label use, including overdose and its treatment
  v) human adverse reactions related to the use of the product
  vi) lack of efficacy
- prescription errors/medication errors, including those associated with invented names or with the presentation of the VMPs that have safety implications, if available.
- information on investigation regarding the validity of withdrawal periods arising from the use of the VMP
- any environmental issues, caused by the VMP under normal conditions of use
- any urgent safety issues that occurred during the period covered:

The evaluation should in particular:

- indicate whether the safety information remain in line with the cumulative experience to date and the SPC or whether changes should be made to the SPC or other product information, and
- ascertain whether further investigations need to be carried out, and
- specify any action recommended and the reasons why.

The overall safety evaluation should primarily be organised by VeDDRA System Organ Class (SOC) –terminology rather than by categories like serious/non-serious or known reactions/new reactions; the latter properties should still be covered under each SOC.

An increase in the frequency of reports for known adverse events is considered as relevant new information. Although increased reporting should be discussed in the PSUR, it is not possible to provide specific guidance as to what constitutes increased reporting or what method should be used for quantifying this. The MAH should provide details of the methods that have been used. Judgement should be used in such situations to determine whether the data reflect a meaningful change in occurrence of adverse events or in the safety profile and whether an explanation can be proposed for such a change (e.g. species or number of animals exposed, duration of exposure).

3.1.10 - Important information received after Data Lock Point

This section is for reporting any important new information received by the MAH since the dataset was locked 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.

3.1.11 - PSUR line listings

All individual reports (A, B, O, O1 and N coded reports) should be presented as line listings.

Expedited reports received during the PSUR reporting period from post-authorisation safety studies should be included in the line listing.

The line listing should be included as an appendix to the PSUR (see **Annex – Template for PSUR line listing**) and, as necessary, separately in a **searchable and sortable format** (e.g. excel spread sheet) to allow for analysis of the data during assessment of the PSUR.

In order to relate the data review to the line listings, it is necessary to separate data e.g. relating to different formulations (dosage form(s) and strength(s)), target species (if the VMP is authorised for use in more than one species), reaction type (that is, serious, non-serious, human adverse event, etc.), and the country where the event occurred. It is preferable to use the following grouping sequence (*):

- **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;
  - Investigations of the validity of withdrawal periods;
  - Transmission of infectious agents;
  - And/or Potential environmental problems.

The standard information required in the line listing of a PSUR for adverse events in animals includes:

i) MAH report reference number (country code where occurring) – EVVet organisation id –report number);

ii) NCA report reference number, if relevant;

iii) Date(s) of treatment(s)/Date(s) of vaccination(s);

iv) Was the VMP used as recommended?

v) Date of adverse event;

iv) Number of animals treated;

vii) Species;

viii) Age(s);

ix) Number of animals reacted (approximate, if the exact number is not available);

x) Number of animals 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, O1, N code).

The standard information required in the PSUR for human adverse reactions related to the use of a VMP includes:

i) MAH report reference number (country code (country where occurring) – EVVet organisation id –report number);

ii) NCA report reference number, if relevant;

iii) Date(s) of exposure;

iv) Date(s) of human reaction;

v) Name(s) and region of address (for cross-reference to avoid duplication);

vi) Occupation;

vii) Nature of accident/exposure:

viii) Nature of human reaction/symptoms;

ix) Outcome of human reaction;

x) MAH comments – brief, informative narrative.

(*) In order to be coincident with sequence on Guideline on "**RECOMMENDATION ON MANAGEMENT AND ASSESSMENT OF PERIODIC SAFETY UPDATE REPORTS (PSURs) OF VEERINARY MEDICINAL PRODUCTS" (**EMEA/CVMP/PhVWP/4550/2006).

3.2 Content of Periodic Safety Update Reports – Non-marketed products

For authorised VMPs that are not marketed or distributed anywhere and for which no adverse events (either in animals or in human beings) was observed in any additional trial (e.g. clinical trial, post-authorisation safety study) abridged PSURs are considered sufficient, which should contain the following elements only:

- trade name of the VMP
- marketing authorisation number(s) of the VMP,
- name and address of the MAH,
- date of EBD/IBD
- chronological order of the PSUR (e.g. 1st 6 monthly PSUR before initial placing on the market)
- a **declaration** of the MAH's **QPPV**, that as the VMP was not marketed or distributed anywhere in the world during the reporting period and as no adverse event (either in animals or in human beings) was observed in any additional trial (e.g. clinical trial, post-authorisation safety study), the benefit-risk balance afforded by the VMP has not changed since the date of the MA.

4 Further guidance on submission and contents of Periodic Safety Update Reports in special situations

4.1 Submission of documents related to safety for Renewal of Marketing Authorisations

As part of the renewal application documents related to safety, the MAH needs to prepare or submit either a PSUR Summary Bridging Report supported, if needed, by a PSUR Addendum Report, **or** one PSUR in circumstances where the PSUR submission schedule is in synchrony with the renewal submission schedule.

4.1.1 PSUR Summary Bridging Report

For the purpose of the renewal application, the MAH should submit a PSUR Summary Bridging Report, bridging all previously submitted PSURs. If, however, a PSUR covering the period since authorisation or last renewal is due at the time of submission of the renewal application, the PSUR replaces the need for a PSUR Summary Bridging Report. It is accepted that previously submitted PSURs should not be re-submitted, provided that a list of original submission dates is appended to the Summary Bridging Report.

The PSUR Summary Bridging Report should not contain any new data but should provide a succinct summary, bridging and summarising previously submitted consecutive PSURs. The PSUR data should not be repeated but cross-referenced to individual PSURs. The format of the PSUR Summary Bridging Report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached (or referenced) PSURs.

A Summary Bridging Report should contain the following for the period covered by all subsequent PSURs:

- Introduction (a brief description of the purpose of the document specifying the time periods covered and cross-referencing any referenced PSURs);
- Worldwide marketing authorisation status (number of countries which have approved the product);
- An overview of regulatory authority or MAH-initiated actions for safety reasons (an integrated summary of actions taken if appropriate);
- An overview of changes (proposed or completed) to the SPC and package leaflet, to the Reference Safety Information Document (if applicable) (See further below), based on pharmacovigilance grounds (significant changes over the entire period);
- An overview of exposure data (estimation of the total number of animals exposed in the time period) as well as incidence data (in animal and in human);
- An overview of individual reports (brief statement outlining the total number of reports presented in the series of PSURs). When there is an important specific safety concern that has not been adequately discussed in one or more PSURs, it may be appropriate to include summary tabulation for the types of reports of concern presenting adverse events, pointing out any differences from prior tabulations. In this case, there should be a clear understanding that the tables should be generated from live databases, which change over time as reports are updated. These tables should then reflect the most up-to-date data available at the time they are generated. It is recognised that the report/event counts in these summary tables may differ somewhat from the contents of the individual tables in the PSURs. A general statement describing the differences should be provided;
- An overview of studies (a brief summary of important targeted post-authorisation safety studies);
- An overview of the reported information related to investigations of insufficient withdrawal period arising from the use of the VMP, lack of expected efficacy, adverse events related to off-label use or any potential environmental problems
- Other information (only highly significant safety information received after the DLP);
- Overview of the safety concerns and conclusion (unresolved key issues).

In addition, the Summary Bridging Report should also contain information highlighting any significant differences between the approved SPC and the proposed SPC.

Depending on the length of time and amount of safety data between the DLP of the previous PSUR and the renewal application, it may become necessary to provide an Addendum Report to the PSUR Summary Bridging Report.

4.1.2 PSUR Addendum Report for renewals

A PSUR Addendum Report is an update to the most recently completed PSUR when a safety update is required outside the usual EBD- or IBD-based PSUR submission schedule for a renewal application.

Because the renewal is an independent process, a PSUR Addendum Report does not change the submission schedule for PSURs nor has it influence on the DLPs of PSURs, as its content will be part of the following regular PSUR.

The Addendum Report should summarise the safety data received between the DLP of the most recent PSUR and the date 60 days prior to the renewal application submission date, or a date as agreed with DGV. In general, DGV accepts any solution provided that it will not be any gap between this PSUR DLP and next PSUR.

It is not intended that the Addendum Report should provide an in-depth analysis of the additional cases, as these should be included in the next regularly scheduled or requested PSUR. Depending on the circumstances and the volume of additional data since the last scheduled report, an Addendum Report may follow the PSUR format or a simplified presentation.

The proposed simplified presentation should include the following sections, containing any new information or changes beyond the most recent PSUR to which the Addendum Report refers:

- Introduction (purpose; cross-reference to most recent PSUR);
- Changes to the sections of the SPC relevant to pharmacovigilance (including a copy of the most recent document if it differs from the one in the PSUR);
- Significant worldwide regulatory authorities' actions relevant to safety;
- Line-listing(s) and/or summary tabulations;
- Conclusions (brief overview).

4.2 Synchronisation of PSUR submission

The periodicity of PSUR submission may be amended, as required for any VMP by DGV, or proposed by the MAH for nationally authorised products. In any way, for VMP authorised less than 5 years ago, and newly authorised generic VMPs or VMPs authorised on the basis of informed consent applications, the calendar defined on point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October, cannot be changed. Additionally, for any VMPs that had been already renewed, submission of PSURs at a lower frequency than once every 3 years is not possible.

Where an amendment is proposed, the Applicant/MAH should submit, as part of the application, a reasoned request for the amendment. For the MAH shortening a reporting period by submitting the PSUR earlier (e.g. for synchronisation of PSUR submissions) is always possible.

In addition, in order to put in place measures facilitating PSUR preparation for MAHs and work sharing of PSUR assessment among NCAs, harmonisation of birth dates, renewal dates and/or PSUR submission schedules for VMPs containing the same active substances may be proposed by the MAH or the NCAs. The principles are outlined on the Heads of Agencies website. In any way, it is stressed that the calendar defined on point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October, must be fulfilled.

4.3 Reference Safety Information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accordance with previous knowledge of the VMP's safety, and to

indicate whether changes should be made to the product information. Reference information is needed to carry out this comparison.

Having one reference safety information document would facilitate a practical, efficient and consistent approach to safety evaluation and make the PSUR a unique report also accepted in other regions of the world.

This information is especially important in the framework of the PSUR synchronisation / PSUR assessment work sharing initiative (see above). It is recommended for MAHs participating in this initiative to prepare a Core Safety Data Document (CSDD) written in English, which consists of an extract of all safety relevant sections from the SPCs of the VMPs for which the synchronised PSUR is submitted. The MAH should indicate in the PSUR which changes, amendments or modifications to this document are considered necessary on the basis of the data evaluated in the PSUR.

The CSDD is strongly encouraged to be submitted in addition to the regularly enclosed SPCs (in national languages, see section 3.1.3) of all VMPs for which the synchronised PSUR is prepared. For more information regarding the CSDD refer to Heads of Agencies website.

PSUR line listing template - PSUR Line listing for suspected adverse events in animals

VETERINARY PHARMACOVIGILANCE SCHEME - PERIODIC SAFETY UPDATE REPORT
MAH FORM FOR REPORTS OF *ANIMAL ADVERSE EVENTS*
TO A VETERINARY MEDICINAL PRODUCT

PRODUCT:
MARKETING AUTHORISATION HOLDER: **MARKETING AUTHORISATION NO:**

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

NO. OF DOSES SOLD ON AN ANNUAL BASIS:
YEAR=……NO.=……YEAR=……NO.=……YEAR=……NO.=.....

A - Nature of Complaint: AnSAE in Target Species:

i - after recommended use

Event Severity: Serious

MAH Case Ref or World Wide Case Number		Date of Treatment/ Vaccination	Date of Event	No. Treated	Species and Age (Juv/Adult)	No. Reacted (a)	No. Died (b)	Used as recommended Yes/No	Other Products used Concurrently	VeDDRA	Presenting Signs/ Diagnosis	Brief Informative Narrative and MAH Comments and Conclusion	Causality (ABON Code)
EEA Reports and then **THIRD COUNTRY REPORTS** (Country Code -Organisation ID -Case Number Ref.)				***(Please ensure that this total is put in)***								*(Please ensure these sections are completed)*	
OVERALL TOTAL OF ALL (EEA) PAGES Total no of (reports): Total no of animal reactions (a): Total no of animals died (b):													

Event Severity: Not Serious

MAH Case Ref or World Wide Case Number		Date of Treatment/ Vaccination	Date of Event	No. Treated	Species and Age (Juv/Adult)	No. Reacted (a)	No. Died (b)	Used as recommended Yes/No	Other Products used Concurrently	VeDDRA	Presenting Signs/ Diagnosis	Brief Informative Narrative and MAH Comments and Conclusion	Causality (ABON Code)

(Please ensure these sections are completed)

EEA Reports and then **THIRD COUNTRY REPORTS** (Country Code -Organisation ID -Case Number Ref.)				***(Please ensure that this total is put in)***									
OVERALL TOTAL OF ALL (EEA) PAGES Total no of (reports): Total no of animal reactions (a): Total no of animals died (b):													

ii - after Not recommended use

Event Severity: Serious

MAH Case Ref or World Wide Case Number		Date of Treatment/ Vaccination	Date of Event	No. Treated	Species and Age (Juv/Adult)	No. Reacted (a)	No. Died (b)	Was Product used as recommended Yes/No	Other Products used Concurrently	VeDDRA	Presenting Signs/ Diagnosis	Brief Informative Narrative and MAH Comments and Conclusion	Causality (ABON Code)
EEA Reports and then **THIRD COUNTRY REPORTS** (Country Code - Organisation ID -Case Number Ref.)				***(Please ensure that this total is put in)***								*(Please ensure these sections are completed)*	
OVERALL TOTAL OF ALL (EEA) PAGES Total no of (reports): Total no of animal reactions (a): Total no of animals died (b):													

Event Severity: Not Serious

MAH Case Ref or World Wide Case Number		Date of Treatment/ Vaccination	Date of Event	No. Treated	Species and Age (Juv/Adult)	No. Reacted (a)	No. Died (b)	Was Product used as recommended Yes/No	Other Products used Concurrently	VeDDRA	Presenting Signs/ Diagnosis	Brief Informative Narrative and MAH Comments and Conclusion	Causality (ABON Code)
EEA Reports and then **THIRD COUNTRY REPORTS** (Country Code - Organisation ID -Case Number Ref.)				***(Please ensure that this total is put in)***								*(Please ensure these sections are completed)*	
OVERALL TOTAL OF ALL (EEA) PAGES Total no of (reports): Total no of animal reactions (a): Total no of animals died (b):													

<u>FOR COMPETENT AUTHORITY USE ONLY:</u> REFERENCE: DATE OF RECEIPT

B - PSUR line listing template - PSUR line listing for suspected human adverse events

VETERINARY PHARMACOVIGILANCE SCHEME – PERIODIC SAFETY UPDATE REPORT

MAH FORM FOR REPORTS OF *HUMAN ADVERSE EVENTS*

INVOLVING A VETERINARY MEDICINAL PRODUCT

MARKETING AUTHORISATION HOLDER

PRODUCT:

MARKETING AUTHORISATION NO:

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

MAH Case Ref or World Wide Case Number		Name(s) or Unique Patient(s) Identification [1]	Occupation	Date of Exposure	Date of Event	Nature of Accident/ Exposure	VeDDRA	Nature of Reaction/ Symptoms	Outcome of Event	Brief Informative Narrative and MAH Conclusion	Causality (ABON Code)
(Country Code -Organisation ID -Case Number Ref.)										*(Please ensure these sections are completed)*	

[1] As appropriate according to national laws