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Committee for Medicinal Products for Veterinary Use

Questions and answers on preparation, management and assessment of periodic safety update reports (PSURs)

Output from the training of veterinary assessors on PSUR assessment and management held on 26-27 November 2008 and 29-30 March 2010 and the Committee for Medicinal Products for Veterinary Use Pharmacovigilance Working Party (PhVWP-V) interested parties meeting of 26 September 2012 held at the European Medicines Agency, London

This question and answer document on periodic safety update reports (PSURs) was originally developed following the training of veterinary assessors held at the European Medicines Agency, London, on 26-27 November 2008 and 29-30 March 2010 to support the implementation of CVMP recommendation on management and assessment of PSURs of veterinary medicinal products (EMEA/CVMP/PhVWP/4550/2006). The questions and answers have now been further developed to incorporate PSUR-related topics discussed at the Committee for Medicinal Products for Veterinary Use Pharmacovigilance Working Party (PhVWP-V) interested parties meeting held at the Agency on 26 September 2012. The document was updated in July 2017 to include new questions on abridged PSURs (question 2), medication errors which are not associated with adverse events (question 11), recommendations for additional electronic line listings (question 16), incidence calculations (questions 29 and 34) and update of product information (question 45). The questions on validation have been removed, in line with the procedural change for PSURs for centrally authorised products (CAPs) as PSURs are no longer validated. The document is intended to facilitate stakeholders understanding of the requirements of Volume 9B of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use for effective implementation of the guidance.

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45. Is it acceptable to delay implementing changes recommended to the product information? For example due to the so-called ‘Weber effect’

PSUR submission

1. The date of first launching always falls after the European birth date (EBD). Therefore are at least five 6-monthly PSURs for new marketing authorisations required (e.g. even if marketing started one day after the data lock point (DLP) set on the last day of the month)?

This interpretation is correct, unless alternative reporting frequencies have been agreed with the national competent authority (NCA) for non-centrally authorised products (non-CAPs) or granted as a condition of the marketing authorisation for CAPs or agreed as part of the PSUR synchronisation and work-sharing initiative.

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2. If a veterinary medicinal product (VMP) is not marketed and/or no adverse events were reported during the PSUR reporting period of the PSUR, is the MAH still required to submit a PSUR?

MAHs are required to submit PSURs once a VMP is authorised in the EU. However, if during the PSUR reporting period the VMP has not been marketed (sold) or distributed anywhere in the world and/or if no adverse event (either in animals or in humans) was observed (in spontaneous and non-spontaneous reporting e.g. clinical trial, post-authorisation safety study) PSURs may be submitted in an 'abridged' format containing the following elements only:

- trade names of VMP;
- marketing authorisation number(s) of the VMP;
- name and address of the MAH;
- date of EBD/international birth date (IBD);
- chronological order of the PSUR;
- declaration from the MAH's qualified person for pharmacovigilance (QPPV) stating that as the VMP was not marketed or distributed anywhere in the world during the reporting period and/or no adverse event (either in animals or in humans) was observed in spontaneous and non-spontaneous reporting, the benefit-risk balance afforded by the VMP has not changed since the date of the MA; and
- estimated date for initially placing the product on the market, if applicable.

The submission cycle would continue to be the same as for full PSURs.

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PSUR content

3. Which date should be used as the basis for inclusion of adverse event reports in PSURs? Reaction start date or date of receipt from the MAH?

Inclusion of reports in PSURs should be based on the date of receipt by the MAH.

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4. On which reports should incidence calculations be based? Those that occurred during the period covered by the PSUR or those that were received by the MAH during the PSUR period?

Incidence calculations should be based on the reports that have been included in the PSURs even if the reaction start date is outside the period covered by the PSUR.

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Non spontaneous reports

5. How should adverse event reports in the published literature be addressed?

The MAH's narrative overview and bibliography of reports from the published literature presented in the PSUR should be evaluated in the PSUR assessment.

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6. Should assessors search the literature?

Assessors could check the literature results using the search strategy used by the MAH or based on their own search strategy, as appropriate.

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7. What type of information is the MAH recommended to provide for literature searches?

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 veterinary medicinal product (VMP) should be included as an appendix to the PSUR. Information on databases searched should be provided and, preferably, the key words used. The literature search should primarily be product-based.

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Data presentation and line listings

8. How should the data in the line listing be presented and what can be done to ensure that the data are well presented?

The format for the line listing is indicated in Volume 9B. The line listing data should be organised by formulation (dosage form(s) and strength(s)) of the VMP, target species, country, chronology and type of event or reaction (serious, non-serious, human) if relevant.

The line listing data should be presented also electronically in a searchable and sortable format (Excel, xml-files) which enables national competent authorities (NCAs) to review the line listings as required. This is especially important for extensive line listings which cannot be managed just in paper format or as pdf-file on CD.

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9. Is presentation according to system organ class (SOC) level of VeDDRA terms acceptable for line-listings?

This is not preferable in line listings. However, in PSURs, it may be useful to present summary tables related to the clinical profile of adverse events by VeDDRA term (e.g. SOC, HLT etc. as appropriate) in order to facilitate the overview of the established clinical profile of adverse events.

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10. Should the MAH include asymptomatic reports (either human or animal) in the line-listing?

No, these are outside the scope of pharmacovigilance, however, the MAH may find it useful to record these events in their own databases.

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11. How should events relating to medication/prescription errors which do not result in adverse events be managed? e.g. intercepted errors or circumstances or information with the potential to lead to medication errors

Where there is no adverse event associated with medication/prescription errors, it is recommended that the MAH keep a record of such events in their own database but these should not be reported as adverse events to EVVet or PSURs. However, where potential risks are identified as a result of medication errors without adverse events e.g. intercepted errors, the information should be summarised in the PSUR together with recommendations for addressing the issue. This is valuable information which may lead to improvements in the product information and the overall safety associated with the use of the product. Where such events have safety implications, impacting on the benefit-risk balance of the medicinal product, they should also be notified to the competent authorities.

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12. What is expected to be included in the "Narrative review of the individual case histories/data review" section of the PSUR?

In this section, the MAH is expected to provide a brief narrative based on the analysis of the adverse events recorded during the period, to identify a potential change in the safety profile of the product. Depending on the number of adverse events and their complexity, this analysis may be provided in a summarised way (using tables for causality assessment and clinical signs, for example), or in a more descriptive way (including an analysis of the adverse events). However, the purpose of this section is not to repeat the "Case narratives" and "MAH comments/conclusions" included in the line listing, therefore detailed description should be provided only if it enhances the MAH's analysis.

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13. In PSURs with less than e.g. 10 adverse event reports, are summary tables or detailed summaries/incidences per countries/years necessary when there is no new information when compared to previous PSURs and with products with well characterised safety profiles? What flexibility can be justified?

Flexibility could be acceptable, however, where deviation from Volume 9B is justified e.g. based on the number or types of reports. It should be highlighted that use of the templates for tables when preparing and assessing PSURs is recommended in Volume 9B but not mandatory.

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14. For adverse events initially reported to the MAH, some companies request the national competent authority (NCA)to send them their internal reference number in order to fill in the line listing template for PSURs. It is not possible via automatic acknowledgement. Do MAHs need this information? Is the worldwide number sufficient?

It is specified in Volume 9B (Part I Section 6.3.1.11) that the MAH should mention the NCA case reference number in the PSUR line listing "if relevant" i.e. if this information is provided to MAHs. During inspections and PSUR assessment, the worldwide case number should be sufficient to check compliance with expedited reporting. Where the NCA reference number is provided to MAHs (e.g. where acknowledgements are sent via EudraVigilance Veterinary (EVVet) gateway or where NCAs add the local report number to the manual acknowledgement) it is expected that the reference number is included in the PSUR line listing as this is considered useful for NCAs.

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15. Where a line listing is provided in a separate sortable format (e.g. Excel) is it also necessary to include the line listing table within the PSUR itself?

Volume 9B states that the line listing should be included as an appendix to the PSUR and, as necessary, separately in a searchable and sortable format (e.g. excel spreadsheet). In principle the provision of a line listing in a separate sortable and searchable format only for PSURs, without additional duplication of the table within the PSUR itself could be acceptable. However, an appropriate cross reference should be included in the PSUR itself and the PSUR and line listings should be provided in the format required by competent authorities who may have specific national requirements (e.g. paper copies). MAHs should contact national competent authorities to confirm their specific national requirements, if applicable.

In Volume 9B it is also strongly recommended that, before submitting the PSUR, the MAH should make sure that all reports from the line listings have been submitted electronically (without duplicate reporting) as described in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

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16. Are separate sortable electronic line listings (e.g. Excel) necessary in addition to the line listing table within the PSUR itself?

It is recommended to submit separate sortable electronic line listings (e.g. Excel) with all PSURs to facilitate their assessment. However, for line listings with less than 20 adverse event reports, it would be acceptable for MAHs not to submit a separate sortable electronic line listing in addition to the line listing already provided in the PSUR.

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Adverse event report evaluation and classification

17. How should assessors distinguish between suspected adverse reactions (SARs) or lack of expected efficacy (LEE) events?

Sometimes it is not easy to distinguish between SARs and LEEs as some clinical signs recorded are in line with the clinical profile of the disease treated. Clear justification should be presented for classifying a report as a SAR or LEE. Where possible, the classification should be mutually exclusive to be in line with the data elements for the electronic submission of adverse reaction reports related to VMPs authorised in the European Economic Area (EEA). See also the relevant data elements guideline: http://eudravigilance.ema.europa.eu/veterinary/006503en.pdf.

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18. Is concomitant use of two or more products considered as recommended or off-label use?

Such reports are considered as off-label use only if such association is included as a contraindication in the summary of product characteristics (SPC) and other product literature. If the product literature states *"No information is available on the compatibility of this vaccine with any other"*, the reports related to concomitant use of two vaccines should be considered as reported after recommended use.

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19. How should causality assessment be approached?

It is desirable to review reports assessed N (unlikely) causality in order to check whether or not a cause or explanation is available to reject the role of the VMP in the event. For expedited reports, it might be possible to check the causality assessment assigned by the competent authority of the country where the event was recorded in EudraVigilance Veterinary.

It is not necessary and not desirable that causality assessments be re-assessed for each individual report.

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20. How should assessors discriminate between reports assessed causality O and causality N?

To assign causality N there must be sufficient information to confirm that the association between the product and the reported event is unlikely. Otherwise, the most appropriate assessment would be causality O. See also the relevant revised recommendation on harmonising the approach to causality assessment: http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000170.jsp&mid=WC0b01ac058002ddca.

It is recommended to review the reports assessed N (unlikely) causality as these may represent potential bias in the method of causality assessment used by the MAH and which may affect identification of potential new signals.

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21. Can changes of SPC sections related to adverse reactions or to overdose be based on reports assessed causality O (unclassifiable)?

Changes to the SPC and other product literature would not be recommended based on individual reports assessed causality O (unclassifiable). However, causality assessment is performed at one given moment, whereas the potential causal association between a clinical sign and a product may evolve overtime, e.g. previously unidentified or unexpected clinical signs, may no longer be classified as "unexpected". For SPC changes the main adverse events in the target species should be included, if they are at least possibly causally related.

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22. Should causality N reports be considered when screening for safety signals?

No, causality N (unlikely) should only be allocated to reports where sufficient information exists to confirm that the VMP (or treatment) was not likely to be associated with the adverse event and where there is no indication of insufficient/unreliable information. See also the revised recommendation on harmonising the approach to causality assessment: http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000170.jsp&mid=WC0b01ac058002ddca.

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Exposure and incidence[1]

23. Are combined sales figures for the European Union or groups of members states (MSs) considered satisfactory or do they require breakdown by individual MSs?

In Volume 9B, it is clearly indicated that each PSUR should contain the number of doses/amount of VMP sold in the relevant MSs and that incidence should be calculated individually for each country. These statements imply a breakdown of sales figures by MS.

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24. Is the number of doses sold equal to the number of daily doses sold? For example, does two injections/day = 2x dose/day = 1 dose for calculation of number of doses sold?

The number of doses is not equivalent the number of daily doses. For estimation of the number of animals treated, the number of doses should be calculated as specified in Volume 9B, taking into consideration the authorised regime recommended in the summary of product characteristics.

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[1] See also further explanation at end of exposure and incidence section

25. How should the number of animals treated be calculated when there is no information available with regard to the distribution of the veterinary medicinal product (VMP)? (For example, one VMP can be recommended for poultry and bovine. Due to the difference in weight between these two species - 2 kg body weight (b.w.) compared with 550 kg b.w. – depending on the animal weight used, large differences in the estimated number of animals treated can result)

The MAH should make a justified estimate for the assessor to review. The same criteria for estimation should be applied over time for the same product. Until further guidance becomes available, it is recommended to check the trend in the ratio of animals treated as follows: Calculate, in the first instance, the ratio of the number of animals experiencing 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. Any increase in this ratio relative to previous PSURs may signal a potential problem and the need for more detailed evaluation of the pharmacovigilance data. Standard mean animal weights should be used. The assessor is primarily interested in using a consistent approach as outlined in Volume 9B and the recommendation on management and assessment of PSURs, unless another approach is justified by the MAH.

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26. For life-long administered products, which duration of treatment should be applied?

A standard duration of treatment should be established. Consider, for example, using a 6-month treatment basis as an average. It should be kept in mind that once an approach is retained for one VMP or a class of VMPs, this approach should be kept for all subsequent PSURs. Alternative durations may be proposed by the MAH, with appropriate justification, which would be considered by the assessor.

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27. How should exposure be calculated for veterinary medicinal products (VMPs) (e.g. tablets) adapted to animal's weight?

Consider the highest weight animal or estimate the number of tablets that could be used for a standard animal weight.

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28. How can the large weight range in species such as dogs/cats be taken into account for exposure estimates? How should tablet strengths be taken into account?

Standard weights recommended for cats and dogs are 5 and 20 kg, respectively. However, when there are formulations dedicated for a specific range of animal weights, the number of treated animals should be estimated by using the specific strengths: for example 'y' small treated dogs (up to 5 kg) and 'z' large treated dogs (greater than 40 kg body weight). Once an approach is established, for one VMP or a class of VMPs, this approach should be kept for all subsequent PSURs.

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29. Which adverse events should be used to calculate the worldwide ratio?

The worldwide ratio calculation should be based on the total number of animals, including target and non-target species, affected by an adverse event during the PSUR period, regardless of causality code assigned.

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30. How should the incidence related to safety issues in the target species be calculated?

As detailed in Volume 9B and the CVMP recommendation on management and assessment of PSURs, incidence should be calculated for events occurring in the target species after recommended and off-label use, based on the number of animals treated according to the recommended treatment regime stated in the SPC.

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31. Should causality O2 reports be considered for the calculation of incidence?

With the implementation of Volume 9B, the causality categories are as follows: A, B, O1, O and N and O2 is no longer applicable. For incidence calculations, only causality N reports should be excluded.

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32. Can MAHs present alternative exposure and incidence estimates, compared with those described in Volume 9B and the CVMP recommendation on management and assessment of PSURs (EMEA/CVMP/PhVWP/4550/2006)?

Yes, if clear justification is provided by the MAH. If the assessor does not agree with the MAH's calculations, the assessor's calculation should be presented and this method could be recommended to the MAH for the preparation of future PSURs.

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33. How can assessors calculate the incidence of lack of expected efficacy (LEE) when the number of animals treated is unclear or not specified?

In such cases it would not be possible to calculate incidence, unless the MAH can provide the number of animals treated. Caution should be given to such calculations due to the quality and the reliability of the data available.

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34. How should the incidence for lack of expected efficacy be calculated?

The incidence (%) of events of lack of expected efficacy in the target species (reports assigned a causality code of A, B or O, including O1) should be calculated by dividing the total number of animals affected during the period by the estimated the number of animals treated during the period of the report and multiplying by 100. This should relate to events where the product has been used in accordance with the recommendations of the SPC e.g. in the target species, for the claimed indications, at the recommended dose, via the recommended route etc.

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35. Sales volumes should be provided per calendar year. Does the breakdown by year also apply for incidence calculations?

Although not precisely stated in Volume 9B Part I Section 6.3.1.5, it is generally considered that the breakdown of sales volume per calendar year applies to Calculation 2 (Incidence) in addition to Calculation 1 (Ratio of animals expressing an adverse event). In order for an incidence calculation to be meaningful, the number of animals treated per presentation should be presented separately and the incidence calculated for each product strength. Most MAHs comply with this, although the need to separate data relating to different formulations is only mentioned in Volume 9B Part I Sections 6.3.1.6 and 6.3.1.11, and not specifically in 6.3.1.5.

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36. In calculation 1 (ratio of animals expressing an adverse event) of Volume 9B Part I Section 6.3.1.5 detailed below is the "no. of doses sold" different from "no. of animals treated"?

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 or O, including O1, N) during a period to the amount of VMP sold during that period should be computed:

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

There is inconsistency in terminology in Volume 9B used for the denominator: animals treated versus doses. There may be potential for flexibility in the use of animals treated or doses provided that a consistent approach is taken for subsequent PSURs and the approach is suitably justified by MAH.

The number of doses sold during the period is linked to the sales volume. Volume 9B states that each PSUR should contain the number of doses/amount of VMP sold within the reporting period and describes possible forms. The ratio is intended to give a rough world-wide overview of the ratio of animals experiencing an event per dose and the data should be manipulated as little as possible to enable comparison of equivalent data over time. For the calculation of animals treated as well the treatment dose, duration of treatment as possible target species are considered and this in practice means manipulation of the data. In certain cases, the number of doses can be equal to the number of animals treated e.g. for flea collars, vaccination etc.

Go back

37. Should overall incidence be calculated for "adverse reactions" (*sensus stricto*, i.e. without the lack of efficacy reports) and a separately for lack of efficacy events routinely be provided in PSURs?

The guidance in Volume 9B is clear, however the terminology used is potentially confusing. Volume 9B does not ask for systematic incidence calculation for LEE events but leaves flexibility stating that this calculation should be performed when relevant. It is up to the MAH and competent authority to decide when it is relevant.

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38. In Volume 9B Part I Section 6.3.1.5 is it necessary to routinely present sales volume and the ratio of adverse events in animals to the amount of VMP sold by calendar year for PSURs covering 3 years?

The breakdown of sales volumes by calendar year is especially useful for NCAs. For example, for comparison of incidence between products especially generic versus originator.

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39. When should third country reports be taken into account for incidence calculation?

This is not a requirement in Volume 9B, however, such information could be included in PSURs when relevant and justified. When necessary, such information could be requested by NCAs.

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Further explanation concerning exposure and incidence calculations according to Volume 9B

The terminology used for incidence calculations is not consistent in Volume 9B and potentially confusing. However, the phrasing used in Volume 9B, especially concerning incidence calculations, was intended to introduce flexibility for applying the recommendations as required, when appropriate and where justified. In general, competent authorities value consistency in the methodology used for calculating exposure and incidence for PSURs. It is acknowledged that the transition from Volume 9 to Volume 9B naturally introduced a change in the approach for incidence calculations which would need to be applied for consecutive PSURs for the same product. However, it is emphasised that deviations from the recommendations in Volume 9B should be justified and preferably explained from the outset in the PSUR.

Recommended actions

40. What is the most effective way to ensure recommendations to amend the SPC and product literature are implemented by the MAH?

Assessors are advised to consult their legal/regulatory departments to explore the opportunities available according to legislation.

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41. Is it an obligation for the MAH to indicate in the PSUR the changes to the SPC and product literature made in other EU Member States and in third countries during the PSUR period covered?

Yes, the MAH should include in the PSUR the changes made to the SPC and product literature i.e. in the section 'Update of regulatory or Marketing Authorisation Holder actions taken for safety reasons'. This applies to all changes related to safety issues. This includes also withdrawal periods and environmental issues. It is recommended that when the SPC has changed significantly in matters relevant to safety during the period covered, the nature of the change(s) should be succinctly explained in the PSUR.

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42. When a competent authority (CA) recommends amendments to the SPC and product literature for a nationally authorised product which is authorised also in other EU Member States, should the CA inform those EU Member States?

It depends on the marketing authorisation (MA) procedure through which the VMP was authorised and the nature of the amendments to the SPC and product literature. For purely nationally authorised products, this may not be necessary (see also below). For products authorised through the mutual recognition procedure or decentralised procedure (MRP/DCP), the reference Member State (RMS) should coordinate the process of informing concerned member states on the conclusion of the PSUR assessment report and recommendations on the need for any regulatory action or other action required (see also below).

However, in certain circumstances, as indicated in Article 78 of Directive 2001/82/EC, and as indicated in Volume 9B within the guidance given on Rapid Alerts and Non Urgent information notifications, NCAs have a responsibility to inform each other of recommended amendments to the SPC and product literature for non centrally authorised products.

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43. Should the rapid alert (RA) or non-urgent information system(NUIS) be used when, after assessment of PSURs, a CA recommends amendments to the SPC and product literature for a national authorised product which is authorised also in other EU member states?

Under certain circumstances, e.g. where the provisions outlined in Article 78 of Directive 2001/82/EC apply, it may be appropriate to use the RA system. In other circumstances, it may be possible to use the NUIS. For further guidance on the use of the RA and NUIS, please refer to Volume 9B.

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44. Do amendments recommended to the SPC and product literature for a nationally authorised product lead automatically to an Article 78 procedure (of Directive 2001/82/EC)?

Only in the case of restriction of the indications or availability, amendment of the posology, addition of a contraindication or addition of a new precautionary measure. The Article 78 procedure is not applicable to changes in withdrawal periods, addition of adverse reactions or changes in frequencies of adverse reactions.

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45. Is it acceptable to delay implementing changes recommended to the product information? For example due to the so-called 'Weber effect?

No it is not acceptable, implementation of recommendations to amend the product information should be implemented as required by the relevant competent authority.

Go back

References

- Committee for Medicinal Products for Veterinary Use (2004) Guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products – to be replaced by Recommendation on harmonising the approach to causality assessment for adverse events to veterinary medicinal products when available (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004995.pdf)
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