Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary

EMEA/CMDv/408477/2007
12 March 2009

CMDv/BPG/014

BEST PRACTICE GUIDE

for

Handling of Periodic Safety Update Reports

Edition number : 00

Edition date: 12 March 2009

Implementation date : 27 March 2009

CMD(v) Secretariat:
7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax. (44-20) 74 18 86 70

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1. INTRODUCTION

Pharmacovigilance for veterinary medicinal products (VMP) is based on the framework laid down in Community legislation in the provisions of Title VII of Directive 2001/82/EC as amended by Directive 2004/28/EC

As described in Article 73 of Directive 2001/82/EC as amended, each Member State (MS) shall have in place a pharmacovigilance system for collection of information useful in the surveillance of VMPs. MS shall communicate information to other MSs and the Agency in accordance with Articles 73 and 76(2)[1] of Directive 2001/82/EC as amended.

Marketing Authorisation Holders (MAH) are required to systematically collect and evaluate information on safety data relating to their VMPs in accordance with Article 74 of Directive 2001/82/EC as amended.

In addition, MAHs should provide Competent Authorities with an update of the world-wide safety experience of a VMP. MAHs are expected to provide summary information on all adverse reactions and their causality assessment. They should address the benefit-risk balance of the product in the light of any new or changing pharmacovigilance information. This 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.

In accordance with Article 75(5) of Directive 2001/82/EC as amended, 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, or immediately upon request. In the light of experience gained with the operation of veterinary pharmacovigilance, requirements for PSUR reporting frequency might be amended by Comitology procedures in accordance with Article 75(6) of Directive 2001/82/EC as amended.

If, in accordance with Article 75(7) of Directive 2001/82/EC as amended, a MAH seeks to amend the frequency with which PSURs for a VMP authorised in accordance with the Directive are submitted to the relevant Competent Authority(ies), such an application should be supported by reasoned argument.

2. AIM AND SCOPE

This Best Practice Guide has been prepared in order to define what should be done by the Reference Member State (RMS) and the Concerned Member States (CMS) regarding handling of PSURs for VMPs authorised via the MRP or DCP.

Guidance is given on the role of the RMS as co-ordinator of PSUR submission and assessment and the role of CMS in relation to reviewing and commenting on PSURs and PSUR assessment reports (AR). This will ensure the submission and assessment of the

[1] Article 76(2) of Directive 2001/82 as amended refer only to 15-day reporting adverse reactions (serious ones and human adverse reactions)

PSURs as well as the follow-up of the conclusions and recommendations of RMS/CMS in an efficient and timely manner.

3. REFERENCES AND RELATED DOCUMENTS

- Directive 2001/82/EC as amended by Directive 2004/28/EC
- The Rules Governing Medicinal Products in the European Union, Volume 9B - Pharmacovigilance for Medicinal Products for Veterinary use[2]
- Recommendation on Management and Assessment of Periodic Safety Update Reports (PSURs) of Veterinary Medicinal Products (EMEA/CVMP/PhVWP/4550/2006)

4. GENERAL

For VMPs authorised via the MRP or the DCP in accordance with Directive 2001/82/EC as amended PSURs should be submitted to the competent authorities of all concerned Member States in accordance with Article 75(5) of Directive 2001/82/EC.

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

For products authorised using the MRP or DCP, the RMS takes the lead role for assessing the PSUR and is responsible for drafting an assessment report (AR) in accordance with agreed time-tables (Annex I) and the Recommendation on Management and Assessment of PSURs of VMPs The CMS are invited to comment on this draft for the finalisation of the AR.

5. DESCRIPTION OF THE PROCEDURE

For all communication with the CMS, the PSUR-V eudranet mailbox should be used.
A 60 or 90 day time-table is proposed. These time frames are recommended timelines.

5.0 Timetable for submission

For products authorised through the MRP or DCP, the PSUR submission schedule should be agreed on between RMS and MAH at the end of a MRP or DCP and be the same for all involved NCAs. The PSUR cycle (Data lock points (DLP)[3]) 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)

The PSUR submission schedule to be followed in the CMS is the one in place in the RMS, unless otherwise agreed during the MRP or DCP. DLP and the date of PSUR submission

[2] Volume 9B is under development

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

should be communicated as part of the Day 90/Day 210 of MR/DC procedures concluding e-mail.

Circumstances where less frequent submission of PSURs may be appropriate include: Products authorised through line-extensions to existing VMPs; newly authorised generic VMPs.

5.1 Submission

Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the DLP.

The MAH will submit the PSUR simultaneously to the RMS and CMS.

5.2 Assessment phase

Precondition for the assessment of a PSUR is that structure and content of the PSUR are in compliance with the requirements of Part I of Volume 9B of the Rules Governing Medicinal Products in the European Union.
The RMS should confirm the receipt of the PSUR documentation to the Applicant.

Within four weeks from the receipt of the PSUR the RMS should start the assessment.

Within 40 days from the start of the assessment the RMS should assess the submitted PSUR and prepare a preliminary PSUR AR in accordance with the Recommendation on Management and Assessment of PSURs of VMPs.
The preliminary PSUR AR should be circulated to all CMS (via PSUR-V mailbox).

CMSs should clearly express their position on the preliminary PSUR AR as well as the conclusions and recommendations of the RMS by day 55 (according to the flow-chart below). If a CMS does not accept the conclusion and/or recommendation presented by the RMS, the CMS should give the grounds for its position in the day 55 comments and clearly indicate, what kind of supplementary information (if any) is required from the MAH.

If a CMS sends no comments, the RMS will consider that the CMS accepts the proposal of the RMS.

If the PSUR as submitted is acceptable to the RMS and the CMS (no change to the benefit/risk profile and no further information is required), the preliminary PSUR AR can be saved as the Final PSUR AR and circulated to all CMS and the Applicant. The procedure can be concluded at Day 60.

If comments from CMS were received, which do not require additional information from the MAH, the RMS includes these comments and circulates the Final PSUR AR. If no further comments are received within 5 days the Final PSUR AR is considered accepted.

If the RMS or any of the CMS does not endorse the PSUR provided by the MAH, the RMS will compile a list of all RMS/CMS questions/comments and send it to the MAH as a Request for Supplementary Information (RSI) by day 59, together with the preliminary PSUR AR. A copy will be circulated to the CMS. If necessary, an updated PSUR may be requested. The

RMS should give a clear deadline to the MAH for submitting the response to the RSI (maximum 60 days). The RMS will stop the clock during this period.

After receiving the supplementary information from the MAH, the RMS assesses the new data and prepares the draft Final PSUR AR. The draft Final PSUR AR with an overall conclusion on the benefit/risk balance of the product and a clear recommendation on the need for regulatory action should be circulated by the RMS within 60 days of receipt of the response. The clock is restarted when the draft Final PSUR AR is circulated to all CMS for comments.

All CMS shall indicate their position and inform the within 25 days following receipt of the draft Final PSUR AR. Any comments received from CMS shall be considered by the RMS and the procedure should be concluded at day 90.

The PhVWP-V is available for advice on any PSUR for MRP or DCP products. Any question in relation to a PSUR AR will, if requested by RMS and CMS, be discussed at the next PhVWP-V meeting. The question to the PhVWP-V needs to be clearly formulated.

5.3 Outcome of the procedure

The Final PSUR AR, including conclusion and clear recommendations on the need for any regulatory action or action required from the MAH should be sent by the RMS to the MAH and the CMS.

The concluding e-mail should include:

- Proposals for an implementation plan, if any regulatory action is required. Implementation planned to be discussed with the MAH and agreed with CMS.
- The date of submission for the next PSUR.

6. ABBREVIATIONS

AR	Assessment Report
CMS	Concerned Member State
DCP	Decentralised Procedure
DLP	Data Lock Point
IBD	International Birth Date
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
MS	Member State
NtA	Notice to applicants
PhVWP-V	Pharmacovigilance Working Party veterinary
PSUR	Periodic Safety Update Report
RMS	Reference Member State
RSI	Request for Supplementary Information
VMP	Veterinary Medicinal Product

ANNEX I

Timetable for Handling Periodic of Safety Update Reports (PSURs)

	Receipt of the documentation, Confirmation to the Applicant,
Day 0	Start of the assessment phase by the RMS (within one month after receipt)
Day 40	RMS circulates a preliminary PSUR AR including conclusions and recommendations to the CMS
Day 55	CMS send any comments on the preliminary PSUR AR to the RMS.
Day 59/60	In absence of comments, there is no need to re-circulate a revised assessment as the final AR. An e-mail indicating that no comments have been received and that the preliminary AR is the Final AR is sufficient. If comments from CMS were received, which do not require additional information from the MAH, the RMS includes these comments and circulates the Final PSUR AR. If no further comments are received within 5 days the FAR is considered accepted. If necessary, RMS sends any RSI to the MAH and the CMS, **clock stop**
Clock off period	Should not be longer than **60 + 60** days (60 days for the MAH to provide the responses and 60 days for the RMS to prepare the draft Final PSUR AR)
Day 85	CMS send final position to the RMS
Day 90	End of the procedure, RMS sends Final PSUR AR, including conclusion and clear recommendations on the need for any regulatory action or action required from the MAH to the MAH and the CMS. RMS provide a proposal for an implementation plan if any regulatory action is required to the MAH and the CMS