EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Compliance and Inspections

Pre-submission instruction on the detailed description of the pharmacovigilance system of a marketing authorisation holder; to be submitted with a marketing authorisation application for a veterinary medicinal product

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1. Introduction

Pharmacovigilance (PhV) involves the detection, understanding and prevention or minimisation of the severity of adverse reactions caused by medicinal products. A PhV system enables the collection, monitoring, assessment and evaluation of information related to adverse events. A Marketing Authorisation Holder (MAH), or proposed MAH, is required to develop such a system and provide a description of that system as part of a Marketing Authorisation Application (MAA). This description must include sufficient information to give assurance to the EU Regulators [the National Competent Authorities (NCAs) in European Member States and the European Medicines Agency (EMA)], that the MAH has an effective system. For the purposes of this document, 'MAH' also refers to 'proposed MAH' where appropriate. This document provides clarification and further explanation of the requirements for a detailed description of the PhV system (DDPS) given elsewhere[1], and describes how the information should be presented in a MAA. It is applicable for any veterinary medicinal product[2], whatever the authorisation procedure used, whether European or National. The DDPS should cover the MAA in question, but where the details differ from the standard system, these particulars must be provided in a Product Specific Addendum (See section 4.8 and appendix D).

The DDPS provides evidence that the MAH has the services of a qualified person responsible for PhV (QPPV), and the necessary means for the notification of adverse events (AE). It is important to remember that the MAH is ultimately responsible for ensuring that all PhV obligations are fulfilled, even if PhV activities are sub-contracted. If a MAH uses a 3rd party (e.g. contractor, licensing partner or other company) for processing PhV information, this must be explained in the DDPS (See final paragraph of section 4.2.2).

The DDPS is a document created for the purpose of assuring the EU Regulators that an effective system is in place at the time of an MAA, and will be checked during a PhV inspection. A Standard Operating Procedure (SOP) for PhV is not equivalent to a DDPS and is not considered acceptable for inclusion in a MAA.

The document should describe all the essential elements of an effective PhV system, but should not include unnecessary information. Step-by-step descriptions of procedures must be laid out in written procedures, e.g. SOPs, and these may be requested at any time by the EU Regulators for inspection or assessment. However, they should not be included within the DDPS. (Inclusion of unnecessary information leads to the need for variations should that information be changed or removed at a later date.)

EU Regulators may request information additional to the contents of the DDPS per se. This should be supplied separately, normally within 2 working days, and should not form part of the DDPS.

Some Member states, due to their national legislation, may require the QPPVs to have specific qualifications or experience. Please contact the Member state in which your QPPV resides to enquire of their requirements.

[1] Eudralex - Volume 9B, 'Guideline on monitoring of compliance with PhV regulatory obligations and PhV inspections for veterinary medicinal products' http://ec.europa.eu/health/files/eudralex/vol-9/pdf/2007_0327_vol9b_guidelines_en.pdf

[2] Subject to any product specific amendments, if applicable (see section 4.8 and appendix D) http://ec.europa.eu/health/files/eudralex/vol-9/pdf/2007_0327_vol9b_guidelines_en.pdf

2. Scope of the DDPS

The description should explain how the PhV system described applies to the proposed MAH, particularly if the PhV system spans a number of differently named subsidiaries and their parent company, and any one of those companies may be the MAH for a particular MAA. MAHs should provide a brief description of the organisation of the companies/subsidiaries/affiliates that may fulfil the role of MAH and are directed by the PhV system described. It should be clear that the MAH named in the MAA is governed by the PhV system. The description should be written so that it can be applied to any MAA, whatever the authorisation procedure or whichever of multiple MAHs is the MAH for a particular MAA. See Appendix A for examples of different company arrangements.

3. Location of the DDPS in the MAA and update of the DDPS

The DDPS of the MAH is submitted in Annex 5.20 of Part IA of a MAA[3]. It should be version-controlled and dated to enable the tracking of updates and corrections. The Notice to Applicants (as above) requires that the CV of the QPPV should also be included in Annex 5.5. Any changes to the DDPS, once the product to which the DDPS applies has been authorised, require a variation[4] or grouped variations.

4. Elements to be included in the DDPS

The DDPS comprises a number of required elements to assure the EU Regulators that the MAH can fulfil responsibility for the PhV of their products and can take appropriate action when necessary. If any of the required elements are not included in the DDPS, the absence should be explained and justified.

4.1. Evidence

Evidence should be presented to show that the MAH has the services of a QPPV and the necessary means for the collection and notification of any AE occurring either in the Community or a third country. The evidence needs to include the following elements:

- A statement, signed by both a representative of the MAH (shown at section 2.4.1 of MAA) and the QPPV (shown at section 2.4.4 of MAA), declaring the availability of the QPPV and the means for reporting AEs (see Appendix B). The representative/person signing the DDPS statement on behalf of the MAH should have the authority to do so. The person signing on behalf of the MAH should not be the same person as the QPPV, unless there is no other suitable person in the MAH.

- *'The name and business contact details of the QPPV within the EEA should be provided'* in section 2.4.4 of the MAA, and not in the DDPS. A list of the contact details of the local PhV contacts or affiliates should be retained by the MAH and may be requested by the EU Regulators. However, this does not form part of the DDPS.

[3] Eudralex - Volume 6B Notice to applicants, Veterinary medicinal products. http://ec.europa.eu/health/files/eudralex/vol-6/b/vol6b_04_2004_final_en.pdf

[4] Commission Regulation 1234/2008 (OJ L334 12.12.2008) http://ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234/reg_2008_1234_en.pdf . and Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ C17 22.1.2010) http://ec.europa.eu/health/files/eudralex/vol-2/c17_1/c17_1_en.pdf

- *'A summary of the Curriculum Vitae of the QPPV with qualifications, training and experience relevant to PhV'* (see Appendix C). The personal and/or business contact details should not be included in the CV. If the QPPV does not hold a veterinary or pharmaceutical qualification, the QPPV should have access to a veterinary surgeon to assist with veterinary assessment of AE reports. Note that lists of scientific publications unrelated to PhV issues should not be included.

- *'A summary of the job description of the QPPV'*, detailing the roles and responsibilities for PhV. Any PhV roles that are delegated to other persons should be listed. Individuals should not be identified by name but by their position in the organisation. Note that roles and responsibilities not related to PhV should not be included. Roles to be included:

    - Establishment and maintenance of PhV system
    - Ensure the accurate recording of AEs
    - Causality assessment of AEs
    - Preparation of AE and Periodic Safety Update Reports (PSUR)
    - Conducting continuous/ongoing/periodic PhV evaluation
    - Timely transmission of reports and provision of other information to EU Regulators, as required
    - Training (i.e. general PhV; VeDDRA terminology; preparation of PSURs).

- Confirmation that alternative or back-up arrangements have been made to manage PhV activities during the absence of the QPPV, and a brief description of those arrangements. If a specific deputy is identified, this should not be by name, but by their position in the organisation. Note that EU Regulators may request the name and contact details of a deputy separately. This information would not be part of the DDPS.

- *'A copy of the registration[5] of the QPPV with the EudraVigilance Veterinary system'* or a letter from the EMA confirming registration, if appropriate[6]. Ensure any password is masked. A copy of a EudraVigilance training attendance certificate is not acceptable as proof of registration. MAHs should check with individual EU Regulators, and the Eudravigilance website[7], to ensure that the national requirements for electronic reporting are satisfied, as they can vary between EU Regulators.

4.2. Organisation

The functional organisation and responsibilities of all units involved in PhV, from the MAH to the point at which the product is received by the customer, should be described. The system description needs to outline the role of the MAH and whether the MAH is the parent company or a subsidiary/affiliate. If the PhV procedures vary with the identity/location of the MAH, the differences should be described. A high level organisation chart should be provided if it helps to clarify the description.

[5] Log in to EudraVigilance Veterinary website at http://eudravigilance.ema.europa.eu/veterinary/index.html using personal log-in credentials. Select 'Manager Profile', 'Printable version' and print page.
[6] Where a MAH receives only a small number of serious SAR reports, then registration for Eudravigilance may not be necessary. However, this should be clarified with the NCA concerned. Note that this is only likely to apply to National MAs. http://eudravigilance.ema.europa.eu/veterinary/mah.html
[7] http://eudravigilance.ema.europa.eu/veterinary/reporting.html

4.2.1. Locations, Relationships and Roles

The following elements are required:

- *'The identification and location of the company units or other organisations involved in the principal EEA and global PhV activities.'* Specific affiliates/distributors should not be listed in the DDPS, but the information must be provided separately at the request of the EU Regulators.

- *'The point(s) in the Community at which PhV data e.g. AEs, PSURs and global PhV data may be accessed must be identified.'* This may be described or indicated in the organisation chart (See 4.2 above) and/or diagram(s).

- *'The location of the main databases involved in PhV'.* A database on a server outside the EEA is acceptable provided it can be accessed from within the EEA.

- The relationships between the different units involved in pharmacovigilance activities e.g. distributors/contractors, local offices/affiliates, head offices/parent companies where appropriate. To include:

    - The location and roles of each unit e.g. head office, local office etc. should be described, identifying which is responsible for data gathering, recording, assessment, reporting and archiving.

    - Reporting interactions and the position of the EEA/national QPPV or local PhV contacts within the organisation must be described. The MAH should clarify whether the QPPV is directly employed by the MAH or subcontracted.

- A summary of the PhV activities conducted at each unit, e.g. receipt of AEs, collection and follow-up of AE information, assessment of seriousness and causality, storage of AEs, preparation of PSURs etc.

4.2.2. Processes and Contractual Arrangements

The following elements should also be described:

- '*The flow of AE report information*' e.g. spontaneous AEs and PSURs '*from the source to the point of receipt by the EU Regulators'* should be described and/or depicted in one or more diagrams showing the timelines involved. The capture of the EU Regulator's case reference should be shown or described. The following should be included, where appropriate:

    - Different types of AE reports
        - Animal AEs including safety, lack of efficacy and unauthorised use
        - Human AE reports
        - Potential environmental problems
        - Investigation of the validity of withdrawal periods
        - Transmission of any infectious agent via a veterinary medicinal product
    - Different sources

- Person administering veterinary medicinal products (owner/farmer)
- Human/animal healthcare professionals
- EU Regulators
- Literature searches

o Different types of reporting (describe legislative reporting procedures including timelines)
- Expedited reports (Serious animal AEs and all human AEs)
- Non-expedited reports (PSURs)

- *Agreements with other organisations, such as co-marketing partners and PhV sub-contractors should be identified and responsibilities for PhV activities briefly described.* It should be clear which organisation is responsible for which PhV activities including translation of primary records, veterinary evaluation and VeDDRA coding as appropriate. However, the actual agreements should not be included in the DDPS.

4.3. Written procedures

It is essential that a PhV system is controlled by clear written procedures, including SOPs if appropriate. Quality management is an essential feature of any system reliant on data. Checking and cross-checking are important steps in the management of data and should be included in written procedures. Assurance should be provided that all relevant topics are covered, or will be by the time the product is marketed. If any topic is not covered, an explanation should be provided. Copies of written procedures or SOPs should not be included in a MAA, nor should the specific titles, numbers or version dates of the SOPs. The Commission guideline provides a full list of the topics that would be expected to be covered by written procedures. However, from the experience of EU Regulators, some topics require further clarification and these are listed below.

- The collection from all sources, follow-up, processing, quality control (including duplicate detection), assessment, classification, veterinary/scientific review, and reporting (including expedited and electronic reporting) of AEs.
- Communication with EU Regulators and animal health professionals regarding changes to benefit-risk balance of products and requests for information.
- Interaction between safety issues (PhV) and product defects (quality) i.e. product defects that could lead to PhV issues
- Staff training.

Note that one or more topics may be covered by a single written procedure, or a single topic may be included in more than one written procedure.

4.4. Databases

The means by which PhV data is recorded should be described, whether paper records, spreadsheets, a database developed in-house or a proprietary database. EU Regulators are flexible as to whether a MAH has an electronic database, depending on the number of reports the MAH receives. However, EU Regulators would prefer all MAHs to have some form of electronic storage for PhV data e.g. spreadsheets. Note that the description should be brief and technical specifications of the database should not be included. The Commission guideline outlines the topics that would be expected to be

included. However, they are individually listed below, with additional information where appropriate, for clarification purposes:

- *'The means of PhV data storage should be identified and briefly described.'*
- *'A statement that the electronic database(s) has been validated.'*
- If the database is capable of assisting the compilation of safety reports and performing expedited and electronic reporting this should be described. The method(s) of electronic reporting, of cases occurring in both the EEA and 3rd countries, via the EudraVigilance Gateway, EVWeb, MAH Simplified Electronic Reporting Form (SERF) or other method, must be indicated. Further information can be obtained from the Eudravigilance veterinary website [7].
- *'A statement regarding the compliance of the systems with internationally agreed standards'*, i.e. data elements e.g. VeDDRA, species, breed etc., *'for electronic submission of AE reports[8]'.* This should be provided, if appropriate.
- The MAH should describe the tools or approaches used for detecting signals.
- *'The person or group responsible for the operation and management of the database should be indicated.'*

It is also preferable that MAHs have databases for the control of submission of PSURs, for product information and for recording of sales information etc.

4.5. Training

Describe the PhV training given to all personnel, including contractors, who may be involved in PhV. Personnel, should only be identified by their position in the organisation, not by name.

- Briefly describe the training system.
  - Describe the type and frequency of training given, and the post holder who provides it.
  - Specify who e.g. technical staff, sales, customer services etc. is trained by whom.
  - *State where the training records of trainees and the CV and job description of the trainer(s) are filed.*

Note that copies of personal training records should not be included in the DDPS.

4.6. Document storage and archiving

PhV documentation should be stored securely. The location of documentation including original AE reports from the primary source, PSURs, QC records relating to AE processing, SOPs and training records etc. should be identified. Also, the site where product sales figures can be accessed for PhV should be identified. The length of time for which paper copies of original reports are archived in the EEA should be indicated. The EU Regulators would expect this to be at least for the life of the product plus some time (to allow for expiry of the product). EU Regulators may request the identification of

[7] http://eudravigilance.ema.europa.eu/veterinary/reporting.html
[8] Guideline on data elements for the electronic submission of adverse reaction reports related to VMPs authorised in the EEA http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017761.pdf

the post holder(s) responsible for archiving, and a description of the validation and quality standards applied to archiving, but this should not form part of the DDPS.

4.7. Quality Management

The overall system should be briefly described, outlining the elements that are covered – as per the Commission guideline. These should include the use of written procedures. Note that, although it may be helpful, there is no requirement for certification to a particular standard. During the assessment of the DDPS additional information or assurance about the Quality Management system may be requested by the EU Regulators, but it should not form part of the DDPS.

4.8. Product specific addendum

Whilst not part of the main system description, this should be provided, if appropriate, in section 5.20 of the MAA in an Annex to the MAH DDPS. Risk management systems or post-authorisation requirements should be included here if appropriate. Where appropriate, a brief description should be given of the nature of any agreements for sub-contracting and co-marketing/co-licensing, specifying regulatory responsibilities and PhV activities. In particular, the co-marketing arrangements within the EEA should be identified and the distribution of the major responsibilities between the parties should be clarified. If there are no subcontracting, co-licensing or co-marketing arrangements within the EEA for the product that is the subject of the product-specific MAA, the MAH should include a clear statement to this effect.

The MAH should identify precisely how the normal system is amended to accommodate the specific product. See Appendix D for an example.

Appendix A – Scope of the DDPS

Examples of different company arrangements that could be described in the DDPS of an MAH.

Example 1. *A small company present in one EEA country with products only authorised in that country.*

Company A, located at one site in the UK, has a number of nationally authorised products, which are sold through wholesalers or veterinary surgeons.

Example 2. *A small company present in one EEA country with products authorised in other EEA countries.*

Company C, based entirely in Belgium, markets its products in Belgium through local wholesalers and in other EEA countries through distributors, either under the MAH's name or the distributor's name.

Example 3. *A larger company, based in one EEA country, but with local subsidiaries in some other EEA countries, which may be MAH of some products.*

Company D, based in an EEA country with subsidiary companies in other EEA countries, markets its products through distributors in those countries where it does not have a local presence. National subsidiary companies are MAH for some products.

Example 4. *A global company based in a non-EEA country, with national subsidiary companies in some EEA countries. These subsidiaries will be MAHs. A global DDPS is submitted.*

Company F, based in the USA with subsidiary companies in some EEA countries, markets its products through distributors in others.

Example 5. *A company that subcontracts its PhV activities to a third party.*

Company G, based in France, with other named sub-companies (affiliates) in France, subsidiary companies in other EEA countries and uses a third party for processing PhV information. Any of the affiliates or subsidiaries may be MAH, but their company name does not indicate that they may be related to Company G.

Appendix B – Statement signed by MAH and QPPV

Statement regarding services of QPPV and availability of necessary means for notification of Adverse Events.

a) Where the DDPS applies directly to the MAH and the declaration is signed by a representative of the MAH (Company A).

The applicant and the QPPV declare that the applicant has the services of a Qualified Person responsible for PhV (QPPV) and has the necessary means for the collection and notification of any adverse reaction suspected of occurring either in the Community or in a third country.
Signed — Signed
For and behalf of Company A (MAH) — QPPV Date: dd/MMM/yy

b) Where the DDPS belongs to a parent company (A) and the declaration is signed by a representative of the parent company, but the MAH (B) is an affiliate, or similar, of that parent company.

[Parent company name (company A], including any affiliates, and the QPPV declare that the applicant has the services of a Qualified Person responsible for PhV (QPPV) and has the necessary means for the collection and notification of any adverse reaction suspected of occurring either in the Community or in a third country.
Signed — Signed
Company A — QPPV Date: dd/mm/yy
Signed
Company B (MAH) — Date:

Appendix C – Curriculum vitae of the QPPV

Curriculum vitae of the QPPV

Contact details

Name:	Dr Jo Brown
Address:	A Company Regulatory Affairs

Qualifications

1986	Degree in Veterinary Medicine Bristol University

Professional experience

2005 - present	Regulatory affairs manager and QPPV at A Company
2000 - 2005	Regulatory affairs officer at A Company
1996 - 2000	Senior partner in mixed practice
1988 - 1996	Junior partner in mixed practice
1986 - 1988	*Locum* veterinary surgeon in small animal practices

Courses and conferences etc.

2006	PhV for the Veterinary Industry	Management Forum, London

Appendix D – Product specific addendum

Product name (National)
Type of Marketing Authorisation (National/MRP/DCP/EUCE)
Marketing Authorisation Holder

Product specific details:

- Scope
    - Identification of position of MAH in organisation described in 2.3
- Evidence
- Organisation
    - QPPV (national and/or EEA) and position in organisation
    - Product specific agreements for sub-contracting and/or co-marketing etc for PhV
    - Named Distributors
    - Differences, from main description, in responsibilities for PhV activities
- Databases
- Training
- Document Storage and Archiving
- Written procedures