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# VOLUME 9B

# of The Rules Governing Medicinal Products in the European Union

– Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use –

# GENERAL OUTLINE OF CONTENTS

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# Introduction

## 1. Legal Basis and Structure of Volume 9B (Veterinary Pharmacovigilance)

Pharmacovigilance has been defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. This principle also applies to medicinal products for veterinary use (VMPs).

Article 77 of Directive 2001/82/EC specifically requires the European Commission in consultation with the European Medicines Agency ("the Agency"), Member States (MS) and interested parties to draw up guidance on the collection, verification and presentation of adverse reaction reports in order to facilitate the exchange of information about veterinary pharmacovigilance within the EU. Iceland, Liechtenstein and Norway have through the Agreement of the European Economic Area (EEA) adopted the complete acquis communautaire (i.e. the legislation at the EU level, guidelines and judgements) on medicinal products, and are consequently parties to the EU procedures. Similarly, Article 51 of Regulation (EC) No 726/2004 includes a requirement for the Commission, in consultation with the Agency, MS and interested parties to draw up a guide.

This guidance is required to include technical requirements for the electronic exchange of pharmacovigilance information in accordance with internationally agreed formats. In addition, the European Commission is also required to publish a reference to an internationally agreed medical terminology.

This Volume 9B has therefore been prepared by the European Commission in close consultation with the Agency, MS and interested parties and is specifically related to veterinary pharmacovigilance concerning VMPs. It brings together general guidance on the requirements, procedures, roles and activities in this field, for Marketing Authorisation Holders (MAHs), National Competent Authorities (NCAs), the Agency and the European Commission.

The definitions of 'adverse reaction', 'serious adverse reaction', 'human adverse reaction' and 'unexpected adverse reaction' are provided in Article 1 of Directive 2001/82/EC, as amended, and in the Glossary (see Annex 1. Glossary).

The definitions of 'adverse event', 'serious adverse event' and 'unexpected adverse event' are provided in the Glossary (Annex 1. Glossary) and are based on the agreed terminology within VICH.

Generally, except when reference is made to the legal framework, the term "adverse event" replaces the use of the term "suspected adverse reaction" throughout this document.

Volume 9B is presented in four parts:

Part I Guidelines for Marketing Authorisation Holders;
Part II Guidelines for Competent Authorities and the Agency;
Part III Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance in the EU;
Part IV Guideline on Public Communication on Medicinal Products for Veterinary Use.

It should be noted, as with all guidance documents in rapidly evolving technical areas, that this guidance is intended to be regularly reviewed and updated, with publication on the European Commission's website: http://ec.europa.eu/health/veterinary-use/index_en.htm

## 2. Legal Framework for Pharmacovigilance

The legal framework for pharmacovigilance of medicinal products for veterinary use (VMP) in the European Union (EU) is given in Regulation (EC) No 726/2004[1] and Directive 2001/82/EC[2] on the Community code relating to medicinal products for veterinary use, as last amended by Directive 2004/28/EC[3] (hereafter referred to simply as Directive 2001/82/EC). It should be noted that although Title III Chapter 3 of Regulation (EC) No 726/2004 and Title VII of Directive 2001/82/EC contain the majority of pharmacovigilance provisions in the legislation, other measures directly relevant to the conduct of pharmacovigilance are also found in other Chapters and Titles of those legislative texts.

The pharmacovigilance obligations apply to all VMPs authorised in the EU, including those authorised before 1 January 1995 and whatever procedure was used for their authorisation.

Article 73 of Directive 2001/82/EC, describes the obligations of the National Competent Authorities (NCAs) of Member States (MS) to administer a system for pharmacovigilance in order to collect, collate and evaluate information about suspected adverse reactions. Article 74 of Directive 2001/82/EC and Article 48 of Regulation (EC) No 726/2004 describe the obligation of MAHs for the establishment and maintenance of a pharmacovigilance system. All relevant information should be shared between the NCA and the MAH, in order to allow all parties involved in pharmacovigilance activities to assume their obligations and responsibilities. The European Medicines Agency (the Agency) and the NCAs cooperate to continuously develop pharmacovigilance systems capable of achieving public health protection for all VMPs, regardless of routes of authorisation, including the use of collaborative approaches, to maximise use of resources available within the EU, in accordance with Article 53 of Regulation (EC) No 726/2004. This requires an intensive exchange of information between the MAH, the NCA, the Agency and the European Commission, as well as procedures to avoid duplication, maintain confidentiality and ensure the quality of the systems and data.

As explained previously, Iceland, Liechtenstein and Norway have through the Agreement of the European Economic Area (EEA) adopted the complete acquis communautaire (i.e. the legislation at the EU level, guidelines and judgements) on medicinal products, and are consequently parties to the EU procedures. Consequently, the Guideline does not only apply with regard to the MAHs obligations towards the Agency or NCAs in MS of the EU but also to those towards the States Iceland, Liechtenstein and Norway. Likewise they apply to the NCAs in these States themselves.

[1] OJ L 136, 30.4.2004, p.1.
[2] OJ L 331, 28.11.2001, p. 1.
[3] OJ L 136, 30.04.2004, p. 58.

# 3. The Roles of the Various Parties

## 3.1 The Marketing Authorisation Holder

The MAH must ensure that it has an appropriate system of pharmacovigilance and risk management, where appropriate, in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary (see PART I: Guidelines for Marketing Authorisation Holders).

## 3.2 The Competent Authorities

### 3.2.1 The National Competent Authorities

The authorities of the MS are the NCAs for VMPs authorised nationally through national procedures, including the mutual recognition and decentralised procedure. The responsibilities for pharmacovigilance rest with the NCAs in which the marketing authorisations are held. In addition the MS are the supervisory authorities for CAPs (see Part II: Guidelines for Competent Authorities and the Agency).

### 3.2.2 The European Commission

For VMPs authorised through the centralised procedure the European Commission is the CA. The European Commission is responsible for the adoption of Decisions on the basis of Committee for Medicinal Products for Veterinary Use (CVMP) Opinions relating to VMPs authorised through the centralised procedure and those products subject to the procedure of Articles 36, 37 and 38 of Directive 2001/82/EC. The European Commission also has responsibilities for the overall EU system of pharmacovigilance and for the legal framework.

## 3.3 The European Medicines Agency

The European Medicines Agency (the Agency) is a decentralised body of the European Union. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

The Agency is responsible for the scientific evaluation of applications for European marketing authorisation for VMPs (centralised procedure). The safety of VMPs is monitored constantly by the Agency through a pharmacovigilance network and the main scientific work of the Agency is conducted by its CVMP. The Agency takes appropriate actions if adverse event reports suggest changes to the benefit-risk balance of a VMP.

## 3.4 The EU Pharmacovigilance System

### 3.4.1 The Role of National Competent Authorities for Products Authorised Through National Procedures

In accordance with Article 73 of Directive 2001/82/EC each MS administers a pharmacovigilance system, for the collection and evaluation of information relevant to the benefit-risk balance of VMPs. The NCA continually monitors the safety profile of the VMPs available on its territory, takes appropriate action where necessary and monitors the compliance of MAHs with their obligations with respect to pharmacovigilance. The NCA should ensure that MAHs implement, when appropriate, risk management systems to effectively monitor and manage risks associated with the safety of their VMPs. Furthermore, the NCA should ensure that pharmacovigilance data are shared between MS and the Agency via the data-processing network EudraVigilance Veterinary (EVVet) (see Part II: Guidelines for Competent Authorities and the Agency and Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

### 3.4.2 The Role of the National Competent Authorities of the Reference Member State for Products Authorised through the Mutual Recognition or Decentralised Procedure

The responsibilities of pharmacovigilance rest with the NCA of all MS in which the Marketing Authorisations (MAs) are held for a VMP. For practical reasons, the NCAs agree that the Reference Member State (RMS) will normally take the lead for VMPs authorised through the mutual recognition or decentralised procedures and responsibility for assessing safety concerns, in accordance with an agreed timetable. The RMS takes responsibility for the coordination of communication with the MAH on such matters and for the monitoring of the compliance of the MAH with his obligations with respect to pharmacovigilance. Furthermore, the NCA should ensure that pharmacovigilance data are shared between MS and the Agency via the data-processing network EVVet (see Part II: Guidelines for Competent Authorities and the Agency and Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU). These arrangements do not replace the legal responsibilities of the MAH with respect to individual CAs. (See Part II Chapter 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure)

### 3.4.3 The Role of the Rapporteur for Products Authorised through the Centralised Procedure

The NCAs are responsible for monitoring centrally authorised VMPs (CAPs) in their respective territories (see Part II Chapter 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure). However, the Rapporteur takes the lead in pharmacovigilance, unless otherwise decided by the CVMP. The Rapporteur is responsible for evaluating and producing assessment reports on safety concerns related to a CAP, in accordance with an agreed timetable (See Part II Chapter 2. Centrally authorised products) and for the monitoring of the compliance of the MAH with its obligations with respect to pharmacovigilance.

### 3.4.4 The Role of the European Medicines Agency

The Agency's scientific committee, the CVMP, aided by its Pharmacovigilance Working Party (PhVWP-V), is responsible for evaluating evidence and formulating opinions on emerging safety concerns with CAPs, based on the Rapporteur's Assessment Report.

The role of the secretariat of the Agency is coordination of the supervision, under practical conditions of use, of VMPs which have been authorised within the EU and the provision of advice on the measures necessary to ensure their safe and effective use, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation.

The Agency secretariat is responsible for communicating with the MAHs of CAPs on such concerns (see Part II Chapter 2. Centrally authorised products) and for the coordination of issues relating to the monitoring of the compliance of the MAH with its pharmacovigilance obligations (see Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections).

The role of the Agency secretariat is also one of coordination in the case of referrals made to the CVMP for application of the procedures laid down in Articles 36, 37 and 38 and the procedure for pharmacovigilance urgent measures under Article 78 of Directive 2001/82/EC. The CVMP, aided by the PhVWP, is responsible for evaluating evidence and formulating Opinions on matters referred to it (see Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

### 3.4.5 The Role of the CVMP Pharmacovigilance Working Party

The mandate of the CVMP PhVWP-V (see Annex 4. References) is to provide advice on the safety of VMPs to CVMP and NCAs and the investigation of adverse reactions, in order to enable effective and

harmonised risk identification, assessment and management, especially in the post-authorisation phase.

# PART I: Guidelines for Marketing Authorisation Holders

# 1. General Principles

## 1.1 Legal Basis of the Marketing Authorisation Holder's Obligations for Pharmacovigilance

The legal basis for the Marketing Authorisation Holder's (MAHs) obligations for pharmacovigilance of medicinal products for veterinary use (VMPs) in the EU is given in Regulation (EC) No 726/2004 and Directive 2001/82/EC.

## 1.2 Roles and Responsibilities of the Marketing Authorisation Holder and the Qualified Person Responsible for Pharmacovigilance

The MAH should ensure that it has an appropriate system of pharmacovigilance in place in order to assume responsibility and liability for its VMPs on the market and to ensure that appropriate action may be taken, when necessary. The MAH should therefore ensure that new information relevant to the benefit-risk balance of a VMP is reported to the National Competent Authorities (NCAs) and the European Medicines Agency (the Agency) fully and promptly in accordance with the legislation, in accordance with Article 41(4) of Regulation (EC) No 726/2004 and Article 27(3) of Directive 2001/82/EC.

When applying for a Marketing Authorisation (MA), the Applicant, in preparation for the role and responsibilities as MAH, should submit a Detailed Description of the Pharmacovigilance System (DDPS) in accordance with Article 12(3)(k) of Directive 2001/82/EC and, where appropriate, of the risk management system, and submit proof that the services of a Qualified Person Responsible for Pharmacovigilance (QPPV), are in place, in accordance with Article 12(3)(o) of Directive 2001/82/EC (see Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections).

The MAH should have permanently and continuously at his disposal a QPPV, residing in the EEA.

The role of the QPPV is very important, and this Chapter therefore describes the role and responsibilities of the QPPV and provides guidance for the MAH on how to adequately support the QPPV.

It is preferable that one person is ultimately responsible for all aspects of the pharmacovigilance system of a company, and therefore each company (i.e. Applicant/MAH or group of MAHs using a common pharmacovigilance system) is strongly recommended to appoint one QPPV responsible for overall pharmacovigilance for all VMPs for which the company holds MAs within the EEA (see also Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections).

The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfil the responsibilities and tasks of the post. If the QPPV is not a veterinarian, access to a person qualified in veterinary medicine should be available.

The name and contact details, including out-of-office hours details, of the QPPV and back-up procedures to ensure business continuity and continued fulfilment of pharmacovigilance obligations should be notified to the NCAs in which MAs are held or, for centrally authorised products, to all NCAs and to the Agency.

### 1.2.1 The Role and Responsibilities of the Qualified Person Responsible for Pharmacovigilance

The QPPV is responsible for

- the establishment and maintenance of a pharmacovigilance system which ensures that information about all adverse events which are reported to any personnel of the MAH, is collected and collated in order to be accessible at least at one point within the EEA;
- the preparation for NCAs, where the VMP is authorised, of the reports referred to in Article 75 of Directive 2001/82/EC and in case of CAPs the preparation for the Agency and NCAs of the reports referred to in Article 49 of Regulation (EC) No 726/2004. Detailed guidance for the preparation of these reports are included in Part I:
  - Chapter 4. Adverse Event Reporting,
  - Chapter 6. Requirements for Periodic Safety Update Reports, and
  - Chapter 7. Company-Sponsored Post-Authorisation Safety Studies;
- the conduct of continuous overall pharmacovigilance evaluation during the post-authorisation period (see Part I Chapter 8. Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action);
- ensuring that any request from the NCAs or the Agency for the provision of additional information necessary for the evaluation of the benefits and the risks of a VMP is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the VMP concerned; and
- provision to the NCAs or the Agency of any other information relevant to the evaluation of the benefits and risks of a VMP, particularly information concerning post-authorisation safety studies, including information regarding the validity of the withdrawal period, arising from the use of the VMP, or lack of expected efficacy or potential environmental problems, arising from the use of the VMP.

The QPPV should have oversight of the pharmacovigilance system in terms of structure and performance and be in a position to ensure in particular the above system components and processes, either directly or through supervision.

The oversight referred to above should cover the functioning of the MAHs pharmacovigilance system in all relevant aspects, including

- quality control and assurance procedures,
- standard operating procedures,
- database operations,
- contractual arrangements,
- compliance data (e.g. in relation to the quality, completeness and timelines for expedited reporting and submission of PSURs),
- audit reports and
- training of personnel in relation to pharmacovigilance.

It is recognised that this role of the QPPV may impose extensive tasks on the QPPV, depending on the size and nature of the pharmacovigilance system and the number and type of VMPs for which the MAH holds MAs. The QPPV may therefore delegate specific tasks, under supervision, to appropriately qualified and trained individuals, e.g. acting as experts on the safety aspects of certain VMPs, provided that the QPPV maintains system oversight and overview of the safety profiles of all VMPs. Such delegation should be documented.

In case of absence, the QPPV should ensure that all responsibilities are undertaken by an adequately qualified person. This person should also reside in the EEA.

The QPPV should also act as the MAHs contact point for pharmacovigilance inspections or should be made aware by the MAH of any inspection and be contactable and ideally be available during inspection.

### 1.2.2 Responsibilities of the Marketing Authorisation Holder in relation to the Qualified Person responsible for Pharmacovigilance

The MAH should adequately support the QPPV and ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant information in place for the fulfilment of the QPPV's responsibilities and tasks.

The MAH should ensure that there is full documentation covering all procedures and activities of the QPPV and that mechanisms are in place to ensure that the QPPV may receive or seek all relevant information. The MAH should also implement mechanisms for the QPPV to be kept informed of emerging safety concerns and any other information relating to the evaluation of the benefit-risk balance. This should include information from ongoing or completed clinical trials and other studies the MAH is aware of and which may be relevant to the safety of the VMP, as well as information from sources other than the specific MAH, e.g. from those with whom the MAH has contractual arrangements.

The MAH should ensure that the QPPV has sufficient authority

- to implement changes to the MAHs pharmacovigilance system in order to promote, maintain and improve compliance; and
- to provide input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and, as appropriate, communication to the general public).

The MAH should assess risks with potential impact on the pharmacovigilance system and plan for business contingency, including back-up procedures (e.g. in case of non-availability of personnel, adverse reaction database failure, failure of other hardware or software with impact on electronic reporting and data analysis).

## 1.3 Contractual Arrangements

A MAH may transfer any or all of the pharmacovigilance tasks and functions, including the role of the QPPV, to (an)other person(s) or organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the MAH. In such cases, it is the responsibility of the MAH to ensure that detailed and clear documented contractual arrangements for meeting pharmacovigilance obligations are in place between MAHs and persons or organisations involved in the fulfilment of pharmacovigilance obligations and to provide the CAs and, if applicable the Agency, with information on such arrangements in line with the requirements set out in Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections. The contracted person(s) or organisation should implement quality assurance and quality control and accept to be audited by or behalf of the MAH.

In cases of contractual arrangements between MAHs in relation to co-marketing of separately authorised VMPs, which are identical in all aspects apart from their invented names, these arrangements should include measures to avoid the duplicate submission of adverse events to EVVet.

# 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections

## 2.1 Introduction

The rapid and effective identification and assessment of safety issues concerning VMPs is dependent on early access to complete information. This is fundamental to CAs, the Agency and MAHs ability to protect public or animal health in taking appropriate action swiftly. MAHs, CAs and the Agency have an obligation to implement legislation concerning VMPs. Non-compliance with pharmacovigilance regulatory obligations could have a potentially serious health impact.

This Chapter sets out the framework of the monitoring of compliance with pharmacovigilance obligations and of pharmacovigilance inspections. In the same context it sets out the information to be supplied in the Marketing Authorisation Application (MAA) giving a Detailed Description of the Pharmacovigilance System (DDPS) of the MAH and proof that the MAH has the services of a QPPV and the necessary means for the notification of adverse events. This guidance is applicable for any VMP, whatever the MA procedure used. The inspection process described hereafter focuses on CAPs, however the principles are generally applicable.

## 2.2 Legal basis

### 2.2.1 Roles of the Marketing Authorisation Holder

The MAHs should ensure that they have an appropriate system of pharmacovigilance in place, in accordance with Article 74 of Directive 2001/82/EC and Article 48 of Regulation (EC) No. 726/2004, in order to assure responsibility for their products on the market and to ensure that appropriate action can be taken, when necessary. This includes the MAH having at its disposal permanently and continuously an appropriately qualified person responsible for pharmacovigilance (QPPV) residing within the EEA[4], and the establishment of a system of pharmacovigilance.

### 2.2.2 Roles of the Agency

The roles of the Agency are set out in Regulation (EC) No 726/2004 and further described elsewhere in this guideline. Regarding the monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections, the following are of particular relevance:

- Article 57(1)(c) of Regulation (EC) No 726/2004 stating "coordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation"
- Article 57(1)(i) of Regulation (EC) No 726/2004 stating "coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations"

### 2.2.3 Roles of the National Competent Authorities

The roles of the NCAs are set out in Directive 2001/82/EC, in Regulation (EC) No 726/2004. Title VII of Directive 2001/82/EC sets out requirements for pharmacovigilance.

### 2.2.4 Pharmacovigilance Inspections

The legal basis for the conduct of Pharmacovigilance inspections concerning VMPs is set out in Article 80 of Directive 2001/82/EC, and in Article 44(1) of Regulation (EC) 726/2004.

[4] As explained in the Introduction to Volume 9B, the EFTA States having signed EEA agreement adopted the complete acquis communautaire on medicinal products, and therefore the QPPV may also reside in the EFTA States having signed the EEA Agreement.

### 2.2.5 Detailed description of the pharmacovigilance system to be included in the application for a marketing authorisation

The applicant of a Marketing Authorisation Application (MAA) is required (Article 12(3)(k) of Directive 2001/82/EC) to provide a detailed description of the system of pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce. This guideline addresses the DDPS that must be supplied with the MAA dossier and supporting documentation that the applicant should maintain and supply to the competent authorities on request.

### 2.2.6 Proof of the services of a Qualified Person Responsible for Pharmacovigilance and of the necessary means to notify adverse events, to be included in the application for a marketing authorisation

The applicant is required (Article 12(3)(o) of Directive 2001/82/EC) to provide proof that they have the services of a QPPV and the necessary means for the notification of any adverse event occurring either in the EEA or in a third country (non EEA).

## 2.3 Detailed description of the pharmacovigilance system

### 2.3.1 Location of the detailed description in the application for a marketing authorisation and update of the detailed description

The DDPS, including the proof of the availability of the services of the QPPV and the proof that the MAH has the necessary means for the collection and notification of any adverse event, should be provided in Part 1 of the MAA.

The DDPS should comprise an overview of the pharmacovigilance system providing information on the key elements of that system. Where aspects of the system such as the organisational arrangements are particular to the product rather than the main system of the MAH/company this should be indicated in a product specific addendum.

The DDPS should be supported by documentation maintained by the company.

Updates to the information provided in the DDPS should be made in accordance with current legislation.

### 2.3.2 Statement of the Marketing Authorisation Holder and the Qualified Person Responsible for Pharmacovigilance regarding their availability and the means for the notification of adverse reactions

The applicant should provide a signed statement from the MAH and the QPPV to the effect that the applicant has their services available as QPPV and has the necessary means for the collection and notification of any adverse event occurring either in the EEA or in a third country. This statement may make reference to the DDPS (see below), indicate what is already in place, and confirm which items will be put in place before the product is placed on the market in the EEA.

### 2.3.3 Elements of the detailed description of the pharmacovigilance system that should be described in the application for a marketing authorisation

All MAHs are required to have an appropriate system of pharmacovigilance in place. The DDPS should include the following elements, as applicable, and be set out in a structured manner consistent with this list. Additional important elements pertinent to a specific situation should be added:

a) QPPV
   - The name of the QPPV located in the EEA. The business address and contact details should be provided in the MAA form. Companies might, for example, use a 24-hour telephone number through which the QPPV or their back-up can be reached, diverting it to the appropriate person according to availability.

- A summary Curriculum Vitae (CV) of the QPPV with the key information relevant to their role (main qualifications, training and experience).
- A summary of the job description of the QPPV.
- A description of the back-up procedure to apply in the absence of the QPPV.

b) Organisation

- Identification and location of the company units or other organisations where the principal EEA and global pharmacovigilance activities are undertaken (in particular those sites where the main databases are located, where adverse events are collated and reported and where PSURs are prepared and processed for reporting to the competent authorities). Identification of affiliates may be made in a general sense, rather than affiliate-by-affiliate.
- Identification of the point(s) in the EEA at which pharmacovigilance data are accessible (to include access to adverse events, PSURs and the global pharmacovigilance data).
- High level organisation chart(s) providing an overview of the global and EEA pharmacovigilance units and organisations (identified above) and, illustrating the relationships between them, with affiliate/parent companies, and contractors. The chart(s) should show the main reporting relationships with management and clearly show the position of the EEA QPPV within the organisation. Individual names of people should not be included here. Licensing partnerships are usually product specific and should be indicated in a product specific addendum, in the MAA for that product, unless a partnership is a consistent feature of the company's organisation, across most products.
- A brief summary of the pharmacovigilance activities undertaken by each of the organisations/units identified above.
- Flow diagrams indicating the flow of safety reports of different sources and types. These should indicate how reports/information are processed and reported from the source, to the point of receipt by the competent authorities. These should be limited to the major processes.

c) Procedures in place, which are documented in writing

An essential element of any pharmacovigilance system is that there are clear, written procedures in place. The following list indicates topics that should usually be covered by these written procedures. The DDPS should indicate for which of these topics there are written procedures in place, but should not list the procedure titles per se. A procedure may cover one or more of the topics or one topic may have one or more procedures depending on its complexity and the organisation of the company. Care should be taken to ensure that quality control and review are appropriately addressed in the various processes, and reflected in the relevant procedures.

- The activities of the QPPV and the back-up procedure to apply in their absence.
- The collection, processing (including data entry and data management), quality control, coding, classification, veterinary review and reporting of adverse events:
  - Reports of different types:
    Organised data collection schemes (solicited), unsolicited, clinical trials, literature
- The process should ensure that reports from different sources are captured:
  - EEA and third countries, veterinarians and other health care professionals, animal owners, sales and marketing personnel, and other MAH personnel, licensing partners, competent authorities, others
  - The follow-up of reports for missing information and for information on the progress and outcome of the case(s)
  - Detection of duplicate reports
  - Expedited reporting
  - Electronic reporting

- PSURs:
  The preparation, processing, quality control, review including veterinary review and reporting

- Global pharmacovigilance activities applying to all products: Continuous safety profile of authorised VMPs (product-specific risk management and pharmacovigilance planning are not addressed in this Chapter):
  - Signal detection and review,
  - Benefit-risk assessment,
  - Reporting and communication notifying CA and health care professionals of changes to the risk-benefit balance of products, etc
- Interaction between safety issues and product defects
- Responses to requests for information from competent authorities
- Handling of urgent safety restrictions and safety variations
- Meeting commitments to competent authorities in relation to a marketing authorisations
- Management and use of databases or other recording systems
- Internal audit of the pharmacovigilance system
- Training
- Archiving

The DDPS should indicate the processes for which written procedures are available. A list and copies of the global and EEA procedures should be available within two working days after receipt by the MAH of competent authorities' request. Any additional local procedures should be available to respond to specific requests.

d) Databases

A listing of the main databases used for pharmacovigilance purposes (e.g. compilation of safety reports, expedited/electronic reporting, signal detection, sharing and accessing global safety information) and brief functional descriptions of these should be provided including a statement regarding the validation status of the database systems.

- A statement should be included regarding the compliance of the systems with the internationally agreed standards for electronic submission of adverse reaction reports as referred to in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU
- A copy of the registration, of the QPPV, with the EudraVigilance Veterinary system and identification of the process used for electronic reporting to the NCAs and the Agency.

There should be an indication of the responsibility for the operation of the databases and their location (with reference to the locations identified above under subheading “Organisation”).

e) Contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations

Links with other organisations such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. The company should identify the major subcontracting arrangements it has for the conduct of its pharmacovigilance activities and the main organisations to which it has subcontracted these (in particular where the role of the QPPV, the electronic reporting of adverse events, the main databases, signal detection, or the compilation of PSURs is subcontracted).

A brief description of the nature of the agreements the company establishes with co-marketing partners and contractors for pharmacovigilance activities should be provided.

Co-licensing or co-marketing arrangements within the EEA should be identified and the distribution of the major responsibilities between the parties made clear.

Since co-licensing or co-marketing arrangements are mainly product specific, any information on these may be provided in a product specific addendum, in the MAA. Likewise if subcontracting is product specific this should be indicated in a product specific addendum.

f) Training

Staff should be appropriately trained for performing pharmacovigilance related activities, taking into account their role within the company. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel, or field trial/clinical research staff. Provide a brief description of the training system and indicate where the training records, CVs and job descriptions are filed.

g) Documentation

Provide a brief description of the locations of the different types of pharmacovigilance source documents, including archiving arrangements. Reference can be made to the organisation charts provided above under subheading "Organisation".

h) Quality management system

Provide a brief description of the quality management system, making cross-reference to the elements provided under the above sections. Particular emphasis should be placed on organisational roles and responsibilities for the activities and documentation, quality control and review, and for ensuring corrective and preventive action.

A brief description of the responsibilities for quality assurance auditing of the pharmacovigilance system, including where appropriate auditing of sub-contractors, should be provided.

i) Supporting documentation

The MAH should ensure that the pharmacovigilance system is in place and documented.

An essential feature of a pharmacovigilance system is that it is clearly documented to ensure that the system functions properly, that the roles and responsibilities and required tasks are clear to all parties involved and that there is provision for proper control and when needed change of the system.

### 2.4 Monitoring of compliance by competent authorities

Guidelines, education programmes, responding to enquiries and systems for electronic reporting have been developed to facilitate the MAHs to meet their obligations concerning pharmacovigilance. NCAs should monitor MAHs for compliance with pharmacovigilance regulatory obligations. Furthermore, NCAs shall exchange information in cases of non-compliance and will take appropriate regulatory action as required. It should be noted that enforcement action is within the competency of individual MS. In addition, Article 84 of Regulation (EC) No 726/2004 sets out the roles of the MS, the Agency and the Commission with respect to the imposition of penalties for infringement of that Regulation or regulations adopted pursuant to it.

Set out below is an outline of how compliance monitoring should be performed. In this context compliance monitoring relates to activities that are separate to inspection activities and are carried out separately to them or as a prelude or follow-up to inspection. Where compliance monitoring raises concerns, these should be highlighted to other NCAs and in the case of CAPs, to the Agency. Deficiencies identified during compliance monitoring may lead to an inspection request.

NCAs and the Agency will ensure that a system of pharmacovigilance is in place within MAHs through scrutiny of the DDPS, procedures, safety reports and through pharmacovigilance inspections.

### 2.4.1 Qualified Person for Pharmacovigilance

NCAs and the Agency will maintain a list of QPPVs within the EEA. This list will include business address and contact details (including out of hours contact).

### 2.4.2 Availability of pharmacovigilance data

NCAs and the Agency, as applicable, should monitor (e.g. by assessment of the DDPS and when inspections are carried out) that pharmacovigilance data are collated and accessible by the MAH at least at one point within the EEA.

### 2.4.3 Change in the evaluation of the benefit-risk balance of a product

One of the key responsibilities of MAHs is to immediately notify the NCAs or the Agency of any change in the balance of benefits and risks of their products. Any failure to do so may pose a significant threat to public or animal health. Any evidence of failure to notify such changes will result in consideration of enforcement action by the competent authorities.

### 2.4.4 Expedited adverse event reporting

Requirements for expedited reporting of adverse events are given in Chapter 4. Adverse Event Reporting. Non-compliance with expedited reporting may include complete failure to report, delayed reporting (i.e. submission beyond 15 calendar days) and submission of reports of poor quality (particularly where evidence suggests that this results from inadequate company follow-up of individual cases). Failure to comply with electronic reporting requirements will be monitored.

Methods available to regulatory authorities for prospective monitoring of compliance with expedited reporting of adverse events could be:

- Monitoring adverse event reports received from MAHs against other sources to determine complete failure to report.
- Monitoring the time between receipt by MAH and submission to NCAs or the Agency to detect late reporting.
- Monitoring the quality of reports. Submission of reports judged to be of poor quality may result in the follow-up procedures of MAHs being scrutinised.
- Monitoring that all adverse events that are kept electronically comply with the requirements for electronic reporting set out in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.
- Checking PSURs to detect under-reporting (e.g. of expedited reports).
- Checking interim and final reports of post-authorisation safety studies to ensure that all qualifying serious animal reports and human reactions have been submitted within 15 calendar days.
- At inspection there may be a review of a sample of reports on the MAH database to assess the quality of data, determine whether the relevant reports have been expedited and have been sent to EVVet or other national electronic systems in place, and to confirm that procedures are in place to follow up reports.

### 2.4.5 Periodic Safety Update Reports

PSURs are important pharmacovigilance documents. They provide an opportunity for MAHs to review the safety profile of their products and ensure that the Summary of Product Characteristics (SPC) and other product information are up to date. They also provide the NCAs and the Agency with a valuable source of pharmacovigilance data. For these reasons the NCAs and the Agency place great importance on compliance with periodic reporting. Non-compliance may include:

- Non-submission: complete non-submission of PSURs, submission outside the correct cycle or outside the correct time frames, non-restart of the cycle of submission when necessary.
- Incorrect format of the document: report not in accordance with Chapter 6. Requirements for Periodic Safety Update Reports.
- Omission of information required by Chapter 6. Requirements for Periodic Safety Update Reports, particularly in the following sections of the report: Update of regulatory competent authority or MAH actions taken for safety reasons, changes to the SPCs, animal exposure (including sales volume and numbers treated), PSUR line listing.
- Poor quality reports: poor documentation of adverse events or insufficient information provided to perform a thorough assessment in the section covering the narrative review of the individual case histories on basis of the line listing of individual reports, new safety signals not or poorly assessed in the section for overall safety information, misuse not highlighted, absence of standardised veterinary terminology.
- SPC: where unauthorised changes have been made to the SPC since the submission of the last PSUR.
- Previous requests from NCAs or the Agency not addressed: submission of a report where previous requests from NCAs or the Agency have not been addressed (e.g. close monitoring of specific safety issues).

### 2.4.6 Requests for information from the NCAs or the Agency

No fixed time frames are laid down in EU legislation or guidelines for responding to a request for information from NCAs and the Agency. This reflects the fact that the appropriate time frame will depend mainly on the urgency of the pharmacovigilance issue and its potential impact on public or animal health. The NCAs and the Agency will ensure that all requests for information from MAHs have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. NCAs and the Agency will liaise with MAHs regarding the appropriate deadline, as required. Failure of MAHs to provide the necessary information/data within the deadline may be considered as non-compliance.

### 2.4.7 Submission of safety variations

EU legislation and guidelines do not specify deadlines for submission of safety variation applications. As with responding to requests for information from NCAs and the Agency, deadlines for submission of safety variations will depend on the urgency and potential public or animal health impact of the pharmacovigilance issue. The NCAs or the Agency will ensure that requests for safety variations have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. The NCAs or the Agency will liaise with MAHs regarding the appropriate deadline, as required. Failure of MAHs to submit the variation application within the deadline may be considered as non-compliance.

### 2.4.8 CVMP commitments in respect of Centrally Authorised Products

EU legislation and guidelines do not specify deadlines for the submission of follow-up measures following the granting of a centralised MA. The timeframe for submission of follow-up measures should be clearly stated in a letter of undertaking signed by the applicant at the time of the CVMP Opinion.

Regulation (EC) No 726/2004 foresees a number of particular possibilities for MAs and post marketing activities. Compliance with the provisions of these measures will be monitored. These include MAs under exceptional circumstances and the specific obligations or follow-up measures as applicable. Normal MAs may also include follow-up measures.

Non-compliance may include:

- Complete non-submission of data, including non-submission of specific obligations before the annual re-assessment
- Submission of data after the deadline agreed in the letter of undertaking from the MAH (without previous agreement from the NCA or the Agency)
- Failure to implement a specific obligation
- Failure to implement a follow-up measure
- Poor quality of a report requested as a follow-up measure
- Poor quality of a report requested as a specific obligation
- Failure to implement an urgent provisional measure

### 2.4.9 Post-Authorisation Safety Studies

Because of the objectives of post-authorisation safety studies there is considerable potential for safety signals to arise or changes in the balance of risks and benefits of products to be identified. Therefore, expedited reporting and submission to competent authorities of interim and final study reports from such studies has an important role in protecting public or animal health. Where appropriate, NCAs and the Agency will scrutinise protocols prior to the initiation of post-authorisation safety studies. NCAs and the Agency should check that relevant adverse event reports are expedited from those studies and will monitor the submission of interim and final study reports. Guidance on post-authorisation safety studies is available in Chapter 7. Company-Sponsored Post-Authorisation Safety Studies.

## 2.5 Pharmacovigilance inspections

To ensure that MAHs comply with their pharmacovigilance regulatory obligations and to facilitate compliance, NCAs will conduct pharmacovigilance inspections. There should be collaboration between NCAs and the Agency to minimise duplication and maximise coverage. Inspections will be routine as well as targeted to MAHs suspected of being non-compliant. The results of an inspection will be routinely provided to the inspected MAH who will be given the opportunity to comment on the findings. The results will be used to help MAHs improve compliance and may also be used as a basis for enforcement action. The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria. The inspection process described focuses on CAPs, however the principles may be generally applicable.

### 2.5.1 Conduct of inspections

The NCA, for inspection of the MAH's pharmacovigilance system, will be the NCA of the MS in whose territory the MAH's QPPV is located. Where an additional facility in another MS requires inspection (e.g. a database) the inspection will be carried out by the NCA of the MS in whose territory the facility is located.

In general, companies have a pharmacovigilance centre in the EEA covering multiple VMPs that are on the market, in the EEA. These centres may also be the global pharmacovigilance centres, or the latter may be located in third countries. Where the global centres, databases, etc are located in third countries (non EEA) the same NCA, as above, will be responsible for purposes of inspection on behalf of the EU, if such an inspection is considered necessary. Where relevant or on request, and in particular for product specific issues, they may be assisted, or the inspection may be conducted, by an inspector and/or expert from the Rapporteur/Co-Rapporteur MS (for CAPs) or the RMS (for MRP/DCP).

### 2.5.2 Routine inspection

Routine inspections are carried out by the NCA(s) referred to above in section 2.5.1. In general, it is anticipated that national inspection programmes will fulfil the need for routine inspections. They may

be carried out on a repeated basis. The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet their regulatory obligations for CAPs. These inspections may be requested with one or more specific VMPs selected as examples for which specific information can be traced and verified through the various processes, in order to provide practical evidence of the functioning of the pharmacovigilance system of the MAH and their compliance with their regulatory obligations.

In cases where an NCA has carried out an inspection covering the scope of that requested, or intends to carry out (conduct) one within the required timeframe, this inspection will suffice and its results will be made available to the CVMP or applicable reviewing agency. Such inspections may be specifically requested by the CVMP.

Where the pharmacovigilance system of a MAH has not been inspected previously, the CVMP will request the relevant NCA to carry out and report on an inspection of the system within 4 years of the placing on the market of the first CAP by that MAH. Where the system has previously been inspected, re-inspection will take place at intervals. The timing of the first inspection and any further inspection will be determined on the basis of risk analysis criteria.

The CVMP in conjunction with the NCA referred to in section 2.5.1 and the CVMP PhVWP-V and the applicable inspectors' working party, will determine a programme for inspection in relation to CAPs. These inspections will be prioritised based on the potential risk to public or animal health, the nature of the products, extent of use, number of products that the MAH has on the EEA market, etc and risk factors such as those identified under section 2.5.3 (Targeted inspections). This programme will be separate from any targeted inspection, but if a targeted inspection takes place it may replace the need for one under this programme dependent on its scope. The NCAs are responsible for determining their national inspection programmes.

### 2.5.3 Targeted inspections

Targeted inspections may be conducted as and when the trigger is recognised and the Agency and/or the NCA determine that inspection is the appropriate course of action.

Targeted inspections may arise when one or more of the following arise:

- Triggers for the inspection are identified which do not relate to specific concerns about a product's safety or actual non-compliance e.g.:
  - The MAH has not previously been inspected
  - The MAH has placed their first product on the market in the EEA
  - The MAH has recently been or is involved in a merger or takeover process
  - The MAH has changed their system significantly (e.g. new database system, contracting out of reporting activities etc)
- Triggers for the inspection are identified which relate to specific concerns about a product's safety or actual non-compliance e.g. significant issues relating to:
  - Delays in carrying out or failure to carry out specific obligations or follow-up measures relating to the monitoring of product safety, identified at the time of the marketing authorisation
  - Delays in expedited or periodic reporting
  - Incomplete reporting
  - Submission of poor quality or incomplete PSURs
  - Inconsistencies between reports and other information sources
  - Change in risk-benefit balance
  - Failure to communicate change in risk-benefit balance

- Previous inspection experience
- Information received from other authorities
- Poor follow-up to requests for information from the competent authorities
- Product withdrawal with little or no advance notice to the EEA competent authorities

The above are examples and other issues may trigger a targeted pharmacovigilance inspection. The presence of a trigger will not always lead to the conduct of an inspection.

### 2.5.4 Pharmacovigilance system inspections

These inspections are designed to review the systems, personnel, facilities in place and their compliance with pharmacovigilance obligations. They may use products as examples to test the system. They may be routine or targeted.

### 2.5.5 Product specific inspections

These inspections focus specifically on a given product and are usually targeted as a result of triggers that have been identified – see section 2.5.3.

### 2.5.6 Requesting and reporting of inspections

Inspection requests are prepared by the Agency inspection sector in conjunction with the Rapporteur / Co-Rapporteur and the relevant NCA. They are presented to the CVMP for adoption and once adopted are carried out by the competent authority referred to in section 2.5.1, on behalf of the Agency.

### 2.5.7 Inspections of contractors, licensing partners

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with, the MAH may be inspected, in order to confirm their capability to support the MAH's compliance with pharmacovigilance obligations.

### 2.5.8 Inspections in EEA

These may be routine or targeted.

### 2.5.9 Inspections in third countries

These may be routine or targeted. They will be included in routine inspections when considered appropriate, particularly where the main pharmacovigilance centre and databases, etc. are located outside the EU, for the MAH and CAP(s) in question. They will be included in targeted inspections whenever this is considered appropriate by the authority requesting the inspection.

### 2.5.10 Fees for inspections requested by the CVMP

An inspection fee(s) (and inspectors' expenses where applicable) will be charged in accordance with the Regulation (EC) No 297/95 on fees, as amended and implementing rules applicable at the time.

### 2.5.11 Procedures for coordination of Pharmacovigilance inspection for Centrally Authorised Products

The Agency will establish procedures for the administration and review of inspection requests and reports in conjunction with the CVMP, PhVWP-V and relevant Inspectors' working party.

These procedures will be adopted and published in line with the policies and procedures of the Agency on such documents.

### 2.5.12 Procedures for Pharmacovigilance inspection

Procedures for pharmacovigilance inspection will be prepared in association with Pharmacovigilance inspectors and representatives of the PhVWP-V and will be updated as needed.

These procedures will be adopted and published in line with the policies and procedures of the Agency on such documents.

### 2.5.13 Unannounced inspection

It is anticipated that the majority of inspections will be announced. However, on occasions, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice.

### 2.5.14 Inspection reports

Each inspection will result in an inspection report, prepared in accordance with an agreed format. The inspection report will be made available to the CVMP. The inspection report will be made available to the MAH.

### 2.5.15 Follow-up of inspection findings

Where an inspection reveals non-compliances the MAH will be required to prepare a remedial action plan to correct the non-compliances and avoid their recurrence. The MAH may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

### 2.5.16 Sharing of inspection information

The NCAs and the Commission, in cooperation with the Agency, will establish procedures for the sharing of information on inspections and their outcomes, in particular through the PhVWP-V and the Inspection Services Groups.

## 2.6 Regulatory action

Under EU legislation, to protect public or animal health, NCAs and the Agency are obliged to implement pharmaceutical legislation and to ensure MAH compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance regulatory obligations is detected, the necessary action will be judged on a case-by-case basis. The action taken will depend on the potential negative public or animal health impact of non-compliance but any instance of non-compliance may be referred for enforcement action. Action may be taken by the Agency, the Commission or the NCAs as appropriate in the context. Reference should also be made to legislation at EU and national level on penalties and sanctions and implementing procedures relating to these.

In the event of non-compliance, regulatory options include the following:

- *Education and Facilitation*
  MAHs may be informed of non-compliance and advised on how this can be remedied.
- *Inspection*
  Non-compliant MAHs may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved.
- *Warning*
  NCAs or the Agency may issue a formal warning reminding MAHs of their pharmacovigilance regulatory obligations.
- *Naming non-compliant MAHs*
  NCAs or the Agency will consider a policy of making public a list of MAHs found to be seriously or persistently non-compliant.
- *Urgent Safety Restriction*
  In accordance with the guidance and rules set out elsewhere.

- *Variation of the MA*
  In accordance with the guidance and rules set out elsewhere.
- *Suspension of the MA*
  In accordance with the guidance and rules set out elsewhere.
- *Revocation of the MA*
  In accordance with the guidance and rules set out elsewhere.

## 3. Requirements for Risk Management Systems

EU legislation requires Applicants/MAHs to provide NCAs and the Agency with a description of risk management systems, when appropriate.

The risk management system is defined as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions.

It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited. This is due to many factors including the limited representation of target animals (number of animals, age, breeds etc) used in the pre-clinical and clinical development of the product. Risks of many potentially affected subpopulations remain to be identified during the clinical use of the product.

A VMP is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk is judged positive for the target population, the user, the consumer of food from food-producing animals as well as the environment. However, not all actual or potential risks are identified when an initial marketing authorisation is granted.

Planning of pharmacovigilance activities will be improved if it were more closely based on product-specific issues identified from pre- or post-authorisation data and from pharmacological principles.

Risk management is defined[5] as the process, distinct from risk assessment, of weighing policy alternatives, considering risk assessment and other factors relevant to ensure quality, safety (including environmental safety) and efficacy of the VMP. Risk management should include, if needed, risk mitigation measures.

Guidance will be developed by the Agency on how MAHs and Applicants should meet the requirements for a description of a risk management system that they will introduce for an individual medicinal product, or a series of medicinal products, in line with EU legislation. This guidance will also, once available, describe how such a risk management system can be presented to NCAs and the Agency.

The guidance will be developed in accordance with the Procedure for EU guidelines and related documents within the pharmaceutical legislative framework (see Annex 4. References).

[5] CVMP Recommendation on the Evaluation of the Benefit-Risk Balance of VMPs EMEA/CVMP/248499/2007

# 4. Adverse Event Reporting

## 4.1 Introduction

The obligations of the MAH for recording and reporting adverse events associated with a VMP for which MAs are held are defined in Directive 2001/82/EC as amended and Regulations (EC) Nos 726/2004 and 540/95. For adverse events, which are required to be reported within 15 calendar days ('expedited' reports), further explanation is provided in this Chapter. Reporting following suspension or withdrawal of the Marketing Authorisation for safety or commercial reasons is described in Part I Chapter 5. Reporting Following Suspension or Withdrawal of the Marketing Authorisation for Safety or Commercial Reasons.

For authorised VMPs, independent of the authorisation procedure, adverse events received from veterinarians and other health-care professionals and other sources should be reported, regardless of whether or not the VMP was used in accordance with the authorised SPC and/or any other conditions laid down for marketing of the product in accordance with applicable legal requirements. Adverse events identified from the worldwide-published peer reviewed scientific literature should also be reported.

Electronic reporting of adverse events is mandatory, save in exceptional circumstances (see Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU). Guidance on electronic reporting of "expedited" as well as "non-expedited reports" can be found in Part III.

The definitions of 'adverse reaction', 'serious adverse reaction', 'human adverse reaction' and 'unexpected adverse reaction' are provided in the Glossary (see Annex 1. Glossary) and in Article 1 of Directive 2001/82/EC.

The definitions of 'adverse event', 'serious adverse event' and 'unexpected adverse event' are provided in the Glossary (see Annex 1. Glossary) and are based on the agreed terminology within the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (see Annex 4. References).

The MAH is expected to validate all adverse events reported by veterinarians and other health-care professionals and the general public to ensure, prior to reporting to the NCAs or the Agency, that the minimum information required is included in the report (see Section 4.5 Required information for adverse event reports). Reports should be followed-up to obtain additional information relevant to the case as necessary, and relevant follow-up information should be reported to the NCAs or the Agency. All available information relevant to the evaluation of the adverse reaction should be provided.

## 4.2 Requirements for expedited reporting

For all VMPs, independent of the authorisation procedure, the MAH should report, on an expedited basis,

- all serious adverse events occurring in the EEA to the NCA in whose territory the incident occurred; and
- all serious and unexpected adverse events in animals, human adverse reactions and suspected transmission of infectious agents occurring outside the EEA to the EVVet database.

The definition of an 'expedited report' is provided in the Glossary (see Annex 1. Glossary).

In veterinary medicine the existence of a large diversity of animal species and husbandry conditions require a modified approach to the classification of a serious adverse event. For example, in intensive food animal production with species such as poultry, fish or bees, a certain level of mortality rate is considered as 'normal' or 'expected'. These species are usually treated as a group/flock and only an increase of mortality rate, or severe signs, or animal production losses exceeding the rates normally expected should be considered as a serious adverse event. However, for food producing animals treated on an individual basis, an individual death or severe symptoms should be regarded as a serious adverse event.

Similarly, for companion animal species, like dogs and cats, a single death or severe symptoms constitutes a serious adverse event.

Article 49 of Regulation (EC) No 726/2004, and Article 75 of Directive 2001/82/EC, as amended, provide the requirements for the reporting of serious suspected adverse reactions.

### 4.2.1 Reporting of serious adverse events including human adverse reactions occurring in the EEA

The MAH should record and report all serious adverse events in animals and all human reactions occurring within the EEA which are brought to his attention, or of which he can reasonably be expected to have knowledge. These reports should be reported promptly, and in no case later than 15 calendar days from receipt, to the NCA in whose territory the serious adverse event occurred. Receipt in this context means becoming aware of an adverse event.

It should be noted that serious adverse events together with all other pharmacovigilance issues should be reported in the PSUR (see Chapter 6. Requirements for Periodic Safety Update Reports).

### 4.2.2 Reporting of serious and unexpected adverse events, including human adverse reactions, and transmission of infectious agents occurring outside the EEA

The MAH should report all serious and unexpected adverse events in animals (both criteria must apply), all human adverse reactions and any suspected transmission of an infectious agent relating to the use of VMPs which have occurred outside the territories of EEA (i.e. third country reports) and which are brought to his attention or of which he can reasonably be expected to have knowledge. These should be reported promptly, and no later than 15 calendar days following receipt to the EVVet database. In this context the relevant date of receipt of the information for European regulatory purposes is considered to be the date of receipt of the information by the MAH and initial reporting may be limited to the minimum information constituting an adverse event report (See Section 4.5 Required information for adverse event reports).

It should be noted that all adverse events from third countries should be reported in the PSUR (see Chapter 6. Requirements for Periodic Safety Update Reports).

**Requirements for expedited reporting**

| **Marketing Authorisation type** | Source | Origin | **Adverse event type** | **Target** | **Timeline** |
|---|---|---|---|---|---|
| All authorised products in the EU | Any source | EEA | All serious adverse events in animals and all human adverse reactions | To NCA in whose territory the adverse event occurred | Within 15 days |
| All authorised products in the EU | Any source | Non EEA | All serious and unexpected adverse events in animals and all human adverse reactions<br>and any suspected transmission via a veterinary medicinal product of an infectious agent | To EVVet DB | Within 15 days |
| *All authorised VMPs in the EU** | *Any source* | *Non EEA* | *All serious expected adverse events* | *To EVVet DB* | *Within 15 days* |

* the information in the last row in italics is highly recommended but not a legal requirement

### 4.2.3 Reporting of lack of expected efficacy

Lack of expected efficacy is defined as the apparent inability of an authorised VMP to have the expected efficacy in an animal, according to the claims of the SPC and following use of the product in accordance with the SPC.

It is important in the first instance to clearly identify if the lack of expected efficacy is due to a possible batch quality problem. However, quality-related issues must be reported according to the relevant requirements as indicated in the Compilation of Community Procedures on Inspections and Exchange of Information (see Annex 4. References).

Directive 2001/82/EC cites the lack of expected efficacy as a reason for refusal or revocation of authorisation. It is an important aspect of the consideration of the benefit-risk balance of a product. Reports of suspected lack of efficacy should be recorded by the person responsible for pharmacovigilance and reported to the competent authorities in the same way as for all adverse events.

### 4.2.4 Reporting of adverse events following off-label use

Off-label use is defined in Article 1(16) of Directive 2001/82/EC as the use of a veterinary medicinal product that is not in accordance with the SPC, including the misuse and serious abuse of the product.

The MAH should collect any available information on adverse events following off-label use related to his VMPs. Reports of adverse events arising from off-label use should be routinely followed up to ensure that information is as complete as possible with regard to the clinical signs, treatment and outcome.

Reports of adverse events arising from off-label use may be obtained;

- On VMPs used outside the terms of the MA, e.g. use of a product in non-authorised species/indications, use at doses differing from those set out in the SPC and package leaflet.
- On VMPs used outside the terms of the MA but in conformity with the provisions of the so-called "Cascade" (Articles 10 and 11 of Directive 2001/82/EC).

Such reports can provide useful information on the safety of the VMP and should be recorded by the person responsible for pharmacovigilance and reported to the NCAs and the Agency in the same way as other adverse events.

## 4.3 Requirements for reporting other pharmacovigilance issues

### 4.3.1 Reporting on investigation of the validity of the withdrawal period

Reports of such cases may arise from different sources including:

- Farmers or veterinarians detecting residues of VMP when testing bulk milk for antibiotics.
- Analytical laboratories or food producers who routinely monitor foodstuffs for residues, for example in slaughterhouses or dairies.
- State or regional authorities conducting residue surveillance on food from food producing animals.

Where levels of VMP residues in tissues or food products of treated food producing animals are above the established maximum residue levels while the recommended withdrawal period of the given VMP has been respected, this information may cast doubt on the validity of the withdrawal period and consequently should be investigated and reported to the relevant CA or the Agency responsible for authorisation of the VMP concerned.

Such reports should not normally be expedited (i.e. reported within 15 days after receipt), but should be discussed in the relevant PSUR (see Part I Chapter 6. Requirements for Periodic Safety Update Reports).

However, in certain specific circumstances, where these reports cast important doubt on the appropriateness of the recommended withdrawal period of the given VMP, the reports should be recorded and reported promptly to the NCAs or the Agency.

The report should contain details about

- the source of the report,
- the VMP, including active ingredient(s),
- MA number and batch number if available,
- the route of administration,
- the withdrawal period applied,
- date of use,
- date of detection of the residues,
- the level of residues detected,
- the location of the case,
- the species,
- the analytical method used to determine the residues,
- any other information necessary for a detailed evaluation of the case, and
- the steps taken by the MAH to investigate the matter.

### 4.3.2 Reporting on potential environmental problems

A potential environmental problem is a situation where animals of non-target species, other animals, human beings or plants are suspected to be adversely affected through exposure to a VMP present in the environment (see also section 4.4.2 Adverse events involving an untreated animal exposed to a VMP via a treated animal).

Any suspected environmental problem related to a VMP exposure should be recorded by the MAH as soon as it comes to his knowledge.

The minimum requirements for any potential environmental problem to be recorded by the MAH and reported to the concerned NCAs or the Agency are:

- the location,
- the animal or plant involved (as appropriate),
- the nature of the suspected environmental problem and
- the suspected product(s).

Reports of potential environmental problems arising from the use of the VMP should not normally be expedited (i.e. reported within 15 days after receipt), but should be discussed in the relevant PSUR (see Chapter 6. Requirements for Periodic Safety Update Reports).

However, in certain specific circumstances, in order to limit further environmental damage and to evaluate the benefit-risk balance, reports of potential environmental problems related to the VMP should be reported promptly to the NCAs or the Agency.

## 4.4 Guidance on particular types of reports

### 4.4.1 Adverse events involving more than one species

If more than one species is concerned in the same adverse event, separate reports should be submitted for each species, although it should be indicated that the reports are linked. This applies when more than one animal species is involved, or when an animal and a human being are involved.

### 4.4.2 Adverse events involving an untreated animal exposed to a VMP via a treated animal

If an adverse event has occurred in an untreated animal exposed to a treated animal, even if of a different species, a single report should be submitted relating only to the animal which experienced the adverse event. In this case a short explanation should be included in the dose details to clearly indicate which animal (or animal species) was treated. In addition, the administration route details should reflect the route by which the affected animal was exposed, e.g. oral route if the contact was by licking or grooming, cutaneous route if there was dermal contact between the treated and untreated animal.

### 4.4.3 Adverse events in offspring exposed through a parent

#### 4.4.3.1 Spontaneous abortion or stillbirth

A report should be submitted relating only to the parent. The animal details should be those of the mother.

#### 4.4.3.2 Adverse events in offspring only

If the offspring experienced an adverse event (e.g. malformation), while the parent was unaffected, a report should be submitted relating only to the offspring. If appropriate, the animal details should record the number of offspring in the litter which reacted. A short explanation should be included in the dose details and narrative to indicate which parent was treated. Information concerning the number of adult animals treated should be included in the case narrative to indicate what proportion of the flock or herd was affected. This is particularly important in cases of suspected lack of efficacy.

#### 4.4.3.3 Adverse events in mother and offspring

In cases where the mother and offspring experienced one or more adverse events following the administration of a VMP to the mother during pregnancy resulting in in utero exposure of the foetus(es), a single report should be submitted relating to both mother and offspring. The animal details to be recorded should be those of the mother. The number of treated animals should be recorded as one animal. The number of offspring which reacted and the fact that their exposure occurred in utero should be recorded in the case narrative. The clinical terms used to describe the adverse event should include the clinical signs observed in the offspring as well as those experienced by the mother. A clinical term indicating the congenital nature of the adverse event should also be included. If the mother or any offspring died, the report should be sent as an expedited report.

## 4.5 Required information for adverse event reports

### 4.5.1 Minimum information for adverse event reports

For a recordable case the MAHs are expected to record all data relevant for the evaluation and provided by the sender or obtained in the context of the case, at least the minimum criteria. If relevant for the evaluation, the MAH is expected to follow-up the adverse events with reasonable effort, to obtain further pertinent information. It is essential for MAHs to provide details as completely as possible, including all relevant clinical information, in order to facilitate assessment. The original words and/or phrases used by the reporter should be provided even if they are also coded using the VeDDRA List of Clinical Terms for reporting adverse events in animals and humans (see Annex 4. References).

The use of controlled terminology is a crucial factor in harmonising the exchange of pharmacovigilance information and the VeDDRA terminology is the most important of the standard lists. It is required that the MAH shall use the VeDDRA terminology. These lists are revised regularly and are available on the Agency website.

Follow-up reports on incomplete adverse event reports should be submitted by the MAH, in particular in cases where only the minimum information was submitted or at least when the investigation of the adverse event is completed.

A report will be considered an acceptable and reportable adverse event report provided that at least the minimum information outlined below is available. These details should be recorded by the MAH for any adverse event, whether non-serious or serious, whether occurring in animals or in human beings, whether occurring in the EEA or outside the EEA, and reported to the NCAs in the MS and/or the Agency as appropriate.

Minimum information for adverse event reports:

1. An identifiable source. Wherever possible this should include the name and address of the primary reporter. Part III Section 4.3 Data privacy laws outlines the policy on forwarding such personal data. Initials, geographic location or other unique identifier should be provided to allow the collection of further information and to avoid any duplication of reports.
2. Animal details: Species, sex, age. Patient details: Sex, age or adult/child. For both animal and human reports it should be stated if sex and/or age are not known.
3. VMP concerned (name and marketing authorisation number).
4. Adverse event details.

The electronic reporting forms contain additional data fields that are marked as mandatory.

Additional criteria to enable electronic reporting:

1. Report number
2. Receiver identifier
3. Date of the reaction. If this is not known, the closest approximation in terms of year (and month if known) should be substituted.
4. The number exposed/affected. If the number exposed is not known, the number affected should be substituted. If neither the numbers exposed nor affected are known, a notional figure should be used, which should be justified. If the exact numbers of animals exposed are not known, an estimation should always be provided. It is not acceptable to omit this information.

These details allow for the management and electronic distribution of adverse event reports, and assist in the detection of duplicate reports.

For adverse events for which deadlines for reporting apply, the reference point for deadlines for submission of reports is the time of receipt of the minimum information.

It should be emphasised that these are minimum requirements and the MAH should consider and try to include, for each adverse event, information on the items in sections 4.5.2 MAH details and original reporter's details to 4.5.11 Human adverse reactions in order to facilitate a full evaluation.

### 4.5.2 MAH details and original reporter's details

1. The name of the sender employed by the MAH.
2. Address, telephone and fax number of the sender.
3. MAH report reference number.
4. Date of receipt of report by MAH (any personnel of the MAH or an organisation having a contractual arrangement with the MAH).

5. Source of report, e.g. spontaneous, post-authorisation safety studies and clinical studies.
6. Details of the original reporter - name (if acceptable under national law), address, profession and speciality (if available).
7. Reporting country (country where the incident occurred).
8. Purchase country (where suspect product was purchased if different from that above).

### 4.5.3 Animal Details

1. Number treated.
2. Characteristics of animals showing signs:
    - Species.
    - Breed.
    - Sex.
    - Age (in days/weeks/months/years).
    - Weight (in kilograms).

### 4.5.4 Suspect veterinary medicinal product details

1. Product name(s)/brand names(s).
2. Approved scientific name(s) (INN - International Non-proprietary Name).
3. Marketing authorisation number.
4. ATCvet code
5. Pharmaceutical form.
6. Batch number.
7. Expiry date of batch - if relevant.
8. Storage details - if relevant.

### 4.5.5 Treatment details

1. The person who administered the VMP (e.g. animal owner, veterinary surgeon etc.).
2. Reason for treatment including diagnosis.
3. Dose (and frequency if relevant) of treatment given.
4. Route of administration.
5. Start date.
6. Stop date and/or duration of treatment.
7. Time between administration and adverse event.
8. Action taken after adverse event (e.g. removal of treatment with VMP, dose reduced).
9. Previous adverse event(s) to the VMP if occurred/reported, (re-challenge information) to include:
    - Approximate date when animal(s) previously treated with product.
    - Description of adverse reaction(s).
    - Outcome including any treatment given.

### 4.5.6 Other products used concurrently

All relevant medicinal treatment preceding the adverse event should be provided when available. This should also include non-prescription medicines, *ex tempore* (magistral) preparations and medicated feedingstuffs if applicable. In the case of *ex tempore* (magistral) preparations, details of individual constituents of the formula should be indicated.

For each medication:

1. Product name(s)/brand names(s).
2. Approved scientific name(s) (INN - International Non-proprietary Name).
3. MA number.
4. ATCvet code.
5. Pharmaceutical form.
6. Batch number if relevant.
7. Expiry date of batch - if relevant.
8. Storage details - if relevant.

Treatment details for other product(s) used concurrently:

1. The person who administered the VMP (e.g. animal owner, veterinary surgeon, etc.).
2. Dose (and frequency if relevant) of treatment given.
3. Route of administration.
4. Start date.
5. Stop date and/or duration of treatment.
6. Other relevant information.

### 4.5.7 Details of the animal adverse event(s)

The case narrative is very important and should contain all known relevant clinical and related information, including animal, exposure or treatment details not otherwise reported, course of adverse event(s) and description of the adverse event(s) including the outcome, diagnosis, and any other information that supports or negates an association between a product and an adverse reaction. The narrative should serve as a complete and comprehensive case report, presented in a logical time sequence, ideally in chronological order. The use of abbreviations and acronyms should be avoided.

1. Description of adverse event(s) including site and severity (intensity of the adverse event), and clinical signs.
2. Start date or onset of adverse event.
3. Stop date or duration of adverse event.
4. Specific treatments adopted against the observed adverse event.
5. Number of animals showing signs.
6. Number of animals dead.
7. De-challenge information (e.g. any obvious effect of removal of treatment).
8. If available the following information should be provided:
    - Number of treated animals alive with sequelae.
    - Number of treated animals recovered.

### 4.5.8 Other information

Any other relevant information available to facilitate assessment of the case should be provided, such as disposition to allergy, changes in feeding habits, or effects on production parameters.

When pre-mixes (as defined in Article 1(5) of Directive 2001/82/EC), which have been incorporated in medicated feedingstuffs, are causing an adverse event in animals or human beings, both the pre-mix and the medicated feedingstuffs should be investigated without delay.

In addition to the standard reporting details, additional factors may need to be examined and reported. Additional important information includes the composition of the medicated feedingstuffs (with a particular focus on other medicated pre-mix(es)), the inclusion levels of active substances of the pre-mix, the operation of the milling process(es), the possibility of cross contamination and, when possible, the estimated dosage administered to individual target animals. In addition, information on feed additives may be important, when available.

### 4.5.9 Investigation

In the event of a fatal outcome the cause of death should be provided and its relationship to the serious adverse event commented upon. Post-mortem examination findings and laboratory results should be provided if such tests were carried out. The nature of the MAH investigation should be described, and a summary of any analysis of product samples should be provided, if relevant.

### 4.5.10 Causality assessment

MAHs should comment on whether they consider there is a causal association between the suspected VMP(s) and adverse event(s) reported and should provide the criteria on which they have made the assessment.

The causality assessment should be carried out using the ABON system. According to this system, five categories of causality can be selected:

- Category A: Probable.
- Category B: Possible.
- Category O: Unclassifiable/Unassessable (events where insufficient information was available to draw any conclusion).
- Category O1: Inconclusive (events where other factors prevented a conclusion being drawn, but a product association could not be discounted).
- Category N: Unlikely to be product related.

In assessing causality the following factors should be taken into account:

1. Associative connection, in time - including dechallenge and rechallenge following repeated administration (in clinical history) - or in anatomical sites.
2. Pharmacological explanation, blood levels, previous knowledge of the drug.
3. Presence of characteristic clinical or pathological phenomena.
4. Exclusion of other causes.
5. Completeness and reliability of the data in the case reports.
6. Quantitative measurement of the degree of contribution of a VMP to the development of an adverse event (dose-effect relationship).

**For inclusion in category "A" (probable)**, it is recommended that all the following minimum criteria should be complied with:

- There should be a reasonable association in time between the administration of the VMP and onset and duration of the reported adverse event.

- The description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology of the product.
- There should be no other equally plausible explanation(s) of the case (if such are suggested, are they valid? What is their degree of certainty?). In particular, concurrent use of other VMPs (and possible interactions) or intercurrent disease should be taken into account in the assessment.

Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information) then such reports can only be classified as "B" (possible), "N" (unlikely), "O1" (inconclusive) or "O" (unclassifiable/unassessable).

**For inclusion in category "B" (possible)**, it is recommended that this be applied when VMP causality is one (of other) possible and plausible causes for the described adverse event but where the data does not meet the criteria for inclusion in category "A".

**For inclusion in category "O" (unclassifiable/unassessable)**, all cases where reliable data concerning an adverse event is unavailable or is insufficient to make an assessment of causality.

**For inclusion in category "O1" (inconclusive),** all cases where a VMP association cannot be discounted but other factors prevent a conclusion being drawn.

**For inclusion in category "N" (unlikely)**, cases where sufficient information exists to establish beyond reasonable doubt that there is an alternative explanation to the adverse event that is not related to a VMP.

Further guidance on how to carry out causality assessment is available in the CVMP Guideline on Harmonising the Approach to Causality Assessment for Adverse Reactions to Veterinary Medicinal Products (see Annex 4. References).

### 4.5.11 Human adverse reactions

Information about any human adverse reactions to VMPs, whether occurring in conjunction with the treatment of animals, the handling of a VMPs or following exposure through the environment, should be provided in accordance with the Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the EU including message and transmission specifications (see Annex 4. References). The minimum information required for a human adverse reaction report is outlined in section 4.5 Required information for adverse event reports.

The MAH should consider and try to include, for each human adverse reaction, information on the items below in order to facilitate a full evaluation. Asymptomatic human events should be recorded but not transmitted to the NCAs or the Agency.

The case narrative is very important and should contain all known relevant information not otherwise reported, including how the exposure occurred, e.g. accidental or routine use, the degree of exposure, e.g. the volume injected or splashed, the course of event(s), medical diagnosis, and any other information that supports or negates an association between a VMP and an adverse event. The narrative should serve as a complete and comprehensive case report, presented in a logical time sequence, ideally in chronological order. The use of abbreviations and acronyms should be avoided.

Information facilitating a full evaluation:

1. Patient identification (as appropriate according to national laws). A name or unique identifier should be provided to allow the collection of further information and to avoid any duplication of reports.
2. Sex.
3. Age, date of birth or adult/child.
4. Occupation/person status, if relevant to exposure to VMP, e.g. veterinary surgeon, farm worker, pet owner.

5. Date VMP used or date exposed to VMP(s).
6. Date of human adverse reaction.
7. Product details: Product/brand name, MA number, active substance and ATCvet code(s). This should be provided for each of the VMPs to which the patient was exposed in the incident.
8. Nature of exposure, including type of exposure, e.g. inhalation, injection, ingestion or dermal, and duration.
9. Description of human adverse reaction including clinical signs and symptoms.
10. Outcome of human adverse reaction, e.g. extent of recovery, specific treatment required.
11. Name, address, telephone number of medical doctor/physician (or Poison Centre) if consulted.
12. MAH conclusions/comments on the human adverse reaction.
13. Animal and treatment data, e.g. method of administration, administration site, number and species of animals being treated.
14. Status (e.g. veterinarian, pharmacist, other health-care professional), name and contact details of the person who reported the human adverse reaction to the MAH, if other than the patient, and if acceptable under national law for the purposes of obtaining further information.

### 4.6 Reporting Time Frames

The MAH should transmit all adverse event reports requiring expedited reporting promptly and no later than 15 calendar days from receipt.

The date the MAH becomes aware of a report which fulfils the minimum information (see Part I Section 4.1) should be considered day 0.

The clock for expedited reporting starts (day 0) as soon as the minimum information (see Part I Section 4.5 Required information for adverse event reports), has been brought to the attention of any personnel of the MAH or an organisation having a contractual arrangement with the MAH concerning conduct of pharmacovigilance.

### 4.7 Reports Published in Peer-reviewed Worldwide Literature

Adverse event reports from peer-reviewed worldwide literature are considered to be reports of which the MAH can reasonably be expected to be aware and have knowledge. The MAH is therefore expected to maintain awareness of possible publications.

Adverse events from the scientific and veterinary literature should be reviewed to identify individual events which might qualify for reporting.

The MAH should report published adverse events associated with the use of its VMPs in accordance with the requirements for adverse event reporting and in PSURs.

Contractual arrangements may be made with a person or organisation to perform literature searches and/or report relevant individual cases to NCAs or the Agency. If another person or organisation is performing these tasks, explicit procedures and detailed agreements should exist between the MAH and this person or organisation to ensure that the MAH is promptly made aware of any individual events described in the worldwide scientific literature to ensure that the MAH can comply with their reporting obligations.

### 4.8 Information on Adverse Events from the Internet

MAHs should review any reports submitted through their websites and determine whether they should be reported in an expedited manner.

MAHs should consider utilising their websites to facilitate adverse event report collection, e.g. by providing adverse event forms for reporting or by providing appropriate contact details for direct communication.

### 4.9 Reports from Other Sources

If a MAH becomes aware of an adverse event report from sources other than those mentioned above, e.g. the lay press or other media, reasonable attempt should be made to obtain the minimum information that constitutes an individual adverse event and to follow-up the report.

### 4.10 Method of Reporting

Electronic reporting of adverse events is mandatory, save in exceptional circumstances.

The available electronic reporting solutions and the procedural steps for all partners are explained in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

All possible data fields for reporting to EVVet are described in detail in the Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the EU including message and transmission specifications (see Annex 4. References). Where there are no appropriate fields in which to record specific details, the information should be provided in the case narrative or as attachments, as appropriate.

A paper reporting form is available for use in exceptional circumstances (see Annex 2.1 EU Template for MAHs for reporting adverse events).

### 4.11 Signal Detection

One of the aims of pharmacovigilance is the detection of new safety signals in relation to the use of VMPs. A signal should be considered as information reported on a possible causal relationship between an adverse event and a VMP, the relationship being unknown or previously incompletely documented.

The regular review and analysis of adverse events in a pre-defined time period for one specific VMP in one particular species might lead to the identification of potential signals when, for example:

- an increase in the number of adverse events in a short period is observed,
- an increase in the frequency of a particular clinical sign is recorded, compared with the expected frequency for that sign,
- new unidentified clinical signs are highlighted,
- a potential impact on public or animal health is suspected.

In the case of an increase in the number of adverse events, investigations should be carried out to clarify whether or not such findings could be considered as “normal”, in order to take appropriate measures.

In the case of signal detection of particular clinical signs, it might be useful to compare the number of citations of such clinical signs either with the number of other clinical signs recorded for the particular VMP, or with the number of the same clinical signs recorded for other VMPs.

### 4.12 Urgent Safety Restrictions

As provided for in Article 22 of Regulation (EC) No 1234/2008, urgent safety restrictions may be taken in the event of a risk to human or animal health or to the environment.

An urgent safety restriction is an interim change to the product information due to new information having a bearing on the safe use of the medicinal product, concerning in particular one or more of the following items in the SPC: therapeutic indications, posology, contraindications, warnings, target species, and withdrawal periods

An urgent safety restriction may be taken by the MAH if no relevant authority or, in the case of a centralised marketing authorisation, the Commission does not raise any objection within 24 hours after the MAH’s notification.

## 5. Reporting Following Suspension or Withdrawal of the Marketing Authorisation for Safety or Commercial Reasons

Reporting requirements remain following suspension of the MA of a VMP (see Part I Chapter 4. Adverse Event Reporting and Chapter 6. Requirements for Periodic Safety Update Reports).

Where an MA is withdrawn or revoked, the former MAH is encouraged to continue to report in line with Part I Chapter 4. Adverse Event Reporting to, for example, facilitate review of delayed onset adverse events and retrospectively notified cases. It may be appropriate to continue submission of PSURs after withdrawal or revocation of the marketing authorisation. This should be addressed and agreed on a case-by-case basis with the relevant NCA or the Agency.

# 6. Requirements for Periodic Safety Update Reports

## 6.1 Introduction

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a VMP to CAs and the Agency 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.

Each PSUR reporting period is defined by a Data Lock Point (DLP). The DLP is the date designated as the cut-off date for data to be included into a particular PSUR. On this date the data available to the author of the PSUR is extracted for review and stored. More information for setting the DLP is given further below.

This Chapter is consistent with VICH Topic GL 29 "Pharmacovigilance of Veterinary Medicinal Products – Management of Periodic Summary Update Reports (PSURs)" (see Annex 4. References).

For CAPs, PSURs should be submitted to the Agency and all NCAs in accordance with Article 49 of Regulation (EC) No 726/2004.

For other VMPs;

- 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;
- other purely nationally authorised,

PSURs should be submitted to the NCAs of the concerned MS in accordance with Article 75 of Directive 2001/82/EC (see list of addresses of NCAs for PSUR submission on the Agency website, Annex 4. References).

The requirement for the submission of a PSUR applies irrespective of whether the VMP is marketed or not, however in certain circumstances an abridged PSUR is considered sufficient (see Chapter 6.3.2 Content of Periodic Safety Update Reports – Non-marketed products)

Submission of electronic copies of signed PSURs (e.g. portable document format, pdf) is strongly encouraged but is subject to agreement with the relevant national NCA. Submissions of electronic copies of PSURs is accepted by the Agency in which case no hard copies are required.

Given the variability of resources available for and approaches across the NCAs on PSUR reports and assessments, work-sharing between NCAs is currently being considered by NCAs. Information on how to avoid duplication of work, on how and where to submit PSURs and on how to circulate PSUR assessment reports is published on Heads of Medicines Agencies website (see Annex 4. References).

## 6.2 General Principles

### 6.2.1 General Scope of Information

MAHs must include in the PSURs of all VMPs, whether authorised nationally or through the centralised procedure, 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 (see Chapter 7. Company-Sponsored 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.

### 6.2.2 Frequency and timing of Periodic Safety Update Reports

#### 6.2.2.1 Submission of PSURs

It is 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.

The periodicity for submission of PSURs is established in Article 49(3) of Regulation (EC) No 726/2004 and Article 75(5) of Directive 2001/82/EC. 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 least 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 a same or similar product granted anywhere in the world, including any VICH region), or the EU HBD (EU Harmonised Birth Date for VMPs included in the work sharing initiative on PSUR assessments).

For PSURs requested for immediate submission by a NCA or the Agency on an *ad hoc* basis, the MAH should liaise with the NCA or the Agency, as applicable, to agree the PSUR submission date, depending on the urgency of the issue.

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.

In the light of experience gained with the operation of veterinary pharmacovigilance, requirements for PSUR reporting frequency might be amended by Comitology procedures.

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 NCA(s), such an application should be supported by reasoned argument.

For all products amendments to the PSUR submission periodicity should be agreed with either the NCAs for nationally authorised VMPs or the Agency for CAPs. In order to reduce the workload for MAHs as well as NCAs special conditions apply for PSUR submission dates for VMPs for which MAHs voluntarily participate in the work sharing initiative (see Heads of Medicines Agencies website, Annex 4. References).

#### 6.2.2.2 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 and overlapping of data 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 a same or similar product granted anywhere in the world, including any VICH region), 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 a same or similar product granted anywhere in the world, including any VICH region. 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 Part I section 6.3.1.10).

For CAPs the PSUR should cover all authorised presentations covering all pharmaceutical forms and target species, whether authorised with the initial MA or at a later time point, e.g. through an extension of the MA. For each subsequent variation to the initial MA it will be decided on a case-by-case basis, as justified on basis of important safety concerns, whether the submission cycle for the PSUR needs to be changed. The DLPs remain based on the date of the initial MA.

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 the NCAs.

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, NCAs should accept that there might be an overlap between the last PSUR based on a national birth date and the first PSUR based on the EU HBD. EU HBDs and related harmonised DLPs of originator products are published on the Heads' of Medicines Agencies website, see Annex 4. References).

On a case by case basis following assessment of the safety profile of the individual nationally authorised VMP, MAHs for similar generic VMPs may use the opportunity to apply to the relevant NCA for the same PSUR submission schedules as those agreed for originator VMPs.

There may be situations where exceptionally, as justified on basis of important safety concerns, the submission of 6-monthly and subsequent yearly PSURs may be re-started, or where other amendments of the periodicity are required by NCAs or the Agency or applied for by MAHs.

### 6.3 Content of Periodic Safety Update Reports

For VMPs authorised via the centralised, mutual recognition, decentralised or ex-concertation procedures, for VMP participating in the PSUR work-sharing project and for VMPs, which have been subject to a referral, the PSUR should be written in English.

For all other authorised VMPs, the PSUR should – if submitted to one Member State only - be written in the national language or in English, as agreed with the concerned NCA. If this PSUR is to be submitted to two or more Member States, the PSUR should be written in English.

The reaction terms used in the PSUR should be in accordance with the VeDDRA terminology (see Annex 4. References). However, when the original reporter's terms are not medically appropriate or meaningful, the MAH should use the best alternative compatible event terms from VeDDRA to ensure the most accurate representation possible of the original terms.

The structure of a PSUR should follow the guidance given in section 6.3.1 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 6.3.2 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 2.3 Templates for tables for use as necessary in preparing and assessing Periodic Safety Update Reports (PSURs).

#### 6.3.1 Content of Periodic Safety Update Reports – Marketed Products

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

##### 6.3.1.1 MAH and product details

Each PSUR should include:

i) The name of the MAH

ii) The VMP name(s)

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 in case of nationally authorised products, or in any one of the countries within the EEA in case of CAP.

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

#### 6.3.1.2 Update on regulatory or MAH actions taken for safety reasons

An overview of regulatory and MAH actions taken anywhere in the world 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.

#### 6.3.1.3 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 6.3.1.9.

- For VMPs authorised through the centralised procedure, MRP or DCP, this will be the centrally or mutually accepted SPC in English.
- For nationally authorised VMPs, the specific national SPC in the language of the MS concerned 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.

#### 6.3.1.4 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;
- 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, a standard duration of treatment should be established and any interval should be 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 VMPs, 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).

#### 6.3.1.5 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 Articles 10 and 11 of Directive 2001/82/EC as amended 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.

A proportion of VMPs is indicated for more than one target animal species. Where this situation pertains it is recognised that it is difficult to calculate individual species incidence of adverse events. However, 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 6.3.1.4). 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 or O, including O1, N) during a period to the amount of VMP sold during that period should be computed:

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

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.

For PSURs covering 3 years, sales volume should be broken down by calendar year and the ratio of the number of animals with adverse event to the amount of VMP sold should be computed for each of the years concerned by the report.

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.

$$\%\ \text{Incidence} = \frac{\text{No of animals reacting during period} \times 100}{\text{Estimated No of animals treated during the period}}$$

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.

#### 6.3.1.6 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). Examples of tables have been developed and may be used (see Annex 2.3 Templates for tables for use as necessary in preparing and assessing Periodic Safety Update Reports (PSURs))

The data review should be structured as follows:

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

Information on the individual adverse event reports should be presented as line listings (see section 6.3.1.11 and Annex 2.4 Templates for PSUR line listings).

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.

#### 6.3.1.7 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. For guidance on progress reports for post-authorisation safety studies, see Part I Section 7.6 Liaison with regulatory authorities and reporting.

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.

#### 6.3.1.8 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.

#### 6.3.1.9 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. Although related terms may be found in different SOCs, they should be reviewed together for clinical relevance.

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).

#### 6.3.1.10 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.

MAHs are reminded that the respective data relating to serious adverse events in animals or human adverse reactions obtained after the DLP must also be reported expeditedly to the relevant NCA and the Agency as expedited reports as described in section 4.2 Requirements for expedited reporting.

#### 6.3.1.11 PSUR line listings

The minimum information constituting a reportable adverse event is listed in section 4.5 Required information for adverse event reports.

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. See also Part I Section 7.6 Liaison with regulatory authorities and reporting.

The line listing should be included as an appendix to the PSUR (see Annex 2.4 Templates for PSUR line listings) 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.

The standard information required in the line listing of a PSUR for adverse events in animals 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 treatment(s)/Date(s) of vaccination(s)
iv) Was the VMP used as recommended?
v) Date of adverse event
vi) Number of animals treated
vii) Species
viii) Age(s)
ix) Number of animals reacted (approximate)
x) Number of animals dead
xi) Other products, including authorised medicated premixes, used concurrently (Trade name and active substances)
xii) Presenting signs/diagnosis, including timing and duration
xiii) VeDDRA terminology (for description of signs/diagnosis)
xiv) MA comments – brief, informative narrative
xv) Causality assessment (A, B, O, O1, N code)

All the individual adverse event information listed above should be presented in the line-listing format given in Annex 2.4 Templates for PSUR line listings.

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

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

b) NCA report reference number, if relevant

c) Date(s) of exposure

d) Date(s) of human reaction

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

f) Occupation

g) Nature of accident/exposure

h) Nature of human reaction/symptoms

i) Outcome of human reaction

j) MAH comments – brief, informative narrative

Information relating to human adverse reactions involving VMPs should be presented in the format given in Annex 2.4 Templates for PSUR line listings.

### 6.3.2 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) were 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.
- estimated date for initially placing the product on the market

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

### 6.4.1 Submission of documents related to safety for Renewal of Marketing Authorisations

The Guideline on the Processing of Renewals in the Centralised Procedure and the Guideline on the Processing of Renewals in the Mutual Recognition and Decentralised Procedures define the different requirements to be respected for the purpose of data submission as part of the renewal application (Annex 4. References). Further guidance is also given in the Best Practice Guide for Handling Renewals in the Mutual Recognition and Decentralised Procedure (see Heads of Agencies website, Annex 4. References).

As part of the renewal application documents related to safety, the MAH needs to prepare or submit a PSUR Summary Bridging Report which is supported, if needed, either by

- a PSUR Addendum Report, or
- one PSUR in circumstances where the PSUR submission schedule is in synchrony with the renewal submission schedule.

The MAH may need to discuss the requirements for pharmacovigilance information for the renewal applications with the relevant NCAs or the Agency, and agree on the appropriate documentation required.

#### 6.4.1.1 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. It is intended to assist NCAs and the Agency with a helpful overview of the referenced 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 previously submitted 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 anywhere in the world 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 and overview of human reactions;
- 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.

#### 6.4.1.2 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 the NCA or the Agency.

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).

### 6.4.2 Synchronisation of PSUR submission

The periodicity of PSUR submission may be amended, as required for any VMP by the NCA or the Agency, or proposed by the MAH for nationally authorised products. This may result in more or less frequent submission of PSURs. For CAPs a lower frequency can only be stipulated at the time of granting the MA, whereas a more frequent submission is always possible. For any VMP, 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, which, if granted, becomes part of the conditions of authorisation. For the MAH shortening a reporting period by submitting the PSUR earlier (e.g. for synchronisation of PSUR submissions) is always possible. If a MAH proposes a prolongation of the reporting period and thus later submission of the PSUR following authorisation (not possible for CAPs), he shall apply for this amendment, which should be supported by reasoned argument. For nationally authorised VMPs amendments to the PSUR submission should be agreed according to national requirements.

For newly authorised generic VMPs or VMPs authorised on the basis of informed consent applications, application for submission of PSURs on a 3-yearly basis may be included in the MAA. PSURs for such products should preferably have the same DLPs as the corresponding originator product. Such applications will be assessed on a case-by-case basis by the concerned NCAs or the Agency.

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 of PSUR synchronisation / PSUR work-share initiative on PSUR assessment are outlined on the Heads of Agencies website, see Annex 4. References.

### 6.4.3 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-share initiative (see above). It is recommended for MAHs participating in this initiative to prepare a Core Safety Data Sheet (CSDS) written in English, which consists of an extract of the core safety 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 CSDS is strongly encouraged to be submitted in addition to the regularly enclosed SPCs (in national languages, see section 6.3.1.3) of all VMPs for which the synchronised PSUR is prepared. For more information regarding the CSDS refer to Heads of Agencies website (See Annex 4. References).

The Reference Safety Information to be used for PSURs for generic VMPs based on EU HBD should consist of the common safety information that is included in all current SPCs of the concerned generic VMP, as authorised in the MS at the time of the DLP. In addition, a summary of the other safety information that was not included in all SPCs should be submitted. The MAH should indicate in the PSUR which changes to the CSDS in use are considered necessary on the basis of the data evaluated in the PSUR.

# 7. Company-Sponsored Post-Authorisation Safety Studies

## 7.1 Introduction

Post-authorisation safety studies are pharmacoepidemiological studies or clinical studies carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised VMP.

This guidance applies to the conduct of post-authorisation safety studies that primarily evaluate the safety of marketed VMPs, when sponsored to any extent by the MAH. The guidance applies to studies where the VMP is provided by the MAH and to studies where it is prescribed and used in the normal conditions of clinical veterinary practice when other forms of sponsoring by the MAH apply.

The study should be designed on a case by case basis for particular VMPs and risks. This Chapter defines the essential principles to be applied in a variety of situations.

It may become necessary to undertake a continuous surveillance of the VMP under field conditions for a defined period of time after the MA is granted.

Post-authorisation safety studies provide additional information on the risks of a VMP, resulting in possible safety concerns being identified which may influence the overall benefit-risk ratio of the VMP. As a result the NCA or the Agency may request, or the MAH may propose appropriate measures of risk prevention or propose studies to further investigate the risk and frequency of its occurrence. Such studies should comply with this guideline.

On basis of Article 51 of Regulation (EC) No 726/2004 concerning CAPs, for a period of five years following the initial placing of the VMP on the market in the EEA the Agency may request that the MAH arrange for specific pharmacovigilance data to be collected from targeted groups of animals. The Agency shall state the reasons for the request. The MAH shall collate and assess the data collected and submit it to the Agency for evaluation. Such studies should also comply with this guideline.

Post-authorisation safety studies should complement spontaneous reporting programmes. Spontaneous reporting programmes are important in the detection of signals, which might indicate a safety concern. However spontaneous reporting systems do not provide a quantitative risk assessment i.e. give the incidence of an adverse reaction in a population. Therefore it is difficult to estimate the relevance of an adverse event described in single reports, without knowing the number of exposed and treated animals within a given time period. Post-authorisation safety studies can provide a denominator and give the answer to specific questions, which have been generated by signals from the spontaneous reporting system.

A commitment to post-authorisation safety studies may be required at the time of MA. In this case the study should be carried out on the basis of information of the SPC and in accordance with existing standards for the planning, conduct, reporting and archival of studies, such as in guidance on veterinary Good Clinical Practice (see Annex 4. References).

The basic types of questions to be addressed in post-authorisation safety studies are:

- long term effects that manifest themselves only after long periods of use, or after long periods of latency,
- low frequency specific effects – effects that can only be detected in large populations,
- uncertainty as to the clinical relevance of a harmful finding observed in pre-clinical studies in animals;
- efficacy in clinical practice, for the confirmation of lack of efficacy
- modifiers of efficacy: concurrent drugs, disease severity, husbandry conditions, feed,
- increase in frequency or severity of known adverse reactions,
- user safety aspects.

Monitoring of resistance to VMPs, investigations on the validity of withdrawal periods or surveillance of possible environmental problems under normal conditions of use might also be an objective of a post-authorisation safety study. Additional scientific guidance may be available for investigation of such specific topics.

### 7.2 Definition of a post-authorisation safety study

Post-authorisation safety studies are pharmacoepidemiological studies or clinical studies carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised VMP.

A post-authorisation safety study is any study of a marketed VMP, sponsored by the MAH, which has the evaluation of clinical safety as a primary objective.

This guidance relates principally to those studies that primarily investigate a safety concern and/or when the number of animals can be justified in view of the expected increase in the knowledge of the safety of the product(s).

Clinical trials for new indications, new methods of administration or new combinations, are therefore excluded from the scope of this guidance.

In cases of doubt as to whether or not a study comes under the scope of this guideline MAHs should discuss the intended protocol with the relevant NCA in whose territory the study is to be conducted or the Agency, if applicable.

### 7.3 Extent and objectives of post-authorisation safety studies

Post-authorisation safety studies may be conducted for the purpose of confirmation of previously undetermined safety issues (hypothesis generation), investigating risks (hypothesis testing in order to substantiate a causal association) or confirming the expected safety profile of a VMP under marketed conditions. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Objectives may be

- to measure the incidence of an adverse event in animals treated with the suspected VMP,
- to compare the incidence of an adverse event in animals treated and not treated with the VMP,
- to identify the risk factors associated with the development of an adverse event in animals treated with the suspected VMP, such as concurrent medications, disease severity, husbandry conditions, breeds, age, feed, etc,
- to identify risk factors responsible for an increased frequency or severity,
- to further clarify biological effects of adverse events due to a suspected VMP.

The design to be used will depend on the objectives of the study, which must be defined in the study protocol. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods.

### 7.4 Design of studies

Several different types of possible study designs may be applied to post-authorisation safety studies, e.g.

- Cohort studies, to provide information about the incidence of an event in a primarily unaffected population group,
- Case control studies, for hypothesis testing in a relatively short time at low cost, usually in retrospect,
- Group surveillance, study groups of animals where problems may arise which could be product-related and to ascertain VMP exposure, or

- Clinical studies

Principles outlined in the Guideline on statistical principles for veterinary clinical trials may be useful (see Annex 4. References).

Further guidance will be given on case by case basis by NCAs or the Agency, as applicable.

### 7.5 Conduct of studies

Responsibility for the conduct of the study shall be vested in the sponsoring MAH and should be conducted in accordance with appropriate standards, e.g. Good Clinical Practice.

### 7.6 Liaison with regulatory authorities and reporting

MAHs proposing or requested by a NCA or the Agency to perform a post-authorisation safety study are advised to discuss the draft protocol at an early stage with the relevant NCA or the Agency. National legislative requirements or guidelines should be taken into account where these exist.

Unless national legislation requires review of study protocols prior to commencing the study, the company is strongly recommended to submit the protocol as well as any proposed communications to veterinarians or other investigators as well as to owners or animal handlers participating in the study, in addition to other relevant information, to the relevant NCA or the Agency in good time before the planned start of the study. The NCA or the Agency may comment as necessary. The responsibility for the conduct of the study will, however rest with the MAH.

The MAH should communicate with the relevant NCA or the Agency, as requested in accordance with national legislation or other agreements, when the study has commenced and will normally provide a report on the progress at regular intervals and in PSURs (see Part I Section 6.3 Content of Periodic Safety Update Reports) or as requested by the authorities.

Recommendations for the content of a progress report for post-authorisation safety studies conducted in animals is presented below. For other types of studies, the progress report contents should be agreed with the NCA or the Agency.

i) Summary tables indicating the number of animals:
   - identified as suitable for the study,
   - entered,
   - treated with study products;
     - treated with the authorised (investigational) product(s),
     - treated with other (control) product(s), including placebo,
   - completed the study (followed up), or
   - lost to follow up,
     - alive or unknown
     - died.

ii) Tabulation of the reasons for stopping treatment during the study
iii) Individual listing of causes for each death
iv) Table of all serious adverse events in animals eligible for expedited reporting and all human adverse reactions
v) Line listing of all serious adverse events in animals eligible for expedited reporting and all human adverse reactions

Generally only the data listed above should be included in the progress report. Other information should not be included without prior discussion with the regulatory authorities. After review of the report NCAs or the Agency may request additional information.

Other recommendations for progress reporting may have been given by relevant NCAs or the Agency.

The reporting requirements for reporting of serious adverse events in animals and human adverse reactions apply (See Part I Chapter 4. Adverse Event Reporting and Chapter 6. Requirements for Periodic Safety Update Reports). All non-serious adverse events should be summarised in the final report.

A final report on the study should be sent to the relevant NCAs or the Agency within a pre-defined time frame. Final results should be summarised and a summary of all adverse events provided in the next PSUR after final results become available.

### 7.6.1 Studies requested by NCAs or the Agency

The contact point will depend on the procedure by which the VMP has been authorised in the EEA:

- For CAPs, the Agency will normally be the contact point.
- For VMPs authorised through the MRP or DCP, the RMS would normally be the contact point.
- For purely nationally authorised VMPs, the NCA requesting the study and the NCA of each MS where the study is to be conducted would be the contact points, unless other arrangements have been made to appoint one contact point.

When the same or a similar study is also requested by other NCAs or the Agency, an effort should be made by the MAH to reach agreement on a common protocol.

### 7.6.2 Studies performed on Marketing Authorisation Holder's initiative

When the study has commenced, the MAH should inform the relevant NCAs where the study is being conducted, as well as the Agency for CAPs and the RMS for VMPs authorised through the MRP or DCP. Any major amendment to the protocol should be reported to the relevant NCAs or the Agency, as applicable, accompanied by a justification for it.

# 8. Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action

## 8.1 Introduction

The MAH and the NCAs must keep up to date with all relevant information in order to fulfil the following responsibilities:

- ensuring that all sources of information are screened regularly to identify potential signals;
- ensuring that appropriate action is taken in response to new evidence which impacts on the benefit-risk balance;
- keeping health-care professionals and animal owners informed on changes to authorised VMP information.

## 8.2 Overall Evaluation

Signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions may arise from any source. Rarely, even a single report of an unexpected adverse reaction may contain sufficient information to represent a signal on or establish a potential causal association with the suspected VMP and impact on the benefit-risk balance.

The responsibilities of the MAH, and in particular of the QPPV, are provided in Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections. It is the responsibility of the QPPV to provide the NCA or the Agency with any information relevant to the evaluation of benefits and risks afforded by a VMP, including appropriate information on post-authorisation safety studies, lack of expected efficacy, information regarding the validity of the withdrawal period or potential environmental problems arising from the use of the VMP.

The MAH is obliged to immediately inform the NCA in all the MS where the VMP is authorised and, for CAPs, the Agency and the Commission, of any prohibition or restriction imposed by the NCAs of any country in which the VMP is marketed and of any other new information which might influence the evaluation of the benefits and risks of the VMP concerned. A comprehensive report evaluating the issue and considering the risks in the context of the benefits should be submitted at the earliest opportunity (and no later than the date agreed between the MAH and the NCA or the Agency) to all relevant NCAs and the Agency, for CAPs, and should also be discussed in the relevant PSUR.

## 8.3 Principles of Benefit-Risk Assessment

The benefit-risk assessment of a VMP is a complex process based on the intended use and the indications of that product in respect to its overall safety. The assessment should describe and objectively compare the benefits and risks of the VMP to evaluate the benefit-risk balance. The reasoning leading to the conclusion should be explained and discussed in a critical manner. Guidance on how to perform and present an evaluation of benefit-risk balance is currently being developed by the CVMP (see Annex 4. References). The guidance will aim to improve the methodology for benefit-risk analyses and to provide a more structured systematic and transparent approach to benefit-risk assessment.

## 8.4 Optimising the Benefit-Risk Balance

The MAH should aim to optimise the safe use and the benefit-risk balance of an individual VMP.

Where necessary, the benefit-risk balance may be improved either by increasing the benefits (e.g. including further explanation of how best to use the VMP) or by reducing the risks by risk mitigation measures (e.g. by contraindicating the use in animals particularly at risk, reducing dosage, or introducing precautions for use). When proposing measures to improve the benefit-risk balance of a VMP, their feasibility under normal conditions of use should be taken into account. If dose reduction is considered as a method of risk minimisation, the impact of dose reduction on efficacy should be carefully evaluated.

The following types of management actions may be necessary and may be initiated by the MAH or by the NCAs, the Commission or the Agency:

- Intensified pharmacovigilance surveillance and post-authorisation safety studies;
- Variation of marketing authorisation(s) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse reactions or other sections of the product literature;
- Direct provision of important safety information to veterinarians and other health-care professionals and animal owners (e.g. through letters, bulletins, via electronic media etc.) (see Part I section 8.5 Communication);
- Urgent Safety Restrictions: in accordance with Article 22 of Regulation (EC) No 1234/2008, urgent safety restrictions may be taken by MAHs in the event of risk to human or animal health or to the environment. If the MAH takes an urgent safety restriction, the MAH shall immediately inform the NCAs for nationally authorised products and, in addition, the Commission and the Agency for CAPs. These measures should be immediately communicated to the relevant NCAs or to the Commission and the Agency, as applicable. If the relevant authority or the Commission, as applicable, have not raised any objections within 24 hours after receipt of the information, the Urgent Safety Restriction is deemed to have been accepted. The corresponding variation application reflecting the urgent safety restriction shall be submitted immediately and in any case not later than 15 days after the initiation of the urgent safety restriction, to the relevant NCAs or the Agency, as applicable. Urgent Safety Restrictions may also be initiated by the NCA or the Commission.
- Suspension or withdrawal of the marketing authorisation of a VMP, in the event that the overall benefit-risk balance is considered unfavourable and proposed risk minimisation measures are considered inadequate. Veterinarians and other health-care professionals and animal owners/the general public should be informed as appropriate (see Part I section 8.5). The action previously described should be differentiated from suspension or withdrawal of a VMP from the market in the framework of a VMP recall for quality/batch-related issues, which may not necessarily affect the MA of the VMP in question.

Such actions may be taken voluntarily by MAHs. However, it is recommended that any such intended measure be discussed at an early stage with all NCAs concerned and, if appropriate, the Agency (see section 8.5). All concerned NCAs and the Agency should be informed immediately of any definite action.

### 8.5 Communication

The MAH may not communicate information relating to pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the relevant NCA, or, for CAPs, to the Agency.

In any case, the MAH shall ensure that such information is presented objectively and is not misleading. It is recommended that such information be submitted to the relevant NCA(s) and, if appropriate, the Agency, for review and approval prior to release, or at least simultaneously to the release.

# Part II: Guidelines for Competent Authorities and the Agency

# 1. Undertaking of Pharmacovigilance Activities by Competent Authorities in Member States

## 1.1 General principles

The basis for undertaking of pharmacovigilance activities is established in EU legislation, as described in Directive 2001/82/EC (mainly Title VII) and Regulation (EC) No 726/2004 (particularly Articles 46-54). The aim of this Chapter is to provide overall guidance for National Competent Authorities (NCAs) and the Agency on the principles described and in accordance with the Mandate of the CVMP Pharmacovigilance Working Party (PhVWP-V) (see Annex 4. References).

For CAPs, the European Commission is the CA.

To meet their legal requirements, NCAs should undertake all appropriate activities, including the following:

- To oblige MAHs to systematically collect information on adverse events and other pharmacovigilance issues related to their veterinary medicinal products and to transmit this information to the NCAs and the Agency as appropriate in accordance with Part I;
- To encourage reporting of adverse events by veterinarians and other health-care professionals and others;
- To encourage animal owners and breeders to communicate any adverse reaction to veterinarians and other health-care professionals or to the NCAs;
- To make adverse event reports available to the NCAs, the Agency and to the concerned MAHs as described elsewhere in this guidance;
- To initiate investigation, as appropriate, and assessment of safety concerns;
- To implement conditions and restrictions with regard to the safe and effective use of CAPs, or VMPs subject to referral procedures, on the basis of Commission Decisions;
- To communicate the outcome of evaluation of safety concerns as appropriate to veterinarians and other health-care professionals and as necessary to the public, through timely and appropriate methods of communication and to assess the impact of such communications. Before or at the same time the communication takes place, the MAH would normally be informed;
- To monitor the compliance of MAHs in relation to their pharmacovigilance activities;

The Agency shall cooperate with relevant international organisations concerned with veterinary pharmacovigilance.

The requirements and procedures involved in a pharmacovigilance system are described in this Chapter, which relates to VMPs authorised in the EU (using either centralised, mutual recognition, decentralised or purely national procedures) and covers collection and evaluation of all information useful in the surveillance of VMPs. This Chapter should be read in association with other relevant Chapters included in this Volume, in particular on

- the conduct of pharmacovigilance for CAPs (see Part II Section 2.1 Conduct of Pharmacovigilance for Centrally Authorised Products),
- the conduct of pharmacovigilance for VMPs authorised through the mutual recognition or decentralised procedure (see Part II Chapter 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure),
- electronic reporting (Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU)
- the Rapid Alert/Non-Urgent Information System (RA/NUIS) (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance)

- Risk Management Systems (see Part I Chapter 3. Requirements for Risk Management Systems), and
- communication to the public (Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use).

### 1.2 Administration of the national veterinary pharmacovigilance system

In accordance with Article 73 of Directive 2001/82/EC, each MS shall administer a national veterinary pharmacovigilance system for receipt and scientific evaluation of all pharmacovigilance data, including animal adverse events and human adverse reactions, lack of expected efficacy, off label use, investigations of the validity of the withdrawal period and potential environmental problems arising from the use of the VMP, and to ensure that appropriate regulatory action may be taken. Such systems, whether involving distribution of activities through regional centres or operated fully by a single national centre, within the Competent Authority, should ensure that pharmacovigilance data are managed in a way that is compatible with the procedures undertaken in other MS and the Agency in order that pertinent data may be shared between MS and the Agency.

In accordance with Article 73a of Directive 2001/82/EC, the management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance should be under the permanent control of the NCAs in order to guarantee their independence. According to Article 67(4) of Regulation (EC) No 726/2004, activities relating to pharmacovigilance, operation of communication networks and market surveillance should receive adequate public funding commensurate with the tasks conferred.

Each NCA should monitor MAH compliance with pharmacovigilance obligations and should undertake pharmacovigilance inspections in accordance with Part I Chapter 2.4 Monitoring of compliance by competent authorities.

The PhVWP-V has been given a Mandate, Objectives and Rules of Procedure (see Annex 4. References) to provide advice on the safety of medicinal products authorised in the EU and on the investigation of adverse events to enable effective identification, assessment, management and communication of risk at any time during the life of a VMP and to provide recommendations for regulatory action to the CVMP and the NCAs. This requires interaction with the CVMP as appropriate, as well as consensus development and coordination of pharmacovigilance issues at the EU level. Each MS should ensure that it actively participates in and cooperates with the PhVWP-V in order to fulfil its pharmacovigilance obligations at EU level.

NCAs and the Agency may also cooperate with regulatory authorities outside the EU on the basis of any formal arrangements in place for exchange of data and other information.

### 1.3 Management of spontaneous reporting programmes

#### 1.3.1 General principles

Each MS should have in place a veterinary pharmacovigilance system for the collection of spontaneous adverse event reports from veterinarians and other health-care professionals, MAHs and other sources. NCAs should liaise with veterinarians and other health-care professionals in their territory, to increase awareness of the reporting system, stressing its importance and encouraging reporting.

To this end, it is desirable that each NCA should ensure that:

- reporting of adverse events is straightforward and reporting tools are accessible to veterinarians and other health-care professionals and, where appropriate, to the general public (by providing a user-friendly reporting system, e.g. free post, telephone and/or web-based systems);
- all adverse event reports are acknowledged where appropriate and further information is forwarded as requested; and

- regular contact is maintained between the NCA and veterinarians and other health-care professionals, for example by:
  - Publication of regular pharmacovigilance bulletins;
  - Communications to the public (see Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use), where appropriate;
  - Provision of information in response to specific requests from veterinarians and other health-care professionals;
  - Provision of lectures and talks to veterinarians and other health-care professionals during scientific meetings and conferences; and
  - Availability of websites that facilitate and encourage reporting of adverse events.

The following recommendations concern spontaneous reporting system procedures:

- A veterinarian or other health-care professional or a MAH reports an adverse event, related to one or more VMPs, to the NCA in whose territory the reaction occurred. Reports from the general public may be made in writing (e.g. using report forms), by telephone, or electronically. Reports from MAHs are received electronically, save in exceptional circumstances.
- Reports are collected and validated by the regional centre or NCA and are entered into a database. Serious events should be handled with the highest priority. The database should be used to identify potential signals and analyse data.
- Reports should be made accessible to the Agency, to the other NCAs, and to the concerned MAHs according to the criteria laid down in legislation, and described in this Part, and in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

The following requirements relate to the NCAs:

- Receipt and validation of adverse event reports;
- Processing of adverse event reports;
- Reporting of adverse event reports;
- Evaluation, including causality assessment, of adverse event reports;
- Signal detection;
- Triggers for investigation;
- Feedback to health-care professionals;
- Quality management; and
- Confidentiality and security.

### 1.3.2 Receipt and validation of adverse event reports

This concerns receipt and validation of primary data, i.e. the data transmitted from the original reporter to the NCA. For validation and management of electronically transmitted reports, the specific requirements should be followed (see Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

A single report concerning an animal adverse event will include one or more animals of the same species, one or more identifiable reporter(s), one or more suspected adverse event(s) and one or more suspected VMP(s) (see Part I Chapter 4. Adverse Event Reporting).

Information on the data to be available in other types of adverse event reports is included in Part I Chapter 4. Adverse Event Reporting.

Adverse events that meet the criteria for expedited reporting should be submitted by the MAH in accordance with the requirements specified in Part I Chapter 4. Adverse Event Reporting.

#### 1.3.2.1 Validation of adverse event reports received from marketing authorisation holders or directly from health-care professionals and general public

NCAs should validate all adverse event reports which they receive electronically from MAHs, as well as all adverse event reports from veterinarians and other health-care professionals and the general public to ensure that the minimum information required (see Part I Chapter 4.5 Required information for adverse event reports) is included in the report.

This minimum information allows the adverse event to be entered into a database and become available for safety monitoring. If the original notification from a veterinarian or other health-care professional is made orally or by telephone to the NCA, it should be confirmed in writing. The information obtained should be as complete as possible.

VMP Details

Details of the VMPs should be recorded together with the batch number(s) of the relevant VMP, if available. It is necessary to establish whether the VMP was used according to the terms of its MA (recommended/non-recommended use). In many cases, it will also be useful to clarify the immediate previous use of the VMP, and whether other VMPs were administered prior to, or concurrently with, the suspected VMP. Where more than one VMP was used, full details of each should be documented.

Animal Details

Details of the number of treated animals, the number reacting and the number of deaths should be recorded. It may be useful to obtain further information on the condition of the animal before treatment, the reason for treatment, and the pregnancy state. Details of the outcome should be recorded. If considered appropriate, especially in the case of serious or unexpected adverse events, copies should be requested of the most important and relevant original documents (e.g. specialist reports, laboratory tests, and post mortem reports).

Human Adverse Reaction Details

It may be necessary to contact the investigating medical doctor or national poison/toxicology investigation centre in order to clarify details of a suspected human adverse reaction. While it is recognised that it may be difficult to obtain medical information about a patient, it is nevertheless important to capture the minimum details (see Part I Section 4.5 Required information for adverse event reports).

Reports should be followed-up to obtain additional information relevant to the adverse event as necessary.

### 1.3.3 Processing of Adverse Event Reports

Electronic data and paper-based adverse event reports should be recorded in a database by the NCA, taking account of the relevant legal requirements. Data storage should ensure on-line accessibility of data in line with the recommendations specified in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

Standard terminologies

The agreed standard terminology VeDDRA List of Clinical Terms for reporting adverse events in Animals to Veterinary Medicinal Products and the VeDDRA List of Clinical Terms for reporting adverse events in Human Beings to Veterinary Medicinal Products (VeDDRA terminology) and other terminologies should be used as referred to in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

Adverse event terms should be entered as the closest term available in the terminology using the appropriate VeDDRA terminology Lowest Level Terms (LLTs), and, if possible, also in the original reporter's words.

Use of standard terminologies should be monitored and validated, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the standard terminologies, and their proficiency verified.

Data Entry

Conformity of stored data with initial and follow-up reports should be ensured by a quality control procedure, which provides for validation against the original data or images thereof.

Storage should ensure traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

Report processing also concerns evaluation of data from adverse event reports, as well as identification of individual cases requiring specific handling, signal detection and evaluation, and any other processing of aggregate data deemed necessary.

Management of Duplicate Reports

Some adverse event reports, especially those which are serious, may be reported to NCAs and the Agency from more than one source, or from a single source through more than one channel. The NCA should ensure that adverse event reports contain as much information as possible in order to identify such duplicates, e.g. from

- animal owner or reporter initials,
- animal names (if appropriate),
- partial address details (such as region or post code)
- date of the reaction and/or other dates,

and are recommended to liaise with relevant MAHs to facilitate identification of possible duplicate reports.

Databases should be reviewed regularly to identify duplicates in accordance with procedures of NCAs and the Agency. After identification, duplicates should be merged into a single new (or merged) adverse event report (see Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

### 1.3.4 Reporting of Adverse Event Reports

Adverse event reports that meet the requirements for expedited reporting (see Part I section 4.2 Requirements for expedited reporting) to other NCAs, the Agency or MAHs should be transmitted in accordance with approved formats and timelines.

All serious adverse events in animals and all human adverse reactions, occurring within a MS and notified to the NCA by a veterinarian or other health-care professional or a member of the general public should be transmitted to the MAH and to the Agency within 15 calendar days of their receipt by the regional/national centre. The clock for expedited reporting starts (day 0) as soon as the minimum information (see Part I Chapter 4.5 Required information for adverse event reports) has been brought to the attention of the NCA.

The data transmitted should be as complete as possible in order to facilitate assessment. A causality assessment is obligatory for electronic reporting. If investigation of the adverse event is not completed within 15 calendar days, further information, including a revised causality assessment if appropriate, should be transmitted in a follow-up report at a later date.

NCAs should ensure that adverse event reports are transmitted electronically to the Agency, as required (see Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

When an NCA receives a report of a serious adverse event in animals or a human adverse reaction that occurred in its territory following the use of a CAP, this NCA is responsible for ensuring that such a reaction is reported to the Agency. Such reports must be submitted to the Agency promptly and in no case later than 15 days following receipt of the information, and they should contain the NCAs assessment in addition to the details provided by the MAH.

Adverse event reports associated with use of VMPs authorised through the MRP or DCP (Articles 31 and 32 of Directive 2001/82/EC), or that are covered by Directive 87/22/EEC, or which have been the subject of a referral procedure (Articles 36, 37 and 38 of Directive 2001/82/EC as amended), possibly provided to the RMS by the MAH should only be transmitted to EVVet by the NCA in whose territory the adverse event occurred. To avoid duplicate reporting, the RMS should not re-transmit these reports to EVVet (see Part II Chapter 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure).

The RMS is responsible for the overall analysis, monitoring and follow-up of any such serious adverse reactions and normally for communicating with the MAH on the pharmacovigilance profile of the product. The initial assessment of an individual adverse event report is the responsibility of the NCA in whose territory the adverse event occurred.

In the case of CAPs, it is the responsibility of the Agency to forward the information received from any NCA on serious animal adverse events as well as human adverse reactions to the national pharmacovigilance systems.

Data from non-serious, expected or unexpected, adverse event reports that are received from all sources should not be reported on an expedited basis, but should be available for transmission to relevant parties, including MAH, NCAs and the Agency, as necessary (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance and Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

Reports on harmful reactions associated with use of human medicinal products should not be transmitted to other NCAs or the Agency.

### 1.3.5 Evaluation, including causality assessment, of Adverse Event Reports

Following validation, the evaluation of adverse event reports includes categorisation of the event as serious or non-serious, and expected or unexpected.

Evaluation of the probability of a causal relationship between the VMPs and the adverse event(s) should be undertaken on each spontaneous adverse event report submitted. Evaluators should be trained in causality assessment. The causality assessment made by a NCA may differ from that of the MAH. If this is the case, the NCA should when possible communicate its conclusion and the reason(s) for the decision to the MAH. More guidance on causality assessment is included in Part I Section 4.5.10 Causality assessment.

### 1.3.6 Signal Detection

One of the aims of pharmacovigilance is the detection of new safety signals in relation to the use of VMPs. A signal should be considered as information reported on a possible causal relationship between reoccurring adverse events and a VMP, the relationship being unknown or previously incompletely documented.

Database functionality should enable users to search and retrieve data to facilitate cumulative data review, signal detection and trend analysis. When a signal is identified, the possibility of a causal relationship should be considered and in these circumstances, all relevant adverse event data should be further analysed. All adverse event reports fulfilling the minimum information requirements (see Part I Section 4.5 Required information for adverse event reports) should be included in the overall analysis. Certain analyses (for example those concerning the role of risk factors) may be confined to cases where sufficient information is available, but it should be made clear that this is a subset of the data.

The regular review and analysis of adverse events in a pre-defined time period for one specific VMP in one particular species might lead to the identification of potential signals when, for example:

- an increase in the number of adverse events in a short period is observed,
- an increase in the frequency of a particular clinical sign is recorded, compared with the expected frequency for that sign,
- new unidentified clinical signs are highlighted,
- a potential impact on public health or animal health is suspected.

In the case of an increase in the number of adverse events, investigations should be carried out to clarify whether or not such findings could be considered as "normal", in order to take appropriate measures.

In the case of signal detection of particular clinical signs, it might be useful to compare the number of citations of such clinical signs either with the number of other clinical signs recorded for the particular VMP, or with the number of the same clinical signs recorded for other VMPs.

Identification of potential signals must take into consideration all information available at the time of the survey (i.e. information provided in the SPC, in PSURs previously assessed, and the bibliography).

The Agency and NCAs in accordance with their responsibilities, and MAHs should inform each other of identified signals, which may impact on the known benefit-risk balance of nationally authorised VMPs and in the case of VMPs authorised through the centralised, mutual recognition or decentralised procedures in accordance with relevant guidance (see Part II Chapters 2. Centrally authorised products and 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure).

It is essential that signals/safety concerns are communicated at an early stage, preferably before a national decision is taken (see Part II section 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance and section 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

Standardised queries may be used for signal detection, in accordance with separate guidance[6].

### 1.3.7 Triggers for investigation

Investigation of the phenomenon of reported adverse events should be initiated by the Agency or an NCA, when at least one of the following criteria is fulfilled and functions as a trigger.

The proposed triggers do not cover for all eventualities and are not intended to limit the initiation of regulatory actions.

Trigger I

Adverse events occur at incidences higher than a baseline (e.g. 1:10 000).

This incidence should be used at national level and may differ between MS depending on reporting practices, the VMP itself, the use of the VMP, nature of the event etc. These events may be of a serious as well as a non-serious nature. The incidence is obtained from the PSUR therefore limiting the use of this trigger to the contents of the PSUR.

Trigger II

Serious unexpected adverse events occurring on three premises within one week or an increased incidence of serious expected adverse events.

Occurrence of serious unexpected reactions on three or more premises will trigger an investigation.

Trigger III

[6] A Guideline on the Use of Data in EVVet is under development.

For animals managed and treated as a group (see Annex 1. Glossary) more than 3 adverse event reports involving mortality above the expected level within three months after the initial placing on the market of a new VMP.

Trigger IV

Doubts are cast on the validity of withdrawal periods, arising from the use of the VMP.

In relation to pharmacovigilance, doubts on the validity of withdrawal periods may for instance relate to off-label use in respect to dose, route of administration, duration of treatment or use in a food producing species of a VMP containing substances for which no MRL has been established.

#### 1.3.7.1 Recommended approach to the investigation and regulatory action

Relevant national and EU legislation regulating VMPs specifies regulatory actions that may be taken when there are safety concerns. Below a series of steps are described that should be followed when investigating safety concerns regarding a VMP. Beginning with the initiation of investigation, based on one or more of the mentioned triggers, this investigation may lead to taking regulatory action. These steps describe the suggested order and nature of activity, the exact manner in which they are taken being subject to the respective national legislative framework of the MS and/or the EU legislative framework.

The responsibility for initiating the investigation depends on the nature of the MA.

For nationally authorised VMPs the investigation is initiated by the NCAs concerned. For MRP and DCP products and products having undergone a referral procedure in accordance with Articles 36, 37 and 38 of Directive 2001/82/EC, the RMS is, however, responsible for the overall pharmacovigilance evaluation. Thus, the RMS will initiate the investigation, in consultation with NCAs in whose territory the event(s) occurred (see Part II Chapter 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure).

Normally, information reported in one MS referring to national adverse events constitutes the basis for calculating triggers. However, considering the actual and substantial differences in pharmacovigilance between MS, resulting in variable quantities of reports both numerically and proportionally, the NCAs may benefit from information originating from other NCAs or third countries and/or use these data in considering the need for investigations.

For CAPs the Agency involving the Rapporteur and the CVMP and the NCA(s) concerned will co-ordinate the initiation of the investigation (see Part II Chapter 2. Centrally authorised products).

Step 1

Decide and document that one of the triggers I, II, III or IV has been met and that there is a need for further investigation of the issue. Establishing causality, if not yet excecuted, is one of the first objectives.

Step 2

Initiate investigation of the reactions by the MAH(s) to clarify potential problems, the MAH(s) being responsible for carrying out the necessary procedures.

The MAH should be contacted, alerted to the concerns of the Agency or the NCA and requested to comment.

Where appropriate, the Agency or the NCA may (for example but not limited to)

- request that investigations be carried out by the MAH in order to clarify the issue,
- contact the other NCAs using the NUI System or the RA System (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance), depending on the urgency of the matter, to obtain a broader data base,
- refer the matter to the CVMP in accordance with the relevant legislation (see also Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and

Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State). Wherever practicable and where provided for in the relevant legislation, MAH(s) should be invited to provide oral or written presentations.

Depending on the outcome of the investigation and on the nature of the issue, the investigation can:

- stop here with the documented conclusion that no further action is necessary to safeguard animal or public health.
- continue to Step 3, where the Agency or the respective NCA take an appropriate regulatory action on the basis of the documented conclusion of the investigation.

Step 3

Take appropriate regulatory action as provided for in the relevant legislation in order to resolve the issue under investigation (see also Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

The action taken by the Agency or the NCA should be appropriate in relation to the severity of the issue under investigation.

#### 1.3.7.2 Limitations of the trigger approach

Handling Rare Events

In general trigger I (the adverse event occurs at an incidence of 1:10 000 or higher) is a useful baseline but not an infallible one. There are good examples of where the adverse event is rare, e.g. thrombocytopaenia or following off-label use where 1:10 000 is not appropriate. In such instances, case-by-case decisions need to be taken.

Feline injection site tumours (fibrosarcomas) are a challenging (new) risk to assess. The long delay between administration of the VMPs and development of the tumours makes the identification of the issue difficult, and so far exact aetiology is unknown. There is also uncertainty whether one or more injections of product stimulate tumour growth. The incidence varies from author to author from 1:10 000 to 1:100 000 and there can be problems in histopathological interpretation.

On a case by case basis, investigation of such issues through a group of experts may be a feasible approach in order to clarify potential problems. Depending on the nature of the issue under investigation such a group may be formed at national level or at the EU level. The MAHs concerned should be invited to participate in the investigation (requests for comments, additional information or investigation). Where appropriate, the other MS should be contacted to obtain as broad a database as possible, using the NUI System or RA System, depending on the urgency of the issue.

### 1.3.8 Feedback to Reporting Health-care Professionals

NCAs should ensure that the original reporter(s) of an adverse event within the EEA is (are) informed promptly at least of its receipt and the allocated reference number. If appropriate, additional information should be requested.

### 1.3.9 Quality Management

Quality management concerns every step in the processes described above. Quality control and quality assurance should be ensured by the Agency and the NCAs, who should devise, document and implement appropriate procedures.

### 1.3.10 Confidentiality and Security

Confidentiality of animal and human reports including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting veterinarians and other health-care professionals or other persons should be kept in confidence, as appropriate and in keeping with national and EU legislation, and in accordance with Directive 95/46/EC on protection of personal data.

At each stage of storage and processing of pharmacovigilance data, measures should be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorised personnel sharing the veterinary, medical and administrative confidentiality of the data. This security extends to the complete data path.

In general, case report information should be provided by NCAs in an anonymous form. This concerns especially data enabling identification of a person, unless the consent from the data subject is obtained (i.e. people whose data are referring to).

In addition, procedures should be implemented to ensure security and non-corruption of data during data transfer.

### 1.4 Company-Derived Pharmacovigilance Data

The Agency and the NCAs, as appropriate, should ensure that the information and contact details for QPPVs and back-up services are documented and accessible to facilitate interaction between the Agency, the NCA and the MAHs via QPPVs, as appropriate.

Company-derived pharmacovigilance data includes the following:

- DDPS and, where applicable, risk management systems
- Adverse event reports;
- PSURs;
- Post-authorisation safety studies;
- Benefit-risk reviews;
- Other Data from MAHs.

This section deals with the procedures to be undertaken by the Agency and the NCA in reviewing company-derived pharmacovigilance data.

#### 1.4.1 Detailed Description of the Pharmacovigilance System and, where applicable, risk management systems

Detailed Descriptions of Pharmacovigilance Systems (DDPS), and Risk Management Systems when such are submitted, should be assessed by the NCAs and the Agency.

The following key points should be considered in the assessment of the elements of the DDPS:

- The availability of the various elements set out in the guideline, unless any omission has been justified by the applicant.
- Considerations of whether the description is of an existing system and special consideration of elements intended to be put in place before the product is placed on the market and missing elements, which would be included in the list of follow-up measures.
- The preparedness of the applicant to have a functioning system at the time of placing the product on the market.
- Any previous Pharmacovigilance system inspection history.
- Estimates of capability of the system described in view of the anticipated volume of safety reports for the product.
- The structure (complexity) of organisational interfaces i.e. subcontractors and licensing partners.
- The role and influence of the QPPV in the system, in view of possible subcontracts.
- History of mergers, if available.
- The specificity of the system for the product in question, and any changes, major or minor, to the system.

- Other information relevant to compliance of the system described.

The assessor is to conclude on whether a pharmacovigilance system inspection, soon after the product is placed on the market, should be recommended.

### 1.4.2 Adverse Event Reports

Each NCA should ensure that adverse event reports submitted by MAHs conform to the requirements described in Part I Chapter 4. Adverse Event Reporting, in order to ensure compliance with reporting of adverse events by MAHs. Furthermore, each NCA should ensure that serious adverse event reports are followed up by MAHs in accordance with the requirements described in Part I Chapter 4. Adverse Event Reporting. The Agency and NCAs should ensure that they have the capability to send and receive adverse event reports electronically. NCAs should ensure that MAHs do so in accordance with agreed legal requirements, procedures and guidance (see Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

### 1.4.3 Periodic Safety Update Reports

A PSUR is intended to provide an update of the worldwide safety experience of a VMP to NCAs or the Agency at defined times post-authorisation (see Part I Chapter 6. Requirements for Periodic Safety Update Reports). The value of the PSUR depends on the availability and quality of data from different sources.

#### 1.4.3.1 Amendments to the PSUR submission frequency

The periodicity of PSUR submission for nationally authorised products may be amended, as required by the NCA or applied for by the MAH. This may result in more or less frequent submission of PSURs.

For CAPs a lower PSUR submission frequency can only be stipulated at the time of granting the MA, whereas a more frequent submission is always possible.

For any VMP the submission of PSURs at a lower frequency than once every 3 years is not possible.

Circumstances where less frequent submission of PSURs may be appropriate include:

- Products authorised through line-extensions to existing VMPs;
- Newly authorised generic VMPs.

Circumstances where more frequent submission of PSURs may be required include:

- Variations introducing new species, new indications, dosage forms and routes of administrations;
- An active substance which is a different salt/ester or derivative (with the same therapeutic moiety);
- The presence of an excipient without an established safety profile; and
- Specific monitoring of a safety concern.

#### 1.4.3.2 PSUR assessment and management

Guidance on PSUR assessment and management is under development (see Annex 4. References).

### 1.4.4 Post-Authorisation Safety Studies

The Agency or NCAs, when requesting post-authorisation safety studies should liaise with the relevant MAHs on preparation and review of study documentation as described in Part I Chapter 7. Company-Sponsored Post-Authorisation Safety Studies. In addition, NCAs and the Agency, as applicable, may ensure that they are notified of post-authorisation safety studies undertaken at the initiative of MAHs.

### 1.4.5 Assessment of safety data in renewal applications

Safety data in renewal applications consist of a Summary Bridging Report on safety. In addition an addendum report or a PSUR may be included (see Part I Section 6.4.1 Submission of documents related to safety for Renewal of Marketing Authorisations).

In accordance with Article 28(3) of Directive 2001/82/EC, as amended, and Article 39(3) of Regulation (EC) No 726/2004, once renewed, the MA shall be valid for an unlimited period, unless the NCA or the European Commission decides - as applicable - on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

In general, if the safety profile of a VMP should be closely monitored this could be achieved by requiring increased reporting by more frequent PSURs, in accordance with the provisions laid down by Article 49(3) of Regulation (EC) No 726/2004, by requiring specific post-authorisation safety studies or a pharmacovigilance inspection (e.g. in case of concerns regarding the MAH's pharmacovigilance system). In accordance with Article 51 of Regulation (EC) No 726/2004, for a period of five years following the initial placing on the market in the EEA, the Agency may request on justified grounds that the MAH arrange for specific pharmacovigilance data to be collected from targeted groups of animals.

As a further tool, the NCA or the Agency could consider requiring one additional five-year renewal which would provide for a new benefit-risk assessment. The following criteria/factors have been agreed:

i) Limited exposure:

- VMPs for which limited safety information is available because of limited exposure due to e.g.
  - recent marketing of the VMP,
  - limited marketing of the VMP (e.g. only in a few member states, only few presentations marketed),
  - limited use in a recently approved new indication or new target species.

  Based on the new PSUR requirements, a recently marketed VMP would still fall within the 6-monthly or yearly reporting frequency at the time of renewal.
- VMP for which the marketing authorisation, or any of its indications, had been suspended.
- VMP currently not marketed as it is intended only to be used in the event of an outbreak of a communicable disease subject to EU Legislation, which has not occurred during the initial period of authorisation.

ii) Safety concerns:

- VMP with a particular safety issue which could impact on the benefit-risk balance of the VMP, e.g.
  - if concerns have been raised after off label exposure in a non-target species or for other than approved indications, and the species has thereafter been approved as a target species or the clinical use has been approved as an indication,
  - VMPs for which specific measures need to be taken and which need to be monitored in order to manage the risks (i.e. specific risk minimisation measures).
- VMPs for which post-authorisation safety studies are ongoing/planned (see Part I Chapter 7. Company-Sponsored Post-Authorisation Safety Studies and Part II Section 1.4.4 Post-Authorisation Safety Studies), the results of which are expected to yield important new safety data which could impact on the benefit-risk balance of the product. Where possible, the renewal date should be considered when agreeing the timing for such studies with MAHs.
- VMPs for which a class review of a serious safety issue is ongoing or imminent.

iii) Other

- VMPs authorised under exceptional circumstances (Article 39(7) of Regulation (EC) No 726/2004):

- if the renewal opinion recommends the MA to be maintained under exceptional circumstances since a (number of) specific obligation(s) are still outstanding, an additional renewal may be appropriate in case of remaining pharmacovigilance concerns, before granting unlimited validity,
- if the renewal opinion recommends a switch to a "normal MA", CVMP could recommend unlimited validity or could consider requiring one additional 5-year renewal taking into account the above-mentioned criteria (as for any other product with a 'normal' MA).

### 1.4.6 Benefit-Risk Reviews

A guideline for Applicants, Rapporteurs and assessors in order to improve the methodology of evaluation of the benefit-risk balance and to improve the consistency and transparency of assessment reports and the decision process is under development[7].

### 1.4.7 Other Data from MAHs

The Agency or NCAs should consider all other pharmacovigilance-related data submitted by or requested from MAHs to facilitate assessment of signals or emerging safety concerns, such as data on volume of sales and prescription of VMPs. These data should be evaluated and the outcome reflected in assessment reports, as appropriate.

## 1.5 Data from Sources Other than the MAH

Data from other sources may include the following:

- VMP usage data;
- Published adverse event reports;
- Data from clinical trials (other than post-authorisation safety studies);
- Significant quality data; and
- Reports on products not currently marketed in MS.

Such information may be important for determining for example frequency, occurrence of unexpected adverse events, new interactions and overall benefit-risk balance. In cases where significant information is received from these sources, these findings may be transmitted to other MS and the Agency using the RA/NUI Systems (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

## 1.6 Procedures for Data Exchange

The communication of pharmacovigilance information between NCAs, between NCAs and the Agency, and between NCAs or the Agency and MAHs should make optimal use of resources for detection and evaluation of pharmacovigilance signals.

For data exchange and communication between NCAs, the Agency and MAHs, only appropriate secure communication systems (e.g. Eudranet and EVVet, as applicable) should be used. EudraLink should only be used when transmission via Eudranet is not possible.

The Agency and NCAs should ensure that their pharmacovigilance personnel are familiar with the rules and procedures involved in the use of these systems and with the requirements for electronic reporting of adverse reactions (see Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

## 1.7 Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action

The Agency and NCAs, as part of their obligation to undertake ongoing evaluation of the benefit-risk balance of VMPs, should ensure that all pharmacovigilance data received and evaluated are taken into account on an ongoing basis.

[7] CVMP Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (draft).

New data on the benefits and risks of VMPs will become available after authorisation of the MA and evaluation of this information should be carried out on an on-going basis by MAHs, the Agency and NCAs, taking account of the relevant authorisation procedures and/or any arrangements in place for work-sharing.

As a consequence of evaluations of pharmacovigilance data, an MA may be varied, suspended, revoked, withdrawn or not renewed, as necessary and according to the appropriate procedure. Criteria for such regulatory action are set out for example in Articles 83 and 84 of Directive 2001/82/EC (see also Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

In the case of CAPs, changes to the MA status or SPC are undertaken according to Chapter III of Regulation (EC) No 1234/2008 and as outlined in Part II Chapter 2. Centrally authorised products.

The procedure to be followed for changes to the MA status or the SPC for veterinary medicinal products authorised via the MRP or DCP is described in Chapter II Regulation (EC) No 1234/2008 and in Part II Chapter 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure. It is the responsibility of the RMS to coordinate the procedure.

In the case of purely nationally authorised VMPs, where updated pharmacovigilance data are considered to impact on the benefit-risk profile of the VMP, the NCA may request a variation to the MA status or the SPC in accordance with national procedures.

Urgent safety restrictions may be taken in the event of a risk to human or animal health or to the environment as provided for in Article 22 of Regulation (EC) No 1234/2008.

If an urgent safety restriction is taken by the MAH, the MAH shall immediately inform the Commission (for CAPs) and all relevant authorities, including NCAs and the Agency. Within 24 hours of receipt of such information, if the Commission or the relevant authority have not raised any objections, the urgent safety restriction shall be deemed to have been accepted.

The European Commission or the NCAs may impose an urgent safety restriction for CAPs and nationally authorised products, respectively.

In the case of a CAP, the Agency will act in accordance with Part II Chapter 2. Centrally authorised products and notify all MS, circulating a Rapid Alert (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

In case of a nationally authorised product, the NCA will notify any urgent safety restriction to the other MS and the Agency circulating a Rapid Alert (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance). Should this concern a product authorised via the mutual recognition or decentralised procedure, the agreed guidance in Part II Chapter 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure should be followed.

An urgent safety restriction should be followed by submission by the MAH of a variation application immediately and in no case later than 15 days after the initiation of the urgent safety restriction.

Under the terms of Article 35 of Directive 2001/82/EC, a MS, the European Commission or the MAH shall refer a pharmacovigilance matter relating to (a) nationally authorised VMP(s), including those authorised through the MRP and DCP, to the CVMP whenever the interests of the Union are involved. These matters may be referred by the CVMP to the PhVWP-V for consideration. The Commission Decision issued on the basis of the CVMP Opinion is binding on all MS concerned (see Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

Any significant change to the MA status or SPC considered or undertaken nationally should be notified to the other MS, the European Commission and the Agency (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

In the case of CAPs, where urgent action to protect human or animal health or the environment is considered essential, a MS may suspend the use of a VMP on its territory, in accordance with Article 45(4) of Regulation (EC) No 726/2004. In such cases, the MS should inform the European Commission and the Agency immediately and no later than the following working day, providing the reasons for its action. In order to meet this legal requirement and to inform the other MS, the MS should circulate a Rapid Alert as described in Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance. The European Commission should immediately consider the reason given by the MS and shall request the Opinion of the CVMP within a specified time limit, determined in accordance with the urgency of the issue (see Part II Chapter 2. Centrally authorised products).

For nationally authorised VMPs, including those authorised through the mutual recognition, decentralised and ex-concertation procedures, where a MS considers, following evaluation of pharmacovigilance data, suspension or revocation of a MA, or its variation resulting in important changes to the product information as described in Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State, the RA System (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance) should be used to notify the other MS and the Agency immediately in accordance with Article 78(1) of Directive 2001/82/EC as well as the European Commission.

Where a MS suspends the marketing authorisation for a nationally authorised VMP (this includes products authorised through the MRP and DCP), in order to urgently protect human or animal health on its territory, the MS should circulate a RA (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance) at the latest one working day after the suspension, informing the other MS, the Agency and the European Commission of this action in accordance with Article 78(2) of Directive 2001/82/EC.

In accordance with Article 78(3) of Directive 2001/82/EC, when the Agency is informed of a suspension, withdrawal or variation (to restrict the indications or availability, amend the posology, add a contraindication or to add a new precautionary measure) of a MA by a MS, the CVMP should prepare an Opinion within a timeframe to be determined depending on the urgency of the matter. On the basis of the Opinion, the European Commission may request MS to take temporary measures immediately and final measures may be taken in accordance with Article 89(3) of Directive 2001/82/EC (see Article 78(3) of Directive 2001/82/EC and Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

If suspension, withdrawal or variation resulting in important changes to the product information as described in Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State seems likely, the MAH should be informed of any intended action at an early stage. In the case of VMPs authorised through purely national procedures, it is the responsibility of the NCAs in the MS concerned to inform the MAH. For VMPs authorised through mutual recognition or decentralised procedures, this task is usually undertaken by the RMS.

For CAPs, the Agency, in consultation with the Rapporteur should inform and liaise with the MAH.

### 1.8 Sanctions

In accordance with Article 75(8) of Directive 2001/82/EC as amended and Articles 49(5) and 84 of Regulation (EC) No 726/2004, MS are required to take the necessary measures to ensure that MAHs who fail to discharge their obligations are subject to effective, proportionate and dissuasive penalties.

## 1.9 Communication and Transparency

On basis of Article 51 of Regulation (EC) No 726/2004 recommendations are included in this guideline concerning the communication of information on adverse events relevant to VMPs, in particular for the benefit of healthcare professionals. See also Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use.

Article 57(e) of Regulation (EC) No 726/2004 requires the Agency to assist MS with the rapid communication of information concerning pharmacovigilance to healthcare professionals.

Article 57(f) of Regulation (EC) No 726/2004 imposes requirements on the Agency to distribute appropriate pharmacovigilance information to the general public.

Communication is considered as part of the risk management process.

Requirements are imposed on NCAs and the Agency for communication to veterinarians and other health-care professionals and the public on matters relating to pharmacovigilance and the safe use of VMPs. For communication within the regulatory network on any relevant safety concern, the RA and NUI Systems are used.

Information to health care professionals and general public on pharmacovigilance and safety concerns for VMPs authorised within the EU is summarised and published at least on an annual basis by the Agency on its website.

NCAs may publish summary information on an annual basis.

The Agency and NCAs should ensure that veterinarians and other health-care professionals, and the general public are informed, where appropriate, of any significant safety issues, including significant changes in the product information (SPC and Package Leaflet), of suspension or withdrawal of a MA due to pharmacovigilance data, and of any suspected or confirmed safety concerns requiring vigilance.

### 1.9.1 Notifications from MAHs on communication to the general public

Upon receipt of a notification from a MAH of its intention to communicate information to the general public relating to pharmacovigilance concerns in relation to its authorised VMP, the Agency or the NCA should review the information and provide the MAH with comments, if necessary, to ensure that the information is presented objectively and is not misleading.

### 1.9.2 Communication by the Agency and NCAs on significant safety issues of EU impact

Means for communication of significant safety issues include publication of relevant information on the Agency's website. The Agency would also communicate the information to NCAs for publication on national websites.

Veterinarians and other health-care professionals, European organisations representing veterinarians, and other health care professionals if necessary, are informed by the Agency. Local organisations for health care professionals would be informed either by the Agency, or their European organisations mentioned before.

OIE (World Organization for Animal Health) would be informed by the Agency on issues relating to public or animal health.

WHO (World Health Organisation) would be informed by the Agency particularly, but not limited to, on issues concerning public health.

VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) partners in other regions would be informed by the Agency of such matters.

Should there be a need for additional communication on any specific safety concern, additional means for communication may be used.

### 1.9.3 Communication by NCAs on significant safety issues of national impact

NCAs publish information using their websites and local veterinary and other health-care professional organisations, as well as any other relevant organisations.

Should there be a need for additional communication on any specific safety concern, additional means for communication may be used.

## 1.10 Stimulating Reporting of Adverse Events

While, in order to respect the confidentiality of VMP product information, the generic name of the active or inactive ingredient contained in the VMP should be used in any report intended for the public, nevertheless, when justified in the opinion of the Agency or the NCA, the proprietary name of the VMP linked to the adverse event may be given. In order to encourage the voluntary notification of adverse events, it is useful to collate and summarise the adverse event reports assessed as probable ("A") or possible ("B") and to make this information available to the concerned health-care professionals in a relevant manner. Direct contact with veterinarians, pharmacists and veterinary investigative laboratories, as well as organisations representing these individuals is advocated. Other means of encouragement are also useful, such as the publication of articles in relevant journals, the participation in discussions at Veterinary Colleges particularly with new graduates, and the stimulation of research in the area of veterinary pharmacovigilance. Ongoing encouragement of reporting is necessary, and annual reporting of the experience of the Agency or the NCAs to the concerned health care professionals is desirable.

# 2. Centrally authorised products

## 2.1 Conduct of Pharmacovigilance for Centrally Authorised Products

### 2.1.1 Introduction

The objective of this Chapter is to describe a framework whereby all CAPs are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these VMPs, so that appropriate action may be taken, when necessary, to protect public and animal health.

The conduct of pharmacovigilance for CAPs is based on obligations and activities placed, through legislation, on a number of parties, notably the NCAs, the European Commission, the Agency and the MAHs. In order to ensure that the obligations are met, it is necessary to clarify the respective roles and responsibilities of the various parties.

This Chapter presents:

- Principles relevant to the conduct of pharmacovigilance for CAPs;
- The functions and procedures for conducting pharmacovigilance for these VMPs;
- The specific roles of the Member States, the CVMP, the PhVWP-V, the (Co-)Rapporteur(s), the Agency, the MAHs and the European Commission, in carrying out functions and procedures for the conduct of pharmacovigilance for CAPs.

### 2.1.2 Legal Framework

The legal provisions regarding the conduct of pharmacovigilance for CAPs are set out in Regulation (EC) No 726/2004, notably but not exclusively in Chapter 3 of Title III, as well as Regulation (EC) No 540/95. The examination of variations to the terms of MA and urgent safety restrictions is the subject of Regulation (EC) No 1234/2008.

### 2.1.3 Principles

The responsibilities and functions of the various partners involved in the centralised procedure have been well defined for the coordination and evaluation of centralised MAAs and subsequent variation applications. This framework should also be applied to the conduct of pharmacovigilance for CAPs. As a matter of principle, the handling and analysis of pharmacovigilance data should always be done in close cooperation between the Agency including the Rapporteur(s) and any NCA who has (have) identified a possible issue.

The Rapporteur should take the lead in pharmacovigilance, acting to evaluate all issues relevant to the CAP.

In the particular case that one would be confronted with a class-related effect and different Rapporteurs were involved in the pre-authorisation assessment of the various CAPs, the CVMP would need to appoint a "leading" Rapporteur.

In view of the large number of issues to be handled after granting the MA for CAPs, the Rapporteur, supported by the Agency's secretariat, will have the responsibility for evaluating and reaching conclusions on these issues in accordance with an agreed timetable, and for determining the issues which need to be considered by CVMP and PhVWP-V.

Information relevant to the benefits and risks of CAPs need to be continuously collected in the EEA. Therefore, each NCA plays an important role in collecting information on adverse events and in identifying and evaluating possible safety concerns for CAPs. The scientific expertise of the EEA will be utilised by the Rapporteurs in carrying out pharmacovigilance evaluations. The Rapporteur will generally use the expertise of the country from which he originates. However, if considered more appropriate, the Rapporteur may work with another Member State, e.g. the Member State that identified the issue under investigation.

In accordance with current legislation the Agency should collect all information about serious adverse events and distribute this information to the MS. The role of the Agency, therefore, is one of continuous coordination of the pharmacovigilance for CAPs. The Agency will ensure that MAHs for CAPs adhere to the requirements for safety reporting in accordance with current legislation. Meetings for MAHs will be organised at the Agency at regular intervals in order to provide guidance on adverse event reporting to the Agency. The PhVWP-V will be informed of such meetings in advance and will be given the opportunity to participate.

The Agency, in close cooperation with the Rapporteur, will inform the CVMP/PhVWP-V of any safety concern whenever there is a need for discussion and subsequent action to be taken. It will, in agreement with the Rapporteur, participate in the identification of signals of possible unexpected adverse events or changes in severity, characteristics or frequency of expected adverse reactions.

The PhVWP-V evaluates potential signals, investigates adverse events and provides advice on the safety of VMPs, enabling effective risk identification, assessment and management in the pre-and post-authorisation phase. Following a CVMP request, their recommendations on CAPs are transmitted to the CVMP for consideration. A tracking system, including CAPs, is in place to track safety issues and is reviewed at each meeting of the PhVWP-V. In addition specific issues relating to PSURs, specific obligations, follow-up measures or the need for safety variations may be discussed by the PhVWP-V at the request of the Rapporteur.

The primary responsibility of the MAH is to assume responsibility for the safety of their VMP. The MAH is obliged to adhere to the legal provisions as to the spontaneous reporting of adverse events as well as to the submission of PSURs and other information. Furthermore, issues requiring clarification, further information or specific actions by the MAH need to be clearly presented to the MAH in writing. Such requirements of the MAH should be prepared in collaboration between the Rapporteur, the Agency and any MS requesting further information, and endorsed where necessary by the CVMP. Meetings with the MAH should involve the Rapporteur, the Agency and others as considered necessary. Minutes of such meetings should be taken and distributed to attendees.

### 2.1.4 Functions and Procedures

#### 2.1.4.1 Reporting of Adverse Events and Other Safety-Related Information

Pre-Authorisation Phase

Once an MAA is submitted to the Agency, in the pre-authorisation phase, new information relevant to the benefit-risk evaluation may become available from the Applicant, or Member States where the product is already in cascade use or from third countries where the product is already marketed. Since it is essential for this information to be included in the assessment carried out by the Agency's assessment teams, the Applicant is responsible for informing immediately the Agency and the (Co-)Rapporteur(s).

In the period between the CVMP reaching a final Opinion and the Commission Decision there need to be procedures in place to deal with information relevant to the benefit-risk balance of CAPs, which were not known at the time of the Opinion. It is essential for this information to be sent to the Agency and (Co-)Rapporteur(s) so that it can be rapidly evaluated to an agreed timetable and considered by the CVMP to assess what impact, if any, it may have on the Opinion. The Opinion may need to be amended as a consequence.

Post-Authorisation Phase

Adverse events related to CAPs may be reported directly by veterinarians and other health-care professionals, to each NCA. MAHs report serious adverse events in animals and human adverse reactions to the NCA in whose territory the reactions occurred, within 15 calendar days of receipt. Each NCA is responsible for following up adverse event reports to obtain further information as necessary.

The NCA should forward to the Agency serious adverse event reports in animals and all human reactions occurring within their territory.

The Agency and all NCAs should receive directly from the MAHs suspected serious and unexpected adverse events and all human reactions that occur in a country outside of the EEA.

The Agency should ensure that all relevant information about serious and unexpected adverse events from outside the EEA are entered into the EVVet database, and NCAs should ensure that data on serious adverse events and human reactions occurring in their territory are uploaded into the EVVet database. For details, see Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

#### 2.1.4.2 Monitoring of the Safety Profile

Signal Detection

It is likely that many potential signals will emerge in the early stages of marketing and it will be important for these to be effectively evaluated.

A signal of possible unexpected adverse events or changes in severity, characteristics or frequency of expected adverse reactions may be identified by:

- the MAHs,
- the Rapporteur,
- the NCA,
- the Agency in agreement with the Rapporteur.

It is the responsibility of each NCA to identify signals from information arising in their territory. However, it will be important for the Rapporteur and the Agency to have the totality of information on serious adverse events in animals and human adverse reactions occurring in the EEA and serious and unexpected adverse events in animals and human adverse reactions occurring outside the EEA in order to have an overall view of the experience gathered with the concerned CAP.

As a matter of routine, the Rapporteur should continually evaluate the adverse events included in the EVVet database and all other information relevant to benefit-risk balance in the context of information already available on the VMP, to determine the emerging adverse events profile. Additional information should be requested from the MAH and MS as necessary, in liaison with the Agency.

When a NCA wishes to request information from the MAH (apart from routine follow-up of cases occurring on their own territory) for the purposes of signal detection, the request should be made in agreement with the Rapporteur and the Agency.

NCAs will inform the Rapporteur(s) and the Agency when performing class-reviews of safety issues which include CAPs.

The PhVWP-V should regularly review data for emerging safety issues which will be tracked.

Signal Evaluation

As signals of possible unexpected adverse events or changes in the severity, characteristics or frequency of expected adverse reactions may emerge from many different sources of data (see above), the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal.

Irrespective of who identified the signal, a signal evaluation should be carried out by:

- the Rapporteur; or
- the NCA where a signal originated.

The Rapporteur should work closely with the identifier of the signal to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the assessment report on the benefit-risk balance, by the Rapporteur or the NCA where the signal originated from, or jointly.

A MS other than that of the Rapporteur should not start a full evaluation prior to having contacted the Agency and the Rapporteur, in order to prevent any unnecessary duplication of effort.

At request of the CVMP, the PhVWP-V evaluates signals arising from any source and keeps any potential safety issues under close monitoring.

PSURs

The MAH is required to provide PSURs to all the NCAs and the Agency, as detailed in Part I Chapter 6. Requirements for Periodic Safety Update Reports. It is the responsibility of the Agency to ensure that the MAH complies with the requirements.

The MAH should submit any consequential applications for amendment of the MA dossier simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort. Amendments may, however, also be requested subsequently by the Rapporteur, after agreement by the CVMP.

It is the responsibility of the Rapporteur to evaluate and provide an assessment report in accordance with the agreed timetable and to determine what issues if any need to be referred to the PhVWP-V. Assessment reports are endorsed by the CVMP.

Actions required following the evaluation of a PSUR will be determined by the Rapporteur and the MAH will be informed by the Agency, after agreement by the CVMP.

Where amendments to the MA are required in accordance with Article 47 of Regulation (EC) No 726/2004 the CVMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision.

Evaluation of Post-Authorisation Safety Studies, Worldwide Literature and Other Information

Final and interim reports of MAH sponsored post-authorisation safety studies and any other studies, and other relevant information, may emerge from the MAH, the NCAs or other countries at times in between PSURs and should be considered in the next PSURs, as applicable (see Part I chapter 6. Requirements for Periodic Safety Update Reports). Any new information which might influence the evaluation of the benefits and risks of the VMP should be received from MAHs between PSURs.

The Rapporteur should receive and assess any relevant information and provide an assessment report where necessary.

The Rapporteur should determine what issues if any need to be referred to the PhVWP-V and CVMP.

The actions required following an evaluation will be determined by the Rapporteur and the MAH will be informed by the Agency, after agreement by the CVMP.

Where amendments to the MA are required in accordance with Article 47 of Regulation (EC) 726/2004 the CVMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision.

The MAH should submit any consequential variations to the MA dossier simultaneously with the data, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CVMP.

Evaluation of Post-Authorisation Commitments

It is the responsibility of the Agency to ensure that the MAH meets the deadlines for the fulfilment of specific obligations and follow-up measures, and that the information provided is available to the Rapporteur and the CVMP.

The MAH should submit any consequential applications for variations of the MA dossier simultaneously with the requested information for the fulfilment of specific obligations/follow-up measures, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CVMP.

For MAs granted under exceptional circumstances, specific obligations will be set out in the CVMP Opinion. Specific obligations should be reviewed by the Rapporteur, at the interval indicated in the MA and at the longest annually, and should be subsequently agreed by the CVMP. As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP-V and CVMP.

For MAs granted under exceptional circumstances, the annual review will include a re-assessment of the benefit-risk balance. The annual review will in all cases lead to the adoption of an Opinion which will be forwarded to the European Commission for preparation of a Decision.

For all MAs (whether or not the MA is granted under exceptional circumstances) follow-up measures may be established, which are included in the CVMP Assessment Report. These will be reviewed by the Rapporteur, and will be considered by PhVWP and CVMP at the Rapporteur's request.

Where changes to the MA are required, the CVMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision.

In the case of non-fulfilment of specific obligations or follow-up measures, the CVMP will have to consider the possibility of recommending a variation, suspension, or withdrawal of the MA.

#### 2.1.4.3 Handling of Safety Concerns

Safety Concerns in the Pre-Authorisation Phase

Following the receipt of adverse event reports or other information relevant to the benefit-risk balance of a product by the Agency and the (Co-)Rapporteur(s), the latter should assess these pharmacovigilance data. The outcome of the evaluation should be discussed at the CVMP for consideration in the Opinion.

If pharmacovigilance findings emerge following an Opinion but prior to the Decision, a revised Opinion, if appropriate, should be immediately forwarded to the European Commission to be taken into account before preparation of a Decision.

Safety Concerns in the Post-Authorisation Phase

A tracking system is in place for safety concerns and is reviewed on a regular basis by the PhVWP-V at its meetings. This system also records relevant actions that have emerged from PSURs, specific obligations, follow-up measures and safety variations.

Following the identification of a signal the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal.

Non-urgent safety concerns

Potential concerns that do not fulfil the criteria for a RA should be brought only to the attention of the Rapporteur and the Agency in the first instance.

Further information may be requested from:

- other NCAs by the originator of the concern, issuing a NUI (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance);
- the MAH by the Agency, in agreement with the originator of the concern and the Rapporteur.

The Agency will coordinate the process.

The Rapporteur should work closely with the originator of the concern during its evaluation.

Following evaluation of the concern, the need for further discussion at the PhVWP-V and CVMP will be determined by the Rapporteur, and any necessary actions will be agreed by CVMP.

The Agency is responsible for transmitting the outcome of the evaluation to the MAH.

However, if deemed necessary, the CVMP should formulate an Opinion on the pharmacovigilance data and forward it to the European Commission accordingly in order to take a Decision.

These issues will be included in the Drug Monitor by the Agency if a NUI has been issued (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

Urgent safety concerns

A RA should be issued by the Rapporteur, the NCA or the Agency when a signal is identified which leads to concern about the benefit-risk balance of a CAP and which could lead to major changes in the MA or its status as further detailed in Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance. If it is the MAH who first identifies a potentially urgent and serious issue, he needs to inform the Agency without delay.

The RA should be transmitted to the contact points of the NCAs, the Agency and the European Commission, and to the Rapporteur of the concerned CAP(s), using the Eudranet communication system (Eudranet mailbox for Rapid Alerts in veterinary pharmacovigilance, see Annex 3. Eudranet mailboxes for use in communication).

The Agency, in agreement with the Rapporteur, should promptly start an inquiry and information exchange with the MAH(s).

The Agency will coordinate the process.

The Rapporteur should work closely with the originator of the concern to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the assessment report on the benefit-risk balance, by the Rapporteur, the NCA where the signal originated from, or jointly.

Following risk evaluation a discussion should be held at the PhVWP-V and subsequently at the CVMP within a defined timeframe.

Any resulting CVMP Opinion on the measures to ensure the safe and effective use of the CAP will be transmitted by the Agency to the European Commission, in order to take a Decision.

In some cases immediate action is essential to protect public or animal health. In such cases the basic steps outlined above need to be followed, but within a much shorter time frame, with the involvement of PhVWP-V and CVMP at a much earlier stage, and with particular mechanisms in place to provide a CVMP Opinion and Commission Decision rapidly. Rapid actions will need to be coordinated across EEA, however in some situations one or a number of NCAs may consider it necessary to take immediate suspensive action before such coordinated action occurs.

Crisis Management:

- Following detection of an urgent safety concern, which could have a serious impact on public or animal health, immediate action needs to be taken to evaluate and consider the options and timescale for action. An urgent safety restriction to be completed within 24 hours may be initiated by the MAH or the European Commission if necessary. A Crisis Management Plan, agreed with the CVMP, has been implemented by the Agency in close consultation with the European Commission (see Annex 4. References).

Action taken by a NCA:

- Upon detection of a safety concern where urgent action is deemed essential to protect human or animal health, a NCA may suspend the use of a VMP on its territory.
- The NCA must inform the Agency, the European Commission and other NCAs no later than the following working day of the reasons for its action. A RA should be issued for this purpose (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

- The European Commission will request the Opinion of the Agency within a time frame which it shall determine depending on the urgency of the matter. In that respect two possible procedures can be envisaged for implementation by the Agency depending on the time frame:
- the first procedure is described in the Crisis Management Plan (see Annex 4. References);
- the second is the convening of an extraordinary CVMP by the Executive Director of the Agency, after consultation with the CVMP Chairperson, in order to provide the European Commission with a recommendation on the measures.

#### 2.1.4.4 Information to veterinarians and other health-care professionals and the general public

Veterinarians and other health-care professionals and, if considered appropriate, the public need to be informed about safety issues relevant to CAPs, in addition to the information provided in product information. It is important that consistent information is provided in all Member States. If there is such a requirement the Rapporteur or the MAH in cooperation with the Rapporteur should propose the content of information for consideration by the PhVWP-V and subsequent discussion and adoption by the CVMP.

The agreed information may be distributed in Member States, for example, by direct health-care professional communication from the MAH, or by NCAs (see Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use). In some cases coordinated press releases, in addition to any CVMP public statements, may be necessary. The text and timing for release of such information should be agreed by all parties prior to their dispatch.

The MAH should notify, at his own initiative, the Agency at an early stage of any information he intends to make public, in order to facilitate consideration by the PhVWP and adoption by the CVMP as well as agreement about timing for release, in accordance with the degree of urgency. MAHs are reminded of their legal obligations under Article 49(5) of Regulation (EC) No 726/2004 not to communicate information relating to pharmacovigilance concerns to the general public without prior or simultaneous notification to the NCAs or the Agency (see Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use).

# 3. Medicinal Products Authorised through the Mutual Recognition Procedure or Decentralised Procedure

## 3.1 Introduction

Directive 2001/82/EC sets the basis for the authorisation of medicinal products through mutual recognition procedure (MRP) or the decentralised procedure (DCP) and for pharmacovigilance procedures and obligations of MAHs, CAs and the Agency thereafter, which are outlined in this volume. Regulation (EC) No 1084/2003 provides the legislative basis for variation of MRP and DCP marketing authorisations including urgent safety restrictions.

The objective of this guidance is to develop a framework whereby all VMPs, which fall under the MRP or DCP, are closely monitored to allow timely evaluation of new information relevant to the benefits and risks of these VMPs, so that appropriate action may be taken, when necessary, to protect public and animal health. VMPs covered by these procedures include those authorised through MRP, DCP or ex-concertation procedure and those previously subject to a referral leading to harmonisation.

Following the completion of the referral procedure, VMPs authorised through MRP or DCP will follow the MRP and DCP, and purely nationally authorised VMPs will be handled through purely national procedures again.

The responsibility for the conduct of pharmacovigilance of any MRP or DCP VMP, including the VMPs harmonised following a referral procedure, rests with the NCAs who have granted the MA.

The smooth running of MRP and DCP is facilitated by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv) in accordance with Article 31 of Directive 2001/82/EC. The CMDv acts to support the development of consensus where differences of view arise so as to minimise the need for arbitration at the level of the CVMP. The MSs have agreed that for pharmacovigilance issues arising with MRP and DCP VMPs, the PhVWP-V is the forum for exchange of information, evaluation and views and that the PhVWP-V will provide advice to the MSs on the safety of these VMPs, the investigation of adverse events and that it advises the CMDv on actions to be taken (see PhVWP-V Mandate: Annex 4. References).

Because of the need to coordinate the process of pharmacovigilance and any consequential regulatory action across all relevant Member States guidance is needed on the cooperation between the CMDv and the PhVWP-V. This should reduce duplication of work and will facilitate harmonised actions in the Member States.

This Chapter presents:

- Principles relevant to the conduct of pharmacovigilance for MRP and DCP products; and
- The specific roles of the different parties involved in carrying out these functions.

## 3.2 Principles and Roles and Responsibilities of the Parties involved

The responsibilities and functions of the various parties involved in the handling of an MA and subsequent variation applications in the MRP and DCP are defined in the legislation. MS have accordingly agreed principles that should be applied for the conduct of pharmacovigilance for MRP and DCP VMPs, with the RMS taking the lead on pharmacovigilance in close co-operation with the Concerned Member States (CMS). Any reference to NCAs below should be taken to mean both the RMS and CMS. Any reference to RMS should be taken to mean either the RMS or a CA designated as RMS. The roles of the relevant parties are presented below:

### 3.2.1 Reference Member State

Article 75 (4) of Directive 2001/82/EC provides for that

- the MAH should ensure that all serious adverse events as well as human adverse events occurring in the EEA are reported in such a way as to be accessible to the RMS and that

- the RMS shall assume the responsibility of analysis and follow-up of any of such adverse events. This is to be understood as the RMS having the overall responsibility for assessment follow up of safety concerns.

For practical reasons, MSs have agreed that the RMS should be responsible for

- evaluating safety concerns on EU level relevant to MRP or DCP products,
- providing assessment reports to the CMS according to an agreed timetable and
- presenting the safety concerns which need to be considered by the PhVWP-V,
- liaising with the MAH on all such matters.

In cases where the RMS is unable to carry out these functions, another MS may be agreed between the NCAs to undertake this task.

In situations where a class-related effect is identified for VMPs with different RMSs, a Lead-RMS may be appointed by agreement between the relevant RMSs to take forward evaluation of the class-related effect. For worksharing purposes, this principle may also be applied.

### 3.2.2 Concerned Member States

The NCAs of all CMS have a responsibility to

- continuously collect information on adverse events and to
- identify and evaluate possible safety concerns for MRP and DCP VMPs within their territory.

The CMS will report to and work closely with the RMS on such concerns, and will respond to proposals from the RMS within an agreed timetable.

### 3.2.3 National Competent Authorities

All NCAs are responsible for ensuring implementation of regulatory action in their territory.

NCAs should aim at a harmonised approach on the conduct of veterinary pharmacovigilance. When differences occur, they should involve CMDv and PhVWP-V, as necessary.

### 3.2.4 Coordination Group for Mutual Recognition and Decentralised Procedures – veterinary

The CMDv will be informed of pharmacovigilance issues relevant to it, by provision of the agendas and minutes of the PhVWP-V or otherwise in accordance with separate guidance on co-operation between PhVWP-V and CMDv.

### 3.2.5 The Agency, CVMP and PhVWP-V

The Agency will be notified about safety data and (proposed) regulatory actions by the NCAs according to Articles 73, 76 and 78 of Directive 2001/82/EC.

The CVMP will become involved in issues relevant to MRP or DCP products whenever there is a procedure triggered on basis of Directive 2001/82/EC, Articles 35, 39, 40 and 41. The Agency will provide administrative support to the PhVWP-V, and coordinate all activities in the event of a referral to the CVMP (see Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

The PhVWP-V facilitates coordination of pharmacovigilance of MRP and DCP VMPs across MSs and the development of consensus on conclusions and proposed actions where differences arise between MSs. PhVWP-V co-operates with CMDv on pharmacovigilance related actions regarding MRP or DCP products.

The PhVWP-V is the forum for discussing pharmacovigilance issues and giving harmonised advice in pharmacovigilance relevant to MRP and DCP VMPs. Items for consultation may be raised by the RMS or CMS. The mandate of the PhVWP-V encompasses consideration of items at the request of the CVMP or a MS.

### 3.2.6 European Commission

The European Commission takes the final decision relating to VMPs on any CVMP Opinion adopted as a result of referrals according to the procedures laid down in Articles 36, 37 and 38, and of CVMP Opinions according to Article 78(3) of Directive 2001/82/EC.

### 3.2.7 Marketing Authorisation Holders

According to Article 75(4) of Directive 2001/82/EC, the MAH should report all serious adverse events and all human adverse reactions with MRP and DCP VMPs occurring in the EEA in such a way as to be accessible to the RMS. The MAH is further obliged to adhere to the other legal requirements for pharmacovigilance (e.g. reporting of adverse events occurring outside the EEA, submission of PSURs and other information including post-authorisation safety studies) for MRP and DCP VMPs, as for any other nationally authorised VMPs. This information should be provided to all involved NCAs at the same time.

NCAs have agreed that the RMS will normally act as the primary liaison with the MAH, specifying issues requiring clarification, further information or specific actions by MAH. This will be clearly presented in writing to the MAH by the RMS working closely with CMS. Meetings with the MAH should involve the RMS, and any other CMS by request. The conclusions of such meetings should be distributed to the PhVWP-V, as necessary, and the CMDv. The RMS may also ask the MAH to present further clarification to the plenary meeting of the PhVWP-V. In the case of bilateral contact between a CMS and the MAH, the relevant CMS should keep the RMS informed.

## 3.3 Functions and Procedures

### 3.3.1 Pre-Authorisation Phase

The RMS should take any new pharmacovigilance information into account when drafting the preliminary or final assessment report as applicable. If the assessment report has already been distributed, the RMS should prepare and distribute either an amended or a supplementary assessment report.

If, in the course of a MRP or DCP and following the assessment of all information relevant to the safety of a product, the RMS considers that a significant risk has emerged affecting the benefit-risk balance, the outcome of the evaluation should be discussed at the PhVWP-V, if necessary.

For an application for a generic product the minimum information related to safety of a Reference VMP in a MS will be made available to all CMS by the RMS and consists of either the latest PSUR or confirmation that the MA of the Reference VMP has not been withdrawn or lapsed due to safety reasons in that MS and/or, if the information is available, in any other MS.

NCAs should ensure that pharmacovigilance information is being exchanged between their pre- and post-authorisation experts.

### 3.3.2 Post-Authorisation Phase

#### 3.3.2.1 Expedited reporting of Adverse Event Reports

Directive 2001/82/EC lays down specific obligations for NCAs and MAHs on the reporting of adverse events within 15 days (expedited reporting). MSs are responsible for collecting, collating, evaluating and transmitting reports occurring in their respective territories to EVVet.

Reports from outside the EEA are sent by the MAH to the EVVet database.

Member States are further obliged to forward reports of serious adverse events in animals and all human adverse reactions received to the respective MAH. For products that have been the subject of a MRP or DCP, the MAH should additionally make these reports available to the RMS. To avoid duplicate reporting the MS where the adverse event occurred transmits the report into EVVet.

#### 3.3.2.2 PSURs and Other Relevant Post-Authorisation Information

The MAH is required to provide all NCAs with PSURs. The PSUR submission schedule should be the same for all NCAs involved in the MRP or DCP. 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.

The RMS should take in account the PSUR synchronisation / PSUR work share initiative on PSUR assessment (see website of the Heads of Medicines Agencies, see Annex 4. References). For active substances which are on the list of PSUR synchronisation, it is recommended that the PSUR submission schedule should follow the listed DLPs.

The RMS will evaluate the PSUR and circulate a preliminary assessment report, in accordance with CMDv guidance documents, to the CMS within the specified time schedule. The CMS should respond on the RMS preliminary assessment report. The RMS will distribute the final assessment report to the CMSs and the MAH. This assessment report will, if requested by the RMS or a CMS due to disagreement or need for advice, be discussed at a PhVWP-V meeting. In case the VMP is participating in PSUR synchronisation / PSUR work share initiative on PSUR assessment the RMS will liaise with the PSUR-RMS (P-RMS) for that product (see website of the Heads of Medicines Agencies, see Annex 4. References)

It should be ensured by the RMS, that any granting of an MA in MRP or DCP, any granting of a renewal, any granting of a variation with impact on the safety profile of a VMP and any PSUR assessment report includes a schedule for future PSUR submission, which has been agreed on by RMS and CMS.

For VMPs authorised through MRP and DCP, amendments to the PSUR submission periodicity applied for by the MAH should be agreed between RMS and CMSs. Adherence to listed DLPs included in PSUR synchronisation / PSUR work share initiative on assessment of PSURs is recommended.

Given the variability of resources available and in order to make the most effective use of these resources without duplication of work the Heads of Medicinal Agencies initiated the PSUR synchronisation / PSUR work share initiative on PSUR assessment. Lists of active substances with harmonised DLPs for harmonised PSUR submission and guidance documents on how to participate in this procedure can be found on the Heads of Medicinal Agency website: http//www.hma.eu.

Because the renewal is an independent process, it does not change the submission schedule and DLP for the PSURs. It should be noted that re-assessment of the benefit-risk balance at the time of renewal is an opportunity for all NCAs and the Agency to review and, if necessary, change the PSUR schedule, or to request a second renewal.

#### 3.3.2.3 Signal Detection

It is possible that potential signals will emerge in the early stages of the marketing of a MRP or DCP VMP especially for a new active substance. It will be important for these signals to be evaluated effectively. A signal of a possible unexpected adverse event or a change in severity, characteristics or frequency of an expected adverse event may be identified from many different sources of information held by the MAHs, the RMS, or any CMS or the Agency.

It is the responsibility of each NCA to transmit reports of serious adverse events in animals and human adverse reactions having occurred in its territory to the EVVet database in an expedited way and to identify signals from information arising in its territory.

It is important for the RMS to have the totality of information in order to have an overall view of the experience gathered in relation to the concerned MRP or DCP VMP.

Additional information requested from the MAH should be provided to the RMS and all CMS simultaneously. The EVVet database services are a very important source of information, since all reports of serious adverse events in animals and all human reactions are included in the database in accordance with the EU legislation (see also Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

As a matter of routine, the RMS should continually evaluate all newly submitted information in the context of information already available on the VMP, to determine the emerging adverse event profile. Signals of a possible safety concern will, if requested by the RMS or a CMS, be discussed at a meeting of the PhVWP-V.

#### 3.3.2.4 Signal Evaluation

As signals of possible unexpected adverse events or changes in severity, characteristics or frequency of expected adverse events emerge, the relevant information needs to be analysed for effective evaluation over a timescale appropriate to the importance and likely impact of the signal.

Any risk evaluation prompted by a signal should normally be carried out by the RMS unless other arrangements are agreed with another NCA, this could be for example the CMS where the original signal was identified. The RMS should in any case work closely with the originator of the alert.

Agreement needs to be reached in each case on the responsibility for the benefit-risk assessment report, by the RMS or the originating NCA, or jointly.

The RMS should liaise with the MAH as appropriate for the provision of additional relevant information, if available, to ensure that all relevant data is taken into account in the evaluation. According to Article 27(3) of Directive 2001/82/EC the MAH may be asked to provide data demonstrating that the benefit-risk balance remains favourable. All data to be provided by the MAH to the RMS should simultaneously be distributed to all CMS.

A Member State other than the RMS should not start a full evaluation prior to having contacted the RMS, in order to prevent any unnecessary duplication of effort.

#### 3.3.2.5 Tracking of pharmacovigilance issues

A tracking system is provided by the Agency for pharmacovigilance issues relevant to all VMPs, summarising RA and NUI System messages (Drug Monitor) (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

#### 3.3.2.6 Proceedings in Case of Safety Concerns

Non-Urgent Safety Concerns

Safety concerns that do not fulfil the criteria for a RA (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance) should be brought to the attention of the RMS. The RMS should work closely with the MS who identified the issue to evaluate the matter. Agreement needs to be reached in each case on the responsibility for the benefit-risk evaluation and assessment report, by the RMS or the originator MS, or jointly.

The RMS should liaise with the MAH as appropriate for the provision of additional relevant information, if available, to ensure that all relevant data is taken into account in the assessment.

The conclusions should be distributed to all MSs through the Eudranet Pharmacovigilance mailbox. The RMS should consider sending a NUI request before concluding on the assessment (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

Following evaluation, the need for further discussion at the PhVWP-V will be at the request of the RMS or CMS.

The CMDv should be informed by the RMS, in case regulation action is required.

Urgent Safety Concerns

The RA System should be used to communicate information on safety concerns with MRP and DCP products which meet the criteria described in Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance.

The RMS should preferably take the lead, but in case the concern was raised in a CMS, agreement needs to be reached who will transmit the RA. The RA should be transmitted to the contact points of the RMS, the CMS, the European Commission and the Agency (see Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance).

The MAH should also be informed by the RMS at the same time. The RMS should work closely with the CMS where the concern was raised (if not the RMS) and responsibilities for management and assessment of the safety concern should be agreed between them. They should also decide what additional information should be requested from the MAH and CMS.

Following risk evaluation, a discussion should be held at the PhVWP-V with the aim of finalising an agreed position between the RMS and all CMS. In cases of particular urgency, a special meeting of the PhVWP-V may need to be requested.

The RMS should keep the CMDv informed.

Any NCA may initiate immediate suspension of the MA and use of the VMP concerned if considered necessary.

Actions Consequential to Safety Concerns

Safety concerns may emerge from the many sources of information considered above which warrant amendment to the conditions of the marketing authorisation, through a short type II variation procedure, or urgent safety restriction procedure. In the case of serious risk, which is considered to outweigh the benefit of a product, there may be a need to withdraw the product from the market or revoke the marketing authorisation. Such actions may be taken either voluntarily by MAH or compulsory by CAs as described below.

*Actions by the Marketing Authorisation Holder*

Variations of the marketing authorisation submitted by the MAH because of safety concerns should be handled through the relevant regulation of variation procedures for MRP and DCP products with the RMS evaluating the variation and circulating an Assessment Report to the CMS within the standardised timetable. For urgent safety concerns, the MAH may submit an urgent safety restriction.

In the case of a MAH wishing to withdraw its VMP from the market for safety reasons, action needs to be coordinated across the CMS and RMS. It is recommended that the MAH notifies the intention for a withdrawal to all CAs concerned at the same time and at an early stage.

The RMS should normally take the lead and coordinate the actions. The RMS and CMS should use the RA System to communicate with each other. The RMS and MAH should agree wherever possible on the timetable to be used for the different steps and actions to be taken. The timetable will depend on the urgency of the situation (see Part I Chapter 8. Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action).

It is important that the same action is followed in all MSs including communication to health-care professionals (see Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use).

*Actions by the Competent Authorities*

If following risk evaluation by the RMS, it is considered that action is necessary to vary the terms of, or to suspend, revoke or withdraw, the marketing authorisation of a veterinary medicinal product, the RMS should inform the CMS, the Agency and the MAH. The RMS should also keep the CMDv informed.

In order to ensure a coordinated approach, efforts should be made to reach a consensus on the proposed action to be taken, through discussion within the PhVWP-V.

Where the RMS concludes that action is necessary, the RMS should communicate with the MAH on the reasons for the conclusions reached by the MS and the action that should be taken by the MAH.

If the MAH does not voluntarily vary, withdraw or suspend the marketing authorisation, an urgent safety restriction procedure should be started by the RMS, or a referral according to Directive 2001/82/EC, Article 35, 40 or 41 to the CVMP should be initiated (see Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

The resulting CVMP Opinion will be followed by a single Decision of the European Commission binding on all MSs and the MAH.

In urgent cases, any MS may initiate immediate suspension of the marketing and use of a medicinal product on its territory, informing all MSs, the European Commission and the Agency within 24 hours. Such action should preferably be taken in all MSs in a coordinated manner facilitated by a proposal from the CVMP and its PhVWP-V to the CAs of MSs.

For CVMP Opinions according to Article 78(3) of Directive 2001/82/EC, see Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State.

#### 3.3.2.7 Communication to Healthcare Professionals and the General Public

When an MA is issued, the NCAs should make publicly accessible without delay the assessment report, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. Thus the RMS is obliged to prepare a public assessment report. The preliminary public assessment report should be provided to the MAH in particular for consideration of any commercially sensitive data or information.

Such a public assessment report needs updating, without delay, once regulatory action in response to a safety concern has been taken.

In case of a referral to the CVMP, the CVMP opinion should be made publicly accessible.

In addition it may be appropriate to inform veterinarians and other healthcare professionals and the general public about safety concerns related to MRP and DCP VMPs in other ways (e.g. public statements). It is important that consistent information is provided in all concerned EU/EEA countries.

In such cases, the RMS should propose the content of the information to be provided, and whenever possible, this should be agreed by the CMS and, if necessary considered by the PhVWP-V. There should be agreement whenever possible, on the method and timing of distribution of the information e.g. by letters from MAH or NCAs, or through NCA bulletins. Agreement should also be reached on the need for and timing of Public Statements and the event to press enquiries.

For guidance on pharmacovigilance communication, see Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use.

# 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance

## 4.1 Introduction

During the marketing period of a VMP urgent measures to safeguard animal or public health or the environment may be necessary. Within the European pharmacovigilance system it is essential that information concerning safety hazards possibly resulting in major changes to the MA status or withdrawal of a VMP, is exchanged between the NCAs, the Agency and the European Commission with the appropriate degree of urgency.

An early exchange of information will enable the NCAs to initiate data research and seek specialist expertise so that necessary decisions may be taken as soon as possible.

To support the rapid notification of safety concerns and the exchange of information required to take the necessary decisions, the NCAs, the Agency and the European Commission operate the Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in accordance with the procedure laid down in this guideline.

In the event that a recall of a product or a VMP batch is necessary, procedures shall apply as outlined in the Compilation of EU Procedures on Administrative Collaboration and Harmonization of Inspections (see Annex 4. References).

The purpose of the RA System is to alert, with the appropriate degree of urgency, other MSs, the Agency and the European Commission and about newly available pharmacovigilance data for VMPs which indicate that action could be needed urgently to protect animal or public health. It is essential that communication of such a problem occurs at an early stage, normally before a decision is taken in a MS.

The NUI System is established to support the collection and exchange of pharmacovigilance information between the NCAs, the European Commission and the EMEA which does not fulfil the criteria for a RA.

For RA and NUI Systems, the notified issue may then be discussed in a broad manner

- at the PhVWP-V on the basis of an assessment report,
- in the CVMP.

The RA System should primarily be used in problems or concerns relating to safety and efficacy concerns of VMPs authorised according to Directive 2001/82/EC, or Regulation (EC) No 726/2004.

The RA System must not be saturated by the exchange of less urgent information. For this purpose the NUI System should be used.

## 4.2 Criteria

### 4.2.1 Rapid Alert

The RA System should be used when a NCA has concern about a change in the balance between benefits and risks of a VMP that could require major changes in the status of the MA such as:

- an urgent safety restriction, or suspension or withdrawal of the MA,
- the recall of the VMP from the market,
- changes in the SPC and product information, e.g.:
  - the restriction in the indications,
  - the restriction in the availability of the medicinal product (legal status of marketing authorisation)
  - the reduction in the recommended dose (posology)
  - the introduction of new contraindications, and

- the introduction of new precautionary measures

- the need to inform veterinarians and other health-care professionals about an identified risk without delay.

Concerns about a change in the benefit-risk balance of a VMP or an active ingredient may be based on:

- a series of report(s) of unexpected and serious adverse events,
- reports of an expected adverse reaction which suggest greater severity or long-term sequelae than known or which identify new risk factors,
- significant increase in the reporting rate of an expected serious adverse reaction,
- evidence from studies (clinical trials or epidemiological studies) indicative of unexpected risk or a change in frequency or severity of a known risk,
- evidence that the risks of a particular product are greater than alternatives with similar efficacy.

### 4.2.2 Non-Urgent Information

For the exchange of potential concerns that do not fulfil the RA System criteria as defined above, the NUI System should be used. It refers e.g. to

- Pharmacovigilance data, which do not require immediate or urgent action and/or where additional information is required from other NCAs to support the evaluation of a potential concern,
- Provision of pharmacovigilance information, which does not require a response.

## 4.3 Procedure

Normally the case relating to the suspicion or concern is formulated by one NCA after evaluation of the data available in that NCA or the receipt of any other relevant important information that should be shared with other NCAs, the Agency and the European Commission. This should also include any action initiated by a MAH.

### 4.3.1 Sending a Rapid Alert or a Non-Urgent Information

The Agency, in consultation with MSs and the European Commission, has set up a data-processing network (EudraNet) for the rapid transmission of data between the EEA CAs in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding VMPs marketed in the EEA.

The electronic submission has replaced the Telefax system used in past to exchange this kind of information. However, in case of urgency e.g. Eudranet access is not available or the network is down, the former Telefax system should be used as alternative communication channel. The electronic communication with partners that are not connected via Eudranet has to be performed in a way that guarantees security and confidentiality of the data exchanged.

The establishment of pre-defined data formats is essential to ensure the collection of similar data, aid in exchange of information within the regulatory network and assist the common evaluation. Proposed forms are enclosed in Annex 2.5 Template for Rapid Alert and Non Urgent Information in Pharmacovigilance - Initial.

To send the form electronically, the established RA or NUI address lists and Eudranet mailboxes should be used which refer to the contact points within the NCAs, the Agency and the European commission (See Annex 3. Eudranet mailboxes for use in communication).

If using the RA/NUI Systems the NCA should comply with the following rules:

a) The template chosen must comply either with the RA System or the NUI System criteria.

b) Clear and concise information on the reasons for RA/NUI should be provided so that there is no need for clarification in the first instance.

c) The NCA or the Agency when generating the RA/NUI should transmit at least the minimal data.

d) Any information required from recipients should be specified clearly.

e) Annexes to the RA/NUI, considered to give sufficient details where necessary, should also be transmitted electronically, if available. The format to be used is the one specified in the Eudranet eMail Policy in the latest version (see Annex 4. References).

f) The RA should be transmitted as follows
   - nationally authorised VMPs including those authorised through the MRP and DCP: to the contact points of the NCAs, the Agency and the European Commission,
   - CAPs: to the contact points of the NCAs, the Agency and the European Commission and the Rapporteur.
   - The RA should in any case also be provided to the chairman of the CVMP.

g) A NUI should be transmitted as follows
   - nationally authorised VMPs: including those authorised through the MRP and DCP to the contact points of the NCAs, the Agency and the European Commission,
   - CAPs: in the first instance only to the Agency and the Rapporteur. The originator of the issue and the Rapporteur may request further information from other NCAs.
   - The NUI should in any case also be copied to the chairman of the CVMP.

h) If the fax is used it has to be transmitted to the established contact points as indicated above. A list of the fax numbers will be also accessible on the EudraNet homepage. Changes related to the fax numbers should be notified to the contact points of the NCAs, the Agency and the European Commission, immediately.

i) In case of urgency, when the NCA concerned has suspended the MA of a VMP or withdrawn the VMP from the market in order to protect animal or human health or the environment, the NCAs, the Agency and the European Commission have to be informed at the latest on the following working day using the RA System.

j) When a RA is circulated
   - nationally authorised VMPs: the initiating NCA should inform the MAHs concerned in his country adequately and promptly. Receiving NCAs are in general responsible for informing MAH(s) in their own country. Information on the MAH(s) may be given via associations of the MAHs both in sending and receiving NCA. For VMPs authorised nationally through the MRP or DCP the RMS should, however, inform the MAH adequately and promptly.
   - CAPs: the Agency Secretariat in agreement with the Rapporteur will promptly start an inquiry and information exchange with MAH(s).

### 4.3.2 Responses to a Rapid Alert or Non-Urgent Information

Responses to a specific RA should be sent only to the all NCAs and the Agency no later than one week of receipt of the alert.

In case of a NUI requested answers should be provided to the originator NCA and the Agency within the time frame indicated by the originator NCA.

The template (see Annex 2.6 Template for Rapid Alert and Non Urgent Information in Pharmacovigilance – Response) is to be used. The information requested by the originator NCA should be provided.

The Agency will summarise the issues related to RAs and NUIs in the Drug Monitor, which will be discussed and updated at each meeting of the PhVWP-V.

### 4.3.3 Assessment of a Rapid Alert

An interim assessment report should be prepared within five weeks after transmission of the initial RA

- *nationally authorised VMPs*: in general by the originating MS taking into account all information received and collated from other MSs,
    - *medicinal products authorised nationally through the mutual recognition procedure*: any risk evaluation should normally be carried out by the RMS unless other arrangements are agreed with MSs. In each case agreement needs to be reached on the responsibility for the management of the alert and the risk/benefit assessment by the RMS, or originator CMS, or jointly.
- *CAPs*: the Rapporteur should work closely with the originator NCA of the RA to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the benefit-risk assessment report, by the Rapporteur or the originating MS, or jointly.

When the collated information provides evidence of a serious safety concern a full benefit-risk assessment report for consideration by the PhVWP-V and/or CVMP should be prepared.

An assessment report should be sent to all NCAs, the Agency and the European Commission and should be discussed at the next meeting of the PhVWP-V.

The assessment report should be distributed electronically using the defined the established mailboxes as indicated in the Eudranet eMail Policy in the latest version (see Annex 4. References and in Annex 3. Eudranet mailboxes for use in communication). The electronic communication with partners that are not connected via Eudranet has to be performed in a way that guarantees security and confidentiality of the data exchanged. Consideration will need to be given to whether the matter is of Union interest and should be referred (see Part II Chapter 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State).

### 4.3.4 Assessment of Non-Urgent Information

On the basis of the Drug Monitor the PhVWP-V will discuss all topics exchanged via the NUI System and will agree on a case to case basis how to process the issue. In the event the preparation of an assessment report is considered necessary the same assessment procedure applies as indicated for a RA.

## 5. Referrals in Case of Safety Concerns Related to Products Authorised in the EU and Commission Decisions Following Suspension, Revocation or Variation of a Medicinal Product for Veterinary Use by a Member State

Guidance on referrals is provided in the Notice to Applicants i.e. Volume 6 of the rules governing medicinal products in the European Union (see Annex 4. References).

A procedure on Opinions issued by the CVMP in accordance with Article 78(3) of Directive 2001/82/EC following notification of consideration of suspension, revocation or variation of the marketing authorisation for a VMP by a MS and on subsequent Commission Decisions is to be developed separately. The procedure to be followed by a NCA for informing the Agency, the Commission and the other NCAs in accordance with Article 78(1) and (2) of Directive 2001/82/EC, in case the NCA considers

- suspension,
- revocation or
- variation to
    - restrict the indications or availability,
    - amend the posology,
    - add a contraindication or
    - add a new precautionary measure

of a MA as a result of veterinary pharmacovigilance data evaluation or where the NCA has suspended the MA of a VMP in order to urgently protect public or animal health is the RA system described in Part II Chapter 4. Rapid Alert and Non-Urgent Information System in Pharmacovigilance. It is a NCAs obligation to inform the MAH according to Article 78(1,2).

## 6. Principles of Cooperation with International Organizations concerned with Veterinary Pharmacovigilance

As laid down in Article 52 of Regulation (EC) No 726/2004, the Agency shall cooperate with international organisations, such as VICH, concerned with veterinary pharmacovigilance.

In addition, such collaboration will be considered, as need arises, by the Agency and would primarily concern WHO, including e.g. FAO, and OIE (See Part II section 1.9.2 Communication by the Agency and NCAs on significant safety issues of EU impact).

# Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU

# 1. Introduction

Part III of the document focuses on the technical and procedural aspects related to electronic reporting between the different partners. In particular the operational requirements and agreed standards for Electronic Data Interchange (EDI) and the secure exchange of Safety and Acknowledgement messages are outlined. For the overall obligations related to expedited reporting and periodic reporting for MAHs and NCAs, please refer to Part I Chapters 4. Adverse Event Reporting and 6. Requirements for Periodic Safety Update Reports, and Part II Section 1.3 Management of spontaneous reporting programmes respectively.

The requirements for the electronic reporting obligations of adverse events on an expedited and periodic basis, save in exceptional circumstances, are defined in EU legislation into Article 49 of Regulation (EC) No 726/2004, and recital 24 and Article 75 of Directive 2001/82/EC. 'Exceptional circumstances' are defined as mechanical, programme, electronic or communication failures that prevent electronic reporting.

Electronic reporting should be conducted by the following partners: NCAs in MSs as well as in Iceland, Liechtenstein and Norway (NCAs), MAHs and the Agency.

To support the fulfilment of these electronic reporting obligations, the European Commission, in collaboration with the Agency and NCAs established EudraVigilance Veterinary (EVVet), the European pharmacovigilance and data-processing network as defined in Article 51 and Article 57(d) of Regulation (EC) No 726/2004, and Article 76 of Directive 2001/82/EC, with the following main objectives:

- Assist with the rapid and secure transmission of adverse events between all partners;
- Fully comply with the respective EU guidelines and international standards;
- Facilitate the electronic reporting by providing the necessary technical tools to the partners;
- Assist the administration and management of adverse events;
- Provide signal detection functionalities and support scientific evaluation of adverse events;
- Establish a central repository of highest quality data on electronically reported adverse events occurring within and outside the EEA

An overview of guidelines and reference documents relative to electronic reporting of pharmacovigilance information can be found in Annex 5. Annexes and References concerning Electronic Reporting. All relevant guidance will also be published and maintained on the dedicated EVVet Website, see Annex 4. References.

## 2. Overview of the available electronic reporting systems in the EU

The following reporting systems have been made available for electronic reporting of adverse events by MAHs and NCAs:

### 2.1 EudraVigilance Veterinary

EVVet is the European data-processing system, as created by the Agency together with the MSs and the Commission, for the exchange, processing and evaluation of adverse events related to veterinary medicinal products authorised in the European Economic Area (EEA). Reporting to EVVet may occur via a Gateway or using the EudraVigilance Veterinary Web Reporting Module (EVWEB). The system is described in further detail in Annex 5. Annexes and References concerning Electronic Reporting, including how to register.

There are three possible ways of exchanging safety, acknowledgement and VMP report messages between pharmacovigilance parties in the EEA that are registered with EVVet:

- **Using a local gateway compliant with the** ICH M2 Gateway Recommendation for the Electronic Standard Transfer of Regulatory Information (ESTRI Gateway)**:**
  A tool providing a fully automated and secure way to exchange safety, acknowledgement and medicinal product report messages e.g. between the locally established pharmacovigilance system of a MAH or a NCA and the pharmacovigilance system of a partner of the EVVet community. For the technical requirements and the testing of the transmission via an ESTRI Gateway please see Annex 5. Annexes and References concerning Electronic Reporting, including Technical Specifications for a local gateway to operate EDI.

- **Using the WEB Trader component of EVWEB**:
  An integrated component of the EudraVigilance system that is made available by the Agency to registered parties (MAHs, NCAs or third parties reporting on behalf of MAHs) that do not have their own ESTRI Gateway established, providing a way to securely generate and exchange safety, acknowledgement and medicinal product report messages in a semi-automatic way directly via the Web.

- **Message Posting function of EVWEB**:
  A tool providing a semi-automatic way to upload safety, acknowledgement and medicinal product report messages that have been generated by the sender using his local pharmacovigilance system, to the Eudra gateway used by the EudraVigilance system, from where the messages will be re-routed to the specified receiver.

Inside the EVVet community, the possible communication scenarios are the following:

- **Reporting to the Agency**:
  In this scenario, MAHs, and competent authorities in the EEA send e.g. safety messages to the EudraVigilance System of the EMEA. The EudraVigilance System of the Agency returns an acknowledgement message to the original sender.

- **Re-routing via the Agency**:
  MAHs can create a message via EVWEB or on their local system and send the safety message to the Eudra Gateway at the Agency from where it is re-routed to the NCA specified as the Report Receiver in the message. The acknowledgement message generated by the receiving NCA is re-routed via the Eudra Gateway to the Report Sender.

Competent authorities can also create a message via EVWEB or on their local system and send the safety messages to the Eudra Gateway from where it is re-routed to the MAH or sponsors specified as the receiver in the message. The acknowledgement message generated by the receiving MAH or sponsor is re-routed via the Eudra Gateway to the Sender of the original safety message.

## 2.2 Simplified electronic reporting form for Marketing Authorisation Holders

The MAH Simplified Electronic Reporting Form (SEF) is a reporting module that has been developed to be used by MAHs with limited experience with direct reporting of adverse events reports using the EVWEB. For many products at present, safety reports are sent only occasionally and the MAH is unlikely to become sufficiently familiar with EVWEB to ensure consistent data input. Such MAHs may, in agreement with the local competent authority, use the SEF.

The SEF is available via the websites of the NCAs and on the EVVet website. No registration is required. It is a Web-based form available in most official EU languages and allows the recording of an adverse event report related to a VMP with the use of standard terminology.

This report will be attached automatically to an email that is sent to the NCA selected by the MAH. On receipt of this email, the NCA will further process and upload the information into the EVVet database.

It should be noted that the message will be sent via standard email. The tutorial available on the EVVet website includes information about more secure methods of transmission if required, see Annex 4. References.

## 2.3 Complementary electronic reporting tools made available in certain Member States

Several NCAs have additional electronic reporting tools available for local MAHs. These NCAs will further ensure that the information collected with these systems is transferred to the EVVet database.

In order to facilitate reporting by veterinarians and other health-care professionals, initiatives have been undertaken by several NCAs and at the Agency to develop electronic reporting tools that allow for easy transfer of the information to the above electronic systems.

All main reporting tools can be accessed via the EVVet website, see Annex 4. References, that contains hyperlinks to the relevant websites of the NCAs.

## 3. Electronic Reporting through company's headquarters or via a third party

If a pharmaceutical company decides to centralise the electronic reporting (e.g. reporting through the company's headquarters) or to outsource this activity, it remains the MAH's (e.g. the local affiliate) responsibility to ensure that adverse event reports are submitted electronically to the NCA as applicable.

The following should be taken into account:

- The arrangement should be clearly specified in the MAH's internal Standard Operating Procedures (SOPs).
- The Agency and the NCAs should be notified in writing about the arrangement (a template is available at the EVVet website, see Annex 4. References).
- The MAH should be registered with EVVet.
- Whoever is the physical Sender of the electronic adverse event reports, the MAH (e.g. local affiliate) will remain the contact point for all pharmacovigilance-related matters and responsible for the compliance with the pharmacovigilance obligations as defined in EU legislation, see Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections.

For the reporting from the NCAs to the MAH, the same principles apply, i.e. NCAs report electronically to the address of the headquarters or the third party instead of that of the local affiliate.

# 4. Creation of an electronic adverse event report

## 4.1 General principles on how to create an electronic adverse event report

The reporting tools available within EVVet are characterised by handling an XML message containing adverse event information structured and standardised in line with the Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the European Economic Area (EEA) including message and transmission specifications, see Annex 4. References.

Tutorials have been made available on the EVVet website (see Annex 4. References) on the actual creation of the reports via EVWEB.

Overall guidance on the required information for adverse events can be found in Part I Section 4.5 Required information for adverse event reports, including on how to report specific cases e.g. involving adverse events observed in offspring or adverse reactions in animals having been in contact with the treated animals.

It is recognised that it is often difficult to obtain all details on a specific case. However, complete information for an individual case, that is available to the Sender, should be reported in each adverse event report. This applies to all types of reports, i.e. reports with initial information on the case, follow-up information and cases highlighted for nullification.

In follow-up reports, new information should be clearly identifiable in the case narrative section.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units.

Where concomitant VMPs cannot be described on the basis of the active substance(s) or the invented name, e.g. in case only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information may be put in the case narrative.

## 4.2 Handling of Languages

Most of the information submitted through EVVet will be coded relevant to the agreed standard terminology (e.g. VeDDRA, species and breeds, country codes etc.). The recommended language for the non-coded information, in particular the narrative section, is English. Also EVWEB, the Web-application, has been set up in the English language while the simplified reporting form for MAHs is available in several EU languages, although the standard terminology that can be referenced with the simplified reporting form has remained in the English language. In case a different EU language has been used for the non-coded sections of adverse event reporting, the Sender should provide translations in English, whenever requested.

## 4.3 Data privacy laws

To comply with EU legislation on the protection of individuals with regard to the processing of personal data, electronic transmission of adverse events should be operated on the principles of anonymised information in accordance with national legislation.

While the detailed information provided by the primary source remains available at either the MAH or the CA to which the report was first sent, this information should be anonymised when creating the first report for submission via EVVet, in particular for the information in the narrative. This may be done by replacing the information with “Withheld”, or by entering only the initials of the First Name and Last Name. However, for later identification of a report and for reasons of duplicate detection it is still advised to include the geographical information (e.g. city and/or country or the first two characters of the Zip Code), and the sex in the fields containing information on the source for patients.

## 5. Transmission of electronic reports

### 5.1 Electronic transmission of adverse events to be transmitted on an expedited basis

Expedited reporting of adverse events relates to the EU reporting requirements for adverse events that are to be submitted within 15 days following receipt of the information to either the relevant NCAs, the Agency and/or the MAHs. For detailed requirements, please see Part I section 4.2 Requirements for expedited reporting.

A table summarising the requirements is included in the schemas for the guidance on the EDI of safety data for veterinary medicinal products in the EEA see Annex 5. Annexes and References concerning Electronic Reporting. These schemas provide an overview of the procedural actions of all partners involved that are dependent on whether the initial report has been sent directly from the primary source to the competent authority, or whether the report has been sent first to the MAH. In some MSs, veterinarians are legally required to inform directly the NCAs.

The MAH should submit the information to the NCA in whose territory the adverse event occurred, if within the EEA.

For serious and unexpected adverse events reporting from third countries, the information should be sent directly to the EVVet database. All serious expected adverse events having occurred in a third country are highly recommended to be sent also directly to the EVVet database.

### 5.2 Electronic transmission of adverse events not transmitted on an Expedited Basis in Electronic Format

The objective of the periodic transmission of adverse events not previously submitted electronically is to obtain a complete set of adverse events. These data, which are used to facilitate the data review and analysis are submitted complementary to the PSUR.

Where possible, it is strongly recommended that non-expedited adverse events are sent to the EVVet database and when required, to the relevant NCAs.

From a practical point of view, the following principles should be taken into account for the transmission of non-expedited reports in electronic format:

- It is recommended that non-expedited adverse event reports (initial and follow-up) are transmitted at regular intervals by the MAH preferably latest by the time of submission of the PSUR.
- It is recommended that transmissions of non-expedited adverse event reports include all adverse events reportable in a PSUR.
- The MAH should verify before sending non-expedited adverse event reports that such reports are not already included in the central database, in order to avoid the creation of duplicate reports. The following checks should be done:
    - Adverse event reports sent previously from an NCA to the MAH are expected to be already in the central database and should not be-resent by the MAH. However, the MAH may always consider sending a follow-up report when additional information has become available.
    - All adverse event reports sent previously to an NCA are expected to be included in the central database and should not be-resent. These include the expedited reports as well as the reports considered non-expedited that would have been submitted to an NCA.
    - When third country reports of similar VMPs need to be submitted, in case when such reports relate to different VMPs in the EEA with different PSURs, due care should be taken to submit such reports only once to the central database.

From the technical point of view, non-expedited reports should preferably be sent via the same reporting systems as being in use for the submission of expedited reports. Similarly, all available case information for non-expedited reports should be submitted in the same format, as complete as

possible. All information for which structured terminology is not available should be added to the narrative section.

The information related to the field R.02 of the Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the European economic area (EEA) including message and transmission specifications, see Annex 4. References; “Type of report submission” should contain the value “periodic”.

For MAHs that operate through the SEF, the non-expedited adverse event reports should be sent to the relevant NCAs in whose territory the event has occurred. It is the responsibility of the NCA to submit the data received via the SEF to the EVVet database.

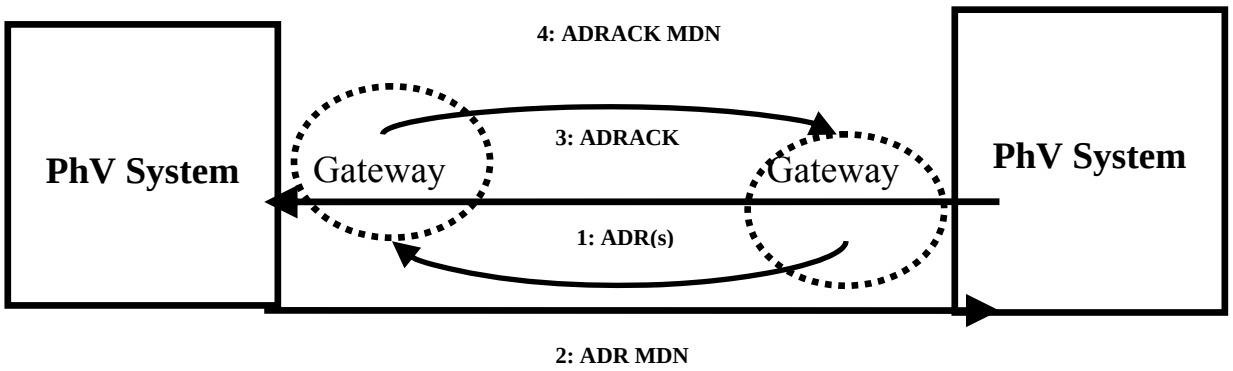
## 6. Processing electronic safety messages and acknowledgement of receipts

This section contains the rules on creating and processing Safety messages and acknowledgement of receipts for reporting via Gateway or via EVWEB within EVVet.

### 6.1 Processing and Acknowledgement of Receipt of Safety Messages through an electronic Gateway

For routine electronic reporting, a Safety Message including one or several adverse event reports is sent by the Report Sender through a Gateway to the Report Receiver. The Gateway of the Report Sender encrypts the message and dispatches it via the Internet. The Report Receiver's Gateway automatically returns a Message Disposition Notification (MDN) upon receipt of the message, decrypts the message and forwards it to the Report Receiver's pharmacovigilance system. This MDN will be referred to hereafter as the SAR-MDN.

The Report Receiver processes the incoming Safety Message in accordance with the Acknowledgement of Receipt procedure, and a corresponding Acknowledgement Message (ADRACK) is returned by the Report Receiver to the Report Sender. This ADRACK will be transmitted from the Report Receiver's Gateway to the Report Sender's Gateway, which then automatically returns a MDN upon receipt of the Acknowledgement Message. This MDN will be referred to hereafter as the ADRACK MDN.




Therefore, there are two levels of acknowledgement, one for the transmission, and the other for the contents:

- The first level of acknowledgment for the transmission of messages via the Gateways of the EDI partners is the MDN, which is automatically sent upon the receipt of an EDI Message being either a Safety or Acknowledgement Message by the Receiver's Gateway, without any content verification. This MDN is the proof to the Sender that a Message was received successfully by the Receiver.
- The second level of acknowledgement is the Acknowledgement Message, which summarises the outcome of the Safety Message and adverse event validation by the Report Receiver.

A Safety Message is successfully recognised and processed when:

| | Action | Documented by |
|---|---|---|
| a | The Sender and the Receiver can be correctly identified in the Safety Message, i.e. both the Sender and the Receiver are registered EDI Partners of the Eudra Gateway | MDN |
| b | The Safety Message adheres to the rules of XML well–formedness | MDN |

| | Action | Documented by |
|---|---|---|
| c | The Safety Message is built in accordance with the "Guideline on Data elements for the Electronic Submission of adverse reaction reports related to Veterinary Medicinal Products authorised in the European Economic Area (EEA) including message and transmission specifications (EMEA/CVMP/065/03)" and the corresponding "CVMP Guideline on Eudravigilance veterinary XML Schema Definition (XSD) (EMEA/CVMP/280/04)" which define each element of the ADR being transmitted and reflect how the various data elements are related to each other, are correct (see Annex 4. References). | ACK |
| d | The Safety Message and the Safety Reports are in full compliance with the business rules (see Annex 5.1 Overview of Guidelines and reference documents relative to Electronic Reporting of pharmacovigilance information). | ACK |

It is the sole responsibility of the Sender to ensure that the above criteria a-d are fully met.

A Safety Message is successfully transmitted when the Report Sender receives an ADR-MDN. This MDN is automatically sent by the Receiver's Gateway upon receipt of an EDI Message**,** and is the proof for the Sender that the Message sent was received successfully by the Receiver, thus fulfilling point a of the above criteria. Please note that the Gateway does not perform **Message content verification.**

The date of the ADR-MDN will serve as the official receipt date of the transmission of the Safety Message by the Eudra Gateway, and, as such, documents the fulfilment of the reporting timelines as defined in EU legislation, provided that the contents of the message are in accordance with the criteria mentioned above in points b, c and d. However in the event that an acknowledgment message has been created with an error, the message did not contain readable information and this should be addressed immediately by the Report Sender.

Acknowledgment procedure

The contents of the message needs to be processed and acceptance confirmed by the receiver via the **Acknowledgement of Receipt procedure.** In this procedure, the Receiver verifies the semantics, syntax, format and content both at the message and at the report levels against the criteria described in points b, c and d above. The Acknowledgment Message generated indicates acceptance or rejection.

- The Acknowledgement Message can return three different types of transmission acknowledgements at **Safety Message** level:
  - ACK code 01: All Safety Reports loaded;
  - ACK code 02: Not all Safety Reports loaded
  - ACK code 03: Message or System Error
- The Acknowledgement Message can return two different types of transmission acknowledgements at **Safety Report** level:
  - ACK code 01: Safety report loaded
  - ACK code 02: Safety Report not loaded

A rejection in the Acknowledgement of Receipt procedure resulting in an ACK code 02 or an ACK code 03 does not meet regulatory compliance obligations.

A single message may contain several reports with one or more of the reports being rejected in which case the message as such is not rejected but the faulty reports inside would be rejected. The Sender of a message that has been rejected by the Eudra Gateway or by EVVet in part or in total has the

obligation to resubmit corrected versions immediately within the reporting timelines as defined in legislation.

The detailed steps in the Acknowledgement of Receipt procedure are as follows:

- Following the successful receipt of the Safety Message, the Report Receiver is responsible for loading the adverse event report(s) into the locally established pharmacovigilance system. Furthermore, the Report Receiver is also responsible for generating, as quickly as possible, an Acknowledgement Message providing the validation status of each adverse event report contained in the Safety Message of that particular transmission.
- An adverse event report that is in full compliance with the Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the European Economic Area (EEA) including message and transmission specifications, see Annex 4. References will be acknowledged with the Safety Report ACK code 01 by the Report Receiver.
- Following receipt of the Acknowledgement Message, if one or more Safety Reports within a Safety Message are assigned the Safety Report ACK code 02, resulting in the Message transmission acknowledgement ACK code 02 (i.e. Not all Safety Reports loaded into the Report Receiver's locally established pharmacovigilance database), it means that the validation rules stated in the document "EV Veterinary 2.2 Message processing and business rules" (see Annex 5.1 Overview of Guidelines and reference documents relative to Electronic Reporting of pharmacovigilance information) have not been met. In such case the Report Sender must correct and retransmit the affected Safety Report(s).
- If, following the receipt of the Acknowledgement Message, the transmission acknowledgement code is ACK code 03, (XML parsing error, meaning that no data can be extracted from the Safety Message), the Report Sender must correct the error and the whole corrected Safety Message must be retransmitted electronically immediately. Safety Messages with the transmission acknowledgement code ACK code 03 do not meet regulatory compliance obligations.
- An Acknowledgement Message is sent by the Report Receiver to the Report Sender. At the Gateway level, an ADRACK-MDN will be returned to the Sender of the Acknowledgement Message.

In the event that the Sender does not receive an acknowledgment, it is recommended the Sender contacts the Receiver by alternative routes to investigate further and when technical problems are suspected contact the Eudra Service Desk.

If for technical reasons the Report Receiver does not return an MDN (being either an ADR-MDN or an ADRACK-MDN), alternative reporting measures may need to be taken by the Report Sender to maintain compliance with reporting timelines as defined in legislation (see Part I, Chapter 4. Adverse Event Reporting).

### 6.2 Processing and Acknowledgement of Receipt of Safety Messages through the WEB Trader

The WEB Trader is an integrated component of EVWEB. It provides an alternative solution to the use of a local Gateway to support the electronic transmission of Safety, Acknowledgement and Medicinal Product Report Messages. The WEB Trader allows registered EDI Partners to exchange EDI Messages with other registered EDI Partners. The WEB Trader is only available to EDI Partners that are not registered as Gateway users in EVVet i.e. organisations that do not have a local Gateway established to support the EDI process in pharmacovigilance.

The tutorials available on the EVVet website provide detailed guidance on the actual creation and sending of an adverse event report with EVWEB, see Annex 4. References.

The message flow using the WEB Trader is presented in Annex 5.5 Schema of Safety Report Transactions using WebTrader. An additional schematic overview of the electronic reporting procedures, describing the actions of the different EDI Partners can be found in "Schemas for the

guidance on the electronic data interchange (EDI) of safety data for VMPs in the EEA", see Annex 6. Schemas for the guidance on the Electronic Data Interchange (EDI) of safety data for VMPs in the EEA.

The contents of the message needs to be processed and acceptance confirmed by the receiver via the **Acknowledgement of Receipt procedure.** In this procedure, the Receiver verifies the semantics, syntax, format and content both at the message and at the report levels. The Acknowledgment Message generated indicates acceptance or rejection. A rejection in the Acknowledgement of Receipt procedure resulting in an acknowledgement code ACK code 02 or ACK code 03 does not meet regulatory compliance obligations.

- The Acknowledgement Message can return three different types of transmission acknowledgements at **Safety Message** level:
  - ACK code 01: All Safety Reports loaded;
  - ACK code 02: Not all Safety Reports loaded
  - ACK code 03: Message or System Error
- The Acknowledgement Message can return two different types of transmission acknowledgements at **Safety Report** level:
  - ACK code 01: Safety report loaded
  - ACK code 02: Safety Report not loaded
- A Safety Report that is in full compliance with the Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the European Economic Area (EEA) including message and transmission specifications, see Annex 4. References will be acknowledged with the ADR acknowledgement ACK code 01 by the Report Receiver.
- Following receipt of the Acknowledgement Message, if one or more Safety Reports within a Safety Message is assigned the ADR acknowledgement code 02, resulting in the Message transmission acknowledgement ACK code 02 (i.e. "Not all Safety Reports loaded" into the Report Receiver's pharmacovigilance database), it means that the validation rules stated in the document "EV Veterinary 2.2 Message processing and business rules", see Annex 4. References, have not been met. In such case the Report Sender must correct and retransmit the affected Safety Report(s).
- If, following the receipt of the Acknowledgement Message, the transmission acknowledgement code is ACK code 03 (Message or System Error, meaning that no data can be extracted from the Safety Message), the Report Sender must correct the error and the whole Safety Message needs to be immediately retransmitted electronically. Safety Messages with the transmission acknowledgement ACK code 03 do not meet regulatory compliance obligations.

In case the Sender does not receive an acknowledgment, it is recommended to contact the Receiver by alternative routes to investigate further and when technical problems are suspected contact the Eudra Service Desk.

## 7. How to Report Follow-up Information

Adverse event reports are sent at different times to multiple receivers. Therefore the initial/follow up status is dependent upon the receiver. The field "date of most recent information" (R.09) taken together with the field "Sender identifier" (H.0.5), the field "Report identification number" (R.01) and the field "Unique case registration number" (R.05) provide a mechanism for each receiver to identify whether the report being transmitted is an initial or follow-up report. For this reason these items are considered critical for each transmission. A precise date should be used (i.e. day, month, year).

The 'date of most recent information" is a mandatory field and should be changed each time follow up information is received by the Sender.

New information should be clearly identifiable in the case narrative section and provided in structured format in the applicable fields.

The Sender should report follow-up information on an expedited basis, if significant new information has been received. Significant new information relates e.g. to new adverse event(s), a change in the causality assessment and any new or updated information on the case that may impact on the interpretation of the case.

Situations where the seriousness criteria and/or the causality assessment related to an individual case are downgraded (e.g. follow up information leads to a change of the seriousness criteria from serious to non-serious; causality assessment is changed from related to non-related) should be also considered as significant change and thus reported on an expedited basis.

## 8. Nullification of Individual Cases

The nullification of individual cases should be used to indicate that a previously transmitted report should be considered completely void (nullified), for example when the whole case was found to be erroneous or in case of duplicate reports. It is essential to use the same R.01 "Report identification number" and R.05 "Unique case registration number" previously submitted when identifying a case to be nullified. A nullified case is one that should no longer be considered for scientific evaluation.

When nullifying a case the following principles need to be taken into account:

- The flag field R.14 "Nullification report" should be set to "Yes" and the nullification reason should be provided in the field R.15 "Reason for nullification". The nullification reason should be clear and concise to explain why this report is no longer considered to be a valid report.
- An individual case can only be nullified by the sending organisation.
- Once an individual case has been nullified, the case cannot be reactivated.
- If it becomes necessary to resubmit the case that has been previously nullified, a new number for field R.01 "Report identification number" and for field R.05 "Unique case registration number" should be assigned.
- Individual versions of case reports cannot be nullified, only the individual case to which they refer.
- Individual cases that have been nullified should not be used for scientific evaluation; however they should remain in the database for auditing purposes.

## 9. Handling of duplicate reports

When a sender has identified a duplicate, it is recommended to nullify one report while ensuring that the remaining report contains all additional information that would be present in the nullified report.

The table below gives examples of different scenarios for which nullifications should and should not be carried out. It will also provide information on what to do in specific situations.

**Examples of different scenarios for which case nullifications should and should not be carried out:**

| **1. Scenarios for which individual cases should be nullified:** | | |
|---|---|---|
| **Nr.** | **Example** | **Action** |
| 1 | An individual case has been identified as a duplicate of another individual case previously submitted. | One of the individual cases should be nullified. The remaining valid case (considered as the master) should be updated with any additional information that had been reported in the nullified case.<br><br>It should be considered to include in the narrative of the master that a duplicate case has been nullified with the corresponding information on the sender, the R.01 "Report identification number" and R.05 "Unique case registration number" of the nullified case.. |
| 2 | A wrong "Unique case registration number" (R.05) was accidentally used. | The report with the wrong "Unique case registration number" (R.05) should be nullified.<br><br>A new case should be created with a correct "Unique case registration number". |
| 3 | A "Unique case registration number" (R.05) was accidentally used the same as already been used for a different report and is therefore not unique. | The last entered report should be nullified and re-entered with a new "Unique case registration number". |
| 4 | On receipt of further information it is confirmed that the adverse event occurred before the suspect drug(s) was taken. | The case should be nullified. |
| 5 | On receipt of further information on an individual case, it is confirmed that the patient did not receive the suspect drug and the minimum reporting criteria are no longer met. | The case should be nullified. |
| 6 | On receipt of further information it is confirmed that the reported adverse event(s) did not occur to the patient. | The case should be nullified. |

| 2. Scenarios, for which individual cases should NOT be nullified | | |
|---|---|---|
| **Nr.** | **Example** | **Action** |
| 7 | On receipt of further information on an individual case, it is confirmed that the patient did not receive the sender's (MAH's) suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for a report are still met. | The case should not be nullified but a follow-up should be sent to update the information. |
| 8 | On receipt of further information the reporter has confirmed that the reported adverse event is no longer considered to be related to the suspect drug(s). | The case should not be nullified.<br><br>A follow-up report should be submitted with the updated information on the case. |
| 9 | Change of the individual case from serious to non-serious (downgrading). | The case should not be nullified. A follow-up report should be submitted with the seriousness flag in field R.18.16.08 set to "No". |

Specific duplicate detection software is also available by the European Medicine Agency and allows screening of the databases for duplicate reports based on a specific algorithm developed and tested for the EVVet data. This application allows linking two or more reports that are considered duplicates, hence no reports would be nullified by the Agency through the use of the duplicate detection software. When reports are linked, one report will be selected as the principal report but there will be no transfer of information from any of the linked duplicate reports, instead it will remain possible to continue sending follow-up reports to any of the linked duplicate reports. The data analysing tools take into account when reports have been linked to avoid e.g. VeDDRA terms to be counted twice.

## 10. Access to EudraVigilance Veterinary Data

Only registered users may send data and/or have direct access to EVVet.

NCA users have “read and write” access to all reports in EVVet.

All other registered users have access to the data that they have submitted to EudraVigilance Veterinary.

Access rights will be defined in the EudraVigilance Veterinary Access Policy, see Annex 4. References.

## 11. EudraVigilance Veterinary Medicinal Product Dictionary

The population of the EudraVigilance Veterinary Medicinal Product Dictionary (EVVetMPD) is necessary to permit the correct identification of VMPs, related to adverse events reported in line with the reporting obligations set out in EU legislation, as well as data analysis and signal detection.

The EVWEB tool allows submitting product information in a structured way.

A procedure is in place between NCAs and the Agency to allow regular data transfers of product information for VMPs that are the subject of adverse event reports already submitted to EVVet. Further initiatives are ongoing to automate the data transfer of the relevant product information from the local NCA product databases to the EVVetMPD.

# Part IV: Guideline on Public Communication on Medicinal Products for Veterinary Use

## 1. Introduction

Communication on pharmacovigilance and safety issues to veterinarians and other health-care professionals and the general public is an important issue.

Further guidance for MAHs, NCAs and the Agency on pharmacovigilance communication will be developed.

## 2. Key Principles for Public Communication on Veterinary Medicinal Products

The following key principles should be considered by MAHs, NCAs and the Agency for public communication on veterinary medicinal products (VMPs) in general:

- Provision of information about the safe and effective use of VMPs supports appropriate use and should be considered as a public health responsibility.
- Communication of such information needs to be considered throughout the risk management process.
- It is essential that such information is communicated to veterinarians and other health-care professionals and relevant partners including veterinary and other health-care professional organisations, learned societies, authorities for food safety and pharmaceutical wholesalers.
- In principle, significant new or emerging information should be brought to the attention of veterinarians and other health-care professionals before the general public, in order to enable them to take action and respond to e.g. animal owners or breeders adequately and promptly. The important function of veterinarians and other health-care professionals in disseminating such information to the general public is recognised and should be supported.
- The overriding principle should be to ensure that the right message is delivered to the right persons at the right time.
- Effective communication on safe and effective use of VMPs authorised in the EU entails:
  - co-operation of all partners;
  - co-ordination between relevant partners, within and, if possible, outside the EEA; and
  - a strategy which meets the requirements resulting from the urgency to communicate and from the expected impact of the information on animal or public health.
- Communication should not usually take place before the corresponding regulatory procedure has been completed, however, exceptionally (e.g. in the case of an urgent safety restriction) there may be a need to disseminate information prior to completion of a procedure. For CAPs, the appropriate point in time for dissemination of information is usually once the CVMP Opinion has been adopted.
- A consultation between the MAH and the NCAs or the Agency (and other partners as appropriate) is advisable on the format and content of the information, recipients and the timetable. If a timetable is agreed for release of the information it should be fully respected by all partners.

# Annexes

## 1. Glossary

| Term | Abbreviation | Definition |
|---|---|---|
| Acknowledgement of Receipt* | - | The procedure by which, on receipt of a Safety Message, the syntax and semantics are checked by the Receiver, and the outcome is transmitted to the Sender (e-term) |
| Acknowledgement Message* | ADRACK | An EDI Message containing information on the result of the Acknowledgement of Receipt procedure, used to acknowledge the receipt of a Safety Message and the Safety Report(s) contained in the Safety File (e-term) |
| Adverse event | - | Any observation in animals, whether or not considered to be product-related, that is unfavourable and unintended and that occurs after any use of VMP (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy according to approved labelling or noxious reactions in humans after being exposed to VMP(s). Ref. VICH Topic GL24 |
| Adverse reaction | - | A reaction to a veterinary medicinal product which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function. Ref. Article 1 (10) of Directive 2001/82/EC, as amended. This guideline will not include the word ”suspected” when making full text reference to adverse reactions, serious adverse reactions, human adverse reactions. |
| The European Medicines Agency | EMA or the Agency | A decentralised scientific body of the European Union which is responsible for the protection and promotion of public and animal health, through the coordination of evaluation and supervision of centrally authorised medicines for human and veterinary use. |
| Animals managed and treated as a group | - | Animals in intensive food animal production concerning species such as poultry, fish or bees which are managed and treated as a group. In these situations a certain level of mortality rate is considered as ‘normal’ or ‘expected’. These species are usually treated as a group/flock and only an increase of mortality rate, or severe signs, or animal production losses exceeding the rates normally expected should be considered as serious. |
| Cascade use | - | Use of a medicinal product<br>- In non-food producing species, and in horses not being intended for slaughter for human consumption, the use of, in the first instance, a veterinary medicinal product which has been authorised for another species or for another condition in the same species in the Member State concerned, or, if such product is not available, the use of a medicinal product authorised for human use in the Member State concerned, or a veterinary medicinal product authorised in another Member State, or, if such product is not available, the use of a product prepared extemporaneously in accordance with the terms of a veterinary prescription in accordance with the provisions of Article 10 of Directive 2001/82/EC.<br>In food producing species, providing that the substances included in the products to be used are included in Table I (allowed substances) of the Regulation 37/2010 and that the veterinarian specifies an appropriate withdrawal period in the first instance, a veterinary medicinal product which has been authorised for another species or for another condition in the same species in the Member State concerned, or, if such product is not available, the use of a medicinal product authorised for human use in the Member State |

| Term | Abbreviation | Definition |
|---|---|---|
| | | concerned, or a veterinary medicinal product authorised in another Member State for in the same or another food-producing species, or, if such product is not available, the use of a product prepared extemporaneously in accordance with the terms of a veterinary prescription in accordance with the provisions in accordance with Article 11(1, 2) of Directive 2001/82/EC. |
| Centrally Authorised Product | CAP | A product for which the marketing authorisation is granted, in accordance with Regulation (EC) No 726/2004, by the European Commission, and once granted is valid in all European Union (EU) and EFTA States (Iceland, Liechtenstein and Norway). |
| Clinical Trials | - | A single scientific experiment conducted in a target species to test at least one hypothesis relevant to the proposed effectiveness claim(s) or to in-use safety in the target animal for a veterinary product under investigation. For the purpose of this guidance, the term clinical study and study are synonymous. This definition originates in the VICH GL9 (GCP) on Good Clinical Practice and is considered synonymous to the term clinical study. |
| Concerned Member State | CMS | A Member State involved in a MRP or DCP in relation to procedures on Marketing Authorisations in accordance with Article 32 of Directive 2001/82/EC. |
| Competent Authority | CA | An authority within the EEA (excluding the Agency and the European Commission) responsible for the granting of marketing authorisations for medicinal products and the supervision of marketing of such products in accordance with the relevant laws and regulations established under EU law. |
| Committee for Medicinal Products for Veterinary Use | CVMP | A scientific committee responsible for preparing the Agency's opinions on all questions concerning veterinary medicinal products, in accordance with Article 30 of Regulation (EC) No 726/2004. |
| Crisis | - | An event, which occurs when new information, which could have a serious impact on animal and/or public health, is received for a veterinary medicinal product and which requires immediate action, in accordance with the Crisis Management Plan regarding Safety Issues for Centrally Authorised Products or Veterinary Use. |
| Data Lock Point | DLP | A cut-off date for data to be included in a PSUR. It may be set according to the European birth date or International birth date of the medicinal product. The MAH should in any case submit the PSUR no later than 60 days after the DLP. |
| Decentralised procedure | DCP | A procedure used in order to obtain marketing authorisations in several Member States where the VMP in question has not yet received a marketing authorisation in any Member State at the time of application. |
| Detailed Description of a Pharmacovigilance System | DDPS | Document by which the applicant describes the pharmacovigilance system he/she intends to put in place. It is to be included in the Marketing Authorisation Application |
| EDI Message* | | A set of segments, structured using an agreed standard, prepared in a computer readable format that can be automatically and unambiguously processed. (e-term) |
| EDI Partner* | | An organisation exchanging EDI Messages in the area of pharmacovigilance in the post-authorisation phase with another organisation. For the purpose of this Guideline EDI partners in the post-authorisation phase in pharmacovigilance are as follows: |

| Term | Abbreviation | Definition |
|---|---|---|
| | | - Competent Authorities in the EEA<br>- Marketing Authorisation Holders in the EEA<br>(e-term) |
| The European Economic Area | EEA | An economic association between all Member States of the European Union and EFTA States (Norway, Iceland and Liechtenstein). |
| Electronic Data Interchange* | EDI* | The electronic transfer, from computer to computer, of commercial and administrative data using an agreed standard to structure an EDI message. (e-term) |
| e-term | | A term used for the electronic exchange of data |
| EU Birth Date | EBD | The date of the first marketing authorisation within the European Union |
| EudraVigilance Veterinary | EVVet | The European data-processing network and database management system for the exchange, processing and evaluation of suspected adverse event reports related to veterinary medicinal products marketed in the European Economic Area (EEA) |
| EudraVigilance Veterinary Database* | EVVet DB | The pharmacovigilance database defined in EU legislation. (e-term) |
| EudraVigilance Veterinary Web reporting tool* | EVWEB | A web based reporting tool that allows the generation of Safety and Acknowledgement Messages and the electronic transmission of these messages in secure way via the EudraVigilance Gateway to any other EDI Partner in the EEA. (e-term) |
| EudraVigilance Veterinary Medicinal Product Dictionary | EVVetMPD | A large reference pharmacovigilance database (the central database) that is built by importing and consolidating data from multiple sources, including information on veterinary medicinal products. |
| Expedited report | | A report of a serious adverse event or serious and unexpected third country report submitted within 15 days following receipt of the information in accordance with the provisions of Articles 75(2) and (3) and Articles 76(2) and (3) of Directive 2001/82/EC and Article 49 of Regulation (EC) No 726/2004. |
| Extensible Markup Language* | XML | A subset of SGML that is completely compatible with SGML. (e-term). A data exchange service, which consists of all core standards and functionality required for supporting the standards as currently defined within the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (e.g. Simple Mail Transfer Protocol/Secure Multipurpose Internet Mail Extension -SMTP/SMIME- protocol). (e-term) |
| Harmonised Birth Date | HBD | A Birth Date agreed amongst MS and industry for one specific product participating in the MS work share initiative on PSUR assessments |
| Human adverse reaction | - | A reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine. Ref. Article 1 (11) of Directive 2001/82/EC.<br>This guideline will not include the word “suspected” when making full text reference to human adverse reactions. |
| International Birth Date | IBD | The date of the first marketing authorization for a same or similar product granted anywhere in the world, including any VICH region. |
| International | VICH | A trilateral (EU-Japan-USA) programme aimed at harmonising |

| Term | Abbreviation | Definition |
|---|---|---|
| Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products | | technical requirements for veterinary product registration. |
| Lack of expected efficacy | - | The apparent inability of an authorised product to have the expected efficacy in an animal, according to the claims of the SPC and following use of the product in accordance with the SPC. In the following text this guideline will not include the word 'suspected' when making full text reference to lack of expected efficacy. |
| Marketing Authorisation | MA | A decision given either by the European Commission, under centralised procedure, or by national competent authorities under national procedures, including decentralised and mutual recognition procedures, authorising the placing on the market of the VMP (in accordance with Regulation (EC) No 726/2004 or Directive 2001/82/EC, as amended) |
| Marketing Authorisation Holder | MAH | A person or entity who/which holds the authorisation of a VMP. |
| Message Disposition Notification* | MDN* | A notification on the receipt of an EDI Message returned by the Receiver's Gateway to the Sender's Gateway. The MDN concludes a Message Transaction performed between two parties in a Gateway to Gateway communication. (e-term) |
| Message Transaction* | | A set of actions encompassing the electronic transmission of an EDI Message (Safety Message, Acknowledgement Message) between a Sender and a Receiver including the return of the Message Disposition Notification for that message. (e-term) |
| Mutual recognition procedure | MRP | A procedure whereby concerned Member States recognize the marketing authorisation already granted by a reference Member State and authorize the placing on the market of the product in their national territory, as outlined in Directive 2001/82/EC. |
| Member State | MS | Any of the 27 countries that holds membership to the European Union |
| National Competent Authority | NCA | The Competent Authority of a Member State having the responsibility for the evaluation and authorisation of MAs. The term includes the competent authorities of Iceland Norway and Liechtenstein. |
| Off-label use | - | The use of a veterinary medicinal product that is not in accordance with the SPC, including the misuse and serious abuse of the product. Ref. Article 1 (16) of Directive 2001/82/EC. |
| Post-authorisation safety studies | - | Pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised veterinary medicinal product. Ref. Article 1 (15) of Directive 2001/82/EC. |
| Primary data | | Data transmitted from the original reporter to a MAH or a CA or the Agency. |
| Periodic Safety Update Report | PSUR | A periodical scientific report on adverse events and other issues within the scope of pharmacovigilance that have been reported to a MAH during a specific period. Ref. Article 1 (14) and Article 75 of |

| Term | Abbreviation | Definition |
|---|---|---|
| | | Directive 2001/82/EC |
| PSUR, abridged | - | A PSUR that contains less information than a full PSUR and that contains only administrative data, and which has been prepared for a non-marketed product for which no reports have been received during the period |
| Receiver* | | An intended recipient of the EDI Message. (e-term) |
| Receiver Identifier* | Receiver ID | An identification or combined EDI qualifier and ID of the recipient. (e-term) |
| Reference Member State | RMS | A Member State responsible for the evaluation of data in MRP and DCP in accordance with Article 32 of Directive 2001/82/EC. |
| Report Receiver* | | An intended recipient of the transmission of a Safety Message, which for the purpose of this guideline is an EDI Partner. (e-term) |
| Report Sender* | | A person or entity creating a Safety Message as EDI Message in order to submit a Safety Report, which for the purpose of this guideline is an EDI Partner. In the Report Transaction the Report Sender will always remain the same, whereas with the exchange of messages the "Sender" and "Receiver" roles will change. (e-term) |
| Report Transaction* | | A complete set of actions in the electronic reporting of Safety Messages to comply with regulatory requirements. (e-term) |
| Safety File* | | An electronic file transmitted in one Message Transaction between one Sender and one Receiver containing one Safety Message. (e-term) |
| Safety Message* | | An EDI Message including the information provided for containing one/more Suspected Adverse Reaction Reports contained in one Safety File exchanged between one Sender and one Receiver in one Message Transaction. (e-term) |
| Sender Identifier* | Sender ID* | Identification (ID) or combined EDI qualifier and ID of the Report Sender. (e-term) |
| Serious adverse event | - | An adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect.<br><br>For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event. See VICH Topic GL 24.<br><br>See also definition for "animals managed and treated as a group". |
| Serious adverse reaction | - | An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated.<br>Ref. Article 1 (12) of Directive 2001/82/EC<br><br>Life-threatening in this context refers to a reaction in which the animal was at risk of death at the time of the reaction.<br><br>See also definition for "animals managed and treated as a group". |
| Simplified Electronic Reporting Form* | SEF* | A reporting module to be used for Marketing Authorisation Holders (MAH) with limited experience in the direct reporting of adverse reaction reports using the EudraVigilance Veterinary Web Reporting Module. (e-term) |

| Term | Abbreviation | Definition |
|---|---|---|
| Standard Generalized Markup Language* | SGML* | An International Standard (ISO 8879) computer language for describing a document in terms of its content (text, image) and logical structure (chapters, paragraphs, etc.) It is a standard for how to specify a document markup language or tag set. Such a specification is itself a document type definition (DTD). SGML is not in itself a document language, but a description of how to specify one. It is a metalanguage. SGML is based on the idea that documents have structural and other semantic elements that can be described without reference to how such elements should be displayed. (e-term) |
| Summary of Product Characteristics | SPC | A document that contains the information on the condition of use of a veterinary medicinal product as developed during the course of the assessment process. |
| Suspected Adverse event report* | SAR report* | A document providing the most complete information on suspected adverse event(s)/suspected unexpected serious adverse event(s) related to the administration of one or more medicinal products at a certain point of time. An adverse event report may also be referred to as a Safety Report. (e-term) |
| Third Country | - | A country outside the EEA area |
| Unexpected adverse event | - | An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labelling or approved documents describing expected adverse events for a VMP. Ref. VICH Topic GL 24 |
| Unexpected adverse reaction | - | An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics<br>Ref. Article 1 (13) of Directive 2001/82/EC |
| Urgent safety restrictions | | An interim change to the product information due to new information having a bearing on the safe use of the medicinal product, concerning particularly one or more of the following items in the SPC: therapeutic indications, posology, contraindications, warnings, target species, and withdrawal periods, Ref. Article 2 of Regulation (EC) No 1234/2008. |
| Veterinary Dictionary for Drug Regulatory Activities | VeDDRA | A list of standard clinical terms to be used in reporting suspected adverse reactions in animals or humans after exposure to veterinary medicinal products |
| Veterinary Medicinal Product | VMP | Any substance or combination of substances, in accordance with Article 1 of Directive 2001/82/EC, presented as having properties for treating or preventing disease in animals; or which may be used in or administered to animals either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis |

*electronic term (e-term)

# 2. Templates

## 2.1 EU Template for MAHs for reporting adverse events

| | | |
|---|---|---|
| Safety issues<br>in animals ☐<br>in humans ☐<br>Lack of expected efficacy ☐<br>Withdrawal period issues ☐<br>Environmental problems ☐ | **SENDER REPORT IDENTIFICATION – CASE REF. No:**<br>Reporting country:<br>Purchase country:<br>Report source: | 1 |

| | |
|---|---|
| **1. ADDRESS OF COMPETENT AUTHORITY** | **2. NAME AND ADDRESS OF SENDER** |
| **Date complaint received by sender:** (dd/mm/yy) | |
| **Type of report:** Initial ☐ Follow-up ☐ (date, case number) | |
| **Person who reported the reaction:** veterinarian ☐ owner ☐ physician ☐ pharmacist ☐ other: | |
| **3. VETERINARIAN / PHYSICIAN / PHARMACIST** | **4. ANIMAL OWNER / HUMAN PATIENT** |
| Name: | Name *(according to ... country)*: |
| Address: | Address: |
| Telephone No. | Telephone No. |

This information should be managed in accordance with national legislation concerning personal data protection.

This information should be managed in accordance with national legislation concerning personal data protection.

| | | | |
|---|---|---|---|
| **5. ANIMAL DATA** | **No. of animals treated:** | **No. of animals showing signs:** | **No. of animals died:** |
| **Animal characteristics (animal(s) showing signs):** | | | |
| Species: | Breed/production type: | | |
| Sex/physiological status: female ☐ male ☐ pregnant ☐ neutered ☐ lactating ☐ other: | | | |
| Weight (kilos): | Age: | | |
| **State of health at time of treatment:** good ☐ fair ☐ poor ☐ critical ☐ unknown ☐ | | | |
| **Reason(s) for treatment (prevention against what disease(s) or initial diagnosis):** | | | |

| | | |
|---|---|---|
| **6. PRODUCT DATA # 1** | | |
| **Trade name** (include dosage form and strength): | | **M.A. number:** |
| **Active substance(s) (INN):** | | **ATC vet code(s):** |
| **Batch No.:** | **Expiry date:** | **Storage details:** |
| **Treatment details:** | | |
| Dose/frequency: | | Route/site of administration: |
| Start date of treatment: | Stop date or duration: | Who administered the product:<br>veterinarian ☐ owner ☐ other ☐ |
| **Use according to label:** yes ☐ unknown ☐ no ☐ explain: | | |
| **Action taken after reaction:** drug withdrawn ☐ dose reduced ☐ other ☐ | | |
| **Did reaction abate after stopping drug ?** yes ☐ no ☐ not applicable ☐ | | |
| **Did reaction reappear after reintroduction ?** yes ☐ no ☐ not applicable ☐ | | |
| **List all other relevant medications given to animal(s):**<br>*Give the list of the other veterinary medicinal products used concurrently and go to special field for completion of details (page 3)* | | |

| SENDER CASE REF. No: | 2 |
|---|---|

**7. EVENT DATA** (*applicable for all types of adverse reaction(s) reported following administration of veterinary product(s)*

**Date of onset of signs:**

**Duration of reaction:**

**Describe the sequence or events including administration of product(s), all clinical signs, site of reaction, severity, pertinent lab tests, necropsy results, possible contributing factors (if necessary use extra sheet): Include details of treatment given to address this adverse reaction.**

**Were the signs treated?**

**No** ☐ **Yes** ☐

**Outcome of reaction to date:**

| | Killed/euthanised | died | under treatment | alive with sequalae | recovered | unknown |
|---|---|---|---|---|---|---|
| No. of animals: | | | | | | |
| Date when: | | | | | | |

**8. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT PRODUCT #1 CAUSED EVENT**

possible ☐ unlikely ☐ no attending vet ☐

**9. PREVIOUS EXPOSURE AND EVENT(S) TO PRODUCT #1**

Previous exposure to this product? no ☐ yes ☐ Date(s):

Previous reaction to this product? no ☐ yes ☐ Describe:

De-challenge information:

**10. DETAILS OF SUSPECTED ADVERSE REACTION(S) IN HUMANS**

Patient details Sex: Age/date of birth: Occupation (with relevance to exposure):

Date of exposure: Date of reaction:

Nature and duration of exposure, reaction details (including symptoms) and outcome:

**11. CAUSALITY ASSESSMENT RELATED TO PRODUCT #1**

**Classification:** A (probable) ☐ B (possible) ☐ O (unclassified) ☐ O1 (inconclusive) ☐ N (unlikely) ☐

**Reason for classification:**

**12. OVERALL CAUSALITY ASSESSMENT RELATED TO ALL SUSPECTED PRODUCTS**

**FOR COMPETENT AUTHORITY USE ONLY**

**To replicate for each product used concurrently**

**SENDER CASE REF. No:** 3

**6. DATA FOR PRODUCTS ADMINISTERED CONCURRENTLY – PRODUCT # <Enter sequential number; 2 or higher>**

**Trade name** (include dosage form and strength): **M.A. number:**

**Active substance(s) (INN)**:: **ATC vet code(s):**

**Batch No.:** **Expiry date:** **Storage details:**

**Treatment details:**

Dose/frequency: Route/site of administration:

Start date of treatment: Stop date or duration: Who administered the product:

veterinarian ☐ owner ☐ other ☐

**Use according to label:** yes ☐ unknown ☐ no ☐ explain:

**Action taken after reaction:** drug withdrawn ☐ dose reduced ☐ other ☐

**Did reaction abate after stopping drug?** yes ☐ no ☐ not applicable ☐

**Did reaction reappear after reintroduction?** yes ☐ no ☐ not applicable ☐

**8. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT REACTION WAS CAUSED BY PRODUCT #**

possible ☐ unlikely ☐ no attending vet ☐

**9. PREVIOUS EXPOSURE AND REACTION(S) TO PRODUCT #**

Previous exposure to this product? no ☐ yes ☐ Date(s):

Previous reaction to this product? no ☐ yes ☐ Describe:

De-challenge information:

**11. CAUSALITY ASSESSMENT RELATED TO PRODUCT #**

**Classification:** A (probable) ☐ B (possible) ☐ O (unclassified) ☐ O1 (inconclusive) ☐ N (unlikely) ☐

**Reason for classification:**

## 2.2 EU template for healthcare professionals for reporting adverse events

| | | |
|---|---|---|
| Form to be sent to (Name and address of the Competent authority)<br><br>Fax n° Phone n°<br>E mail Website address | | IN CONFIDENCE<br>*For official use only*<br>Ref. Number |
| IDENTIFICATION | NAME AND ADDRESS OF SENDER | NAME & ADDRESS/ REF. OF PATIENT |
| Safety issue<br>in animals ☐<br>in humans ☐<br>Lack of expected efficacy ☐<br>Withdrawal period issues ☐<br>Environmental problems ☐ | Veterinarian ☐ Pharmacist ☐ Other ☐<br><br>Phone n°: Fax n°: | *(according to national law)*<br>This information should be managed in accordance with national legislation concerning personal data protection. |

PATIENT(S) *Animal(s)* ☐ *Human(s)* ☐ *(for humans fill only age and sex below)*

| Species | Breed | Sex | Status | Age | Weight | Reason for treatment |
|---|---|---|---|---|---|---|
| | | Female ☐<br>Male ☐ | Neutered ☐<br>Pregnant ☐ | | | |

VETERINARY MEDICINAL PRODUCTS ADMINISTERED BEFORE THE ADVERSE EVENT
*(if more products are administered concurrently than the number of boxes available, please duplicate this form)*

| | 1 | 2 | 3 |
|---|---|---|---|
| Name of the veterinary medicinal product (VMP) administered | | | |
| Pharmaceutical form & strength (ex: 100 mg tablets) | | | |
| Marketing Authorisation number | | | |
| Batch number | | | |
| Route/site of administration | | | |
| Dose / Frequency | | | |
| Duration of treatment /Exposure<br>Start Date<br>End Date | | | |
| Who administered the VMP? (veterinarian, owner, other) | | | |
| Do you think that the reaction is due to this product? | Yes ☐ / No ☐ | Yes ☐ / No ☐ | Yes ☐ / No ☐ |
| Has the Marketing Authorisation Holder (MAH) been informed? | Yes ☐ / No ☐ | Yes ☐ / No ☐ | Yes ☐ / No ☐ |

| SUSPECTED ADVERSE REACTION DATE<br>____/____/____ | **Time between administration and event** in minutes, hours or days | Number treated ____<br>Number reacted ____<br>Number dead ____ | Duration of the adverse reaction in minutes, hours or days |
|---|---|---|---|

**DESCRIPTION OF THE EVENT** *(Safety issues in animals or Safety issues in humans/Lack of expected efficacy/Withdrawal period issues/Environmental problems) – Please describe:*

**Indicate also if the reaction has been treated, how and with what and what was the result?**

**OTHER RELEVANT DATA (ATTACH FURTHER PAPERS IF NECESSARY e.g. investigations carried out or ongoing, a copy of medical report for human cases)**

**HUMAN CASE**
**If the reported case refers to a human being, please also complete the details of exposure below**

I. Contact with treated animal ☐

***Figure: 1.*** **ORAL INGESTION** ☐

***Figure: 2.*** **TOPICAL EXPOSURE** ☐

***Figure: 3.*** **OCULAR EXPOSURE** ☐

***Figure: 4.*** **INJECTION EXPOSURE** ☐ **FINGER** ☐ **HAND** ☐ **JOINT** ☐ **OTHER** ☐

Figure: 5. Other (deliberate….) ☐

Exposure dose:

If you do not agree that your complete name and address are send to the MAH if further information requested, please tick the box ☐

**Date:** **Place:** **Name and signature of sender:**

***Contact point (phone)*** (if different from the number on page 1)

## 2.3 Templates for tables for use as necessary in preparing and assessing Periodic Safety Update Reports (PSURs)

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

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

| **Period** | **PSUR 1** | | | **PSUR 2** | | |
|---|---|---|---|---|---|---|
| | *<Year* | *Year* | *Year* | *Year* | *Year* | *Year>* |
| Number of animals <*reacting, experiencing lack of efficacy*> during the period | | | | | | |
| <*Number of doses sold during period, sales volume**> (<*insert sort e.g. Litres, Doses*>) | | | | | | |
| Ratio (number of animal/number of doses) | | | | | | |

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

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

| **Country*** | **Total sales volume** | **Number of animals treated ****** | **Number of animals reacted in SARs assessed A, B or O** | **Incidence******* |
|---|---|---|---|---|
| **Austria** | | | | |
| **Belgium** | | | | |
| **Bulgaria** | | | | |
| **Cyprus** | | | | |
| **Czech Republic** | | | | |
| **Denmark** | | | | |
| **Estonia** | | | | |
| **Finland** | | | | |
| **France** | | | | |
| **Germany** | | | | |
| **Greece** | | | | |
| **Hungary** | | | | |
| **Ireland** | | | | |
| **Italy** | | | | |
| **Latvia** | | | | |
| **Lithuania** | | | | |
| **Luxembourg** | | | | |
| **Malta** | | | | |
| **Netherlands** | | | | |
| **Poland** | | | | |
| **Portugal** | | | | |
| **Romania** | | | | |
| **Slovakia** | | | | |
| **Slovenia** | | | | |

| Country* | Total sales volume | Number of animals treated ** | Number of animals reacted in SARs assessed A, B or O | Incidence*** |
|---|---|---|---|---|
| **Spain** | | | | |
| **Sweden** | | | | |
| **United Kingdom** | | | | |
| | | | | |
| **Iceland** | | | | |
| **Liechtenstein** | | | | |
| **Norway** | | | | |
| | | | | |
| **TOTAL EU/EEA** | | | | |
| | | | | |
| **Third countries** | | | | |
| | | | | |
| **TOTAL** | | | | |

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

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

*** <please explain here the assumptions underlying the incidence calculation– see also Part I, Chapter 6, section 6.3.1 >

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

| Reports | (EEA) | | | Third Countries (Non EEA) | | |
|---|---|---|---|---|---|---|
| | Reports (No) | Number of reported animals (No) | Deaths (No) | Reports (No) | Number of reported animals (No) | Deaths (No) |
| Target species | | | | | | |
| Non-target species | | | | | | |
| Human | | | | | | |
| Total | | | | | | |

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

| Use of product | Category of species | Number of reports | | |
|---|---|---|---|---|
| | | Serious | Non-serious | TOTAL |
| As recommended in SPC | Target species | | | |
| Off label use | Target species | | | |
| | Non-Target species | | | |
| Unknown | Target species | | | |
| Total | All | | | |

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

| Reports | A (probable) + B (possible) + O (unclassifiable) | | N (unlikely) | |
|---|---|---|---|---|
| | Number of reported animals (No) | Deaths (No) | Number of reported animals (No) | Deaths (No) |
| Suspected adverse events | | | | |
| Lack of efficacy | | | | |
| Total | | | | |

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

| Reports | EEA | | | Third Countries (Non EEA) | | |
|---|---|---|---|---|---|---|
| | Reports (No) | Number of reported animals (No) | Deaths (No) | Reports (No) | Number of reported animals (No) | Deaths (No) |
| Target species | | | | | | |
| Used as recommended | | | | | | |
| Off label use | | | | | | |
| Unknown | | | | | | |
| Non-target species | | | | | | |
| TOTAL | | | | | | |

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

| Species | Clinical sign VeDDRA terms, <SOC, HLT, PT > level | Number of events* |
|---|---|---|
| | | |

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

## 2.4 Templates for PSUR line listings

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

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

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

**PERIOD OF REPORT FROM .../.../... TO .../.../....**

| MAH CASE REF | CA CASE REF | 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 CONCLUSION | CAUSALITY (ABON CODE) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EEA REPORTS<br><br>(COUNTRY CODE - ORGANISATION ID - CASE NUMBERREF + NAME & COUNTRY) | | | | *(Please ensure that this total is put in)* | | | | | | | | *(Please ensure these sections are completed)* | |
| OVERALL TOTAL OF ALL (EEA) PAGES<br>Total no of (reports): Total no of animal reactions (a): Total no of animals died (b): | | | | | | | | | | | | | |

| MAH CASE REF | CA CASE REF | 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 CONCLUSION | CAUSALITY (ABON CODE) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THIRD COUNTRY REPORTS<br><br>(COUNTRY CODE - ORGANISATION ID - CASE NUMBER) | | | | *(Please ensure that this total is put in)* | | | | | | | | *(Please ensure these sections are completed)* | |
| OVERALL TOTAL OF ALL (3rd country) PAGES | | | | | | | Total no of (reports): | | | | Total no of animal reactions (a):<br>Total no of animals died (b): | | |

**FOR COMPETENT AUTHORITY USE ONLY: REFERENCE:** **DATE OF RECEIPT**

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

**VETERINARY PHARMACOVIGILANCE SCHEME – PERIODIC SAFETY UPDATE REPORT**

**MARKETING AUTHORISATION HOLDER FORM FOR REPORTS OF**

***HUMAN ADVERSE EVENTS IN HUMANS***

**INVOLVING A VETERINARY MEDICINAL PRODUCT**

**PRODUCT:**

**MARKETING AUTHORISATION HOLDER**

**MARKETING AUTHORISATION NO:**

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

| MAH CASE REF | CA CASE REF | NAME(S) OR UNIQUE PATIENT(S) IDENTIFICATION [8] | 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| (COUNTRY CODE - ORGANISATION ID - CASE NUMBERREF + NAME & COUNTRY) | | | | | | | | | | |

**FOR COMPETENT AUTHORITY USE ONLY: REFERENCE**: **DATE OF RECEIPT**: **NUMBER OF INCIDENTS:**

[8] As appropriate according to national laws

**2.5 Template for Rapid Alert and Non Urgent Information in Pharmacovigilance - Initial**

*Logo and name of the Competent Authority of the Member State/EMA*

| **<*RAPID ALERT | NON-URGENT INFORMATION*> IN VETERINARY PHARMACOVIGILANCE** | | |
|---|---|---|---|
| Reference: | N$^{o}$ of attachments: | Date: |
| FROM: | | |
| TO: (ALL) MEMBER STATES<br>EFTA countries concerned<br>EMA<br>EUROPEAN COMMISSION<br>CHAIR-CVMP<br>RAPPORTEUR (if applicable)<br>RMS (if applicable) | | |
| **SUBJECT:**<br>Please fill in the appropriate fields<br>Brandname(s):<br>International Non-proprietary Name (INN, DCI) or Class:<br>Strength(s):<br>Pharmaceutical Form(s) and Dosage(s):<br>Route of Administration(s):<br>Therapeutic Classification (ATC code):<br>Marketing Authorisation Holder:<br>Indication(s): | | |
| **REASONS FOR <*ALERT | NON-URGENT INFORMATION*>:**<br>(Relevant Summarised Evidence)<br>(Text) | | |
| **Source of Information:** | Please select:<br>Spontaneous Reports<br>Post-authorisation safety study<br>Clinical Trial<br>Preclinical Study<br>Other (please indicate) | |

## PROPOSED ACTION AND ACTION TAKEN:

(Text)

## INFORMATION REQUESTED:

(Text)

## ADDITIONAL INFORMATION:

(Text)

Please respond by --/--/--

**Name of person responsible for sending message:**

## 2.6 Template for Rapid Alert and Non Urgent Information in Pharmacovigilance – Response

*Logo and name of the Competent Authority of the Member State/EMA*

| **ANSWER TO <*RAPID ALERT | NON-URGENT INFORMATION*> IN VETERINARY PHARMACOVIGILANCE** | | |
|---|---|---|---|
| Reference: | N$^{o}$ of attachments: | Date: |
| FROM: | | |
| IN ANSWER TO THE ORIGINAL MESSAGE FROM <*MEMBER STATE*> DATED --/--/--<br><br>TO: (ALL) MEMBER STATES<br>EFTA Countries concerned<br>EMA<br>EUROPEAN COMMISSION<br>CHAIR-CVMP<br>RAPPORTEUR (if applicable)<br>RMS (if applicable) | | |
| Respond requested by originator for --/--/-- | | |
| **SUBJECT:**<br>**Please fill in the appropriate fields**<br><br>Brandname(s):<br><br>International Non-proprietary Name (INN) or Class:<br><br>Strength(s):<br><br>Pharmaceutical Form(s) and Dosage(s):<br><br>Route(s) of Administration:<br><br>Therapeutic Classification (ATC code):<br><br>Marketing Authorisation Holder:<br><br>Indication(s): | | |
| **ANSWER TO <*RAPID ALERT | NON-URGENT INFORMATION*>:**<br>(Text) | | |

## PROPOSED ACTION AND ACTION TAKEN:

(Text)

## ADDITIONAL INFORMATION:

(Text)

**Name of person responsible for sending message:**

## 3. Eudranet mailboxes for use in communication

| Name of Eudranet Mailbox | Use for correspondence regarding |
|---|---|
| CVMP | Committee for Veterinary Medicinal Products |
| V-PHARMACOVIGILANCE | Pharmacovigilance (general)<br>PhVWP-V<br>Non Urgent Information |
| V-RA | Rapid Alert (Pharmacovigilance) |
| V-PSUR | Periodic Safety Update Reports, Centrally authorised products |
| V.CMD-PSUR | Periodic Safety Update Reports:<br>MRP/DCP, PSUR synchronisation / work share initiative on PSUR assessment |

## 4. References


1) Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, in European Commission: The Rules Governing Medicinal Products in the European Union – Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use (http://ec.europa.eu/health/documents/eudralex/index_en.htm)

2) European Commission. Regulation (EC) No 540/95 of 10 March 1995 laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorized in accordance with provisions of Council Regulation (EC) No 2309/93, in European Commission: The Rules Governing Medicinal Products in the European Union – Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use (http://ec.europa.eu/health/documents/eudralex/index_en.htm)

3) European Commission: The Rules Governing Medicinal Products in the European Union. Brussels. (http://ec.europa.eu/health/documents/eudralex/index_en.htm), e.g.

   - Volume 6 - Notice to Applicants and Regulatory Guidelines for Medicinal products for Veterinary use
     - Volume 6A - Procedures for marketing authorisation - Chapter 3 - Community Referral Procedure
     - Volume 6C - Regulatory Guidelines
       Guidelines on Summary of Product Characteristics (SPC)
       Guideline on the Processing of Renewals in the Mutual Recognition Procedure and Decentralised Procedure
       Guideline on the Processing of Renewals in the Centralised Procedure
   - Volume 7 – Scientific guidelines for medicinal products for veterinary use
     - Volume 7A - General, Efficacy, Environmental risk assessment.
       Good clinical practice for the conduct of clinical trials on veterinary medicinal products in the European Union

4) European Medicines Agency. Best Practice Guide for Handling Renewals in the Mutual Recognition and Decentralised Procedure (Doc. Ref. EMEA/CMDv/115373/2006) (http://www.hma.eu/164.html)

5) European Medicines Agency. CMDv guidance on documentation to be submitted by a MS when reference medicinal product is not authorised in the MS (http://www.hma.eu/161.html )

6) European Medicines Agency. Compilation of Community Procedures on Inspections and Exchange of Information (Doc. Ref. EMEA/CVMP/227/01) (http://www.ema.europa.eu/)

7) European Medicines Agency. Crisis Management Plan regarding Safety Issues for Centrally Authorised Products or Veterinary Use (Doc. Ref. EMEA/CVMP/159/04) (http://www.ema.europa.eu/)

8) European Medicines Agency. CVMP Guideline on Harmonising the Approach to Causality Assessment for Adverse Reactions to Veterinary Medicinal Products. (Doc. Ref. EMEA/CVMP/552/03-FINAL) (http://www.ema.europa.eu/)

9) European Medicines Agency. CVMP Guideline on Statistical Principles for Veterinary Clinical Trials. (Doc. Ref. EMEA/CVMP/816/00-Final) (http://www.ema.europa.eu/)

10) European Medicines Agency. CVMP Recommendation on management and assessment of Periodic Safety Update Reports (PSURs) of veterinary medicinal products (EMEA/CVMP/PhVWP/4550/2006) (http://www.ema.europa.eu/)

11) European Medicines Agency. Eudranet eMail Policy (http://www.eudra.org/eudraportal2/displayWelcome.do)

12) European Medicines Agency. Mandate, Objectives and Rules of Procedure for the CVMP Pharmacovigilance Working Party (PHVWP-V) (Doc. Ref. EMEA/CVMP/PhVWP/133883/2004-Rev.1-Updated) (http://www.ema.europa.eu/)

13) European Medicines Agency. Procedure for EU guidelines and related documents within the pharmaceutical legislative framework (Doc. Ref. EMEA/P/24143/2004) (http://www.ema.europa.eu/)

14) European Medicines Agency. Procedures related to Rapid Alerts on suspected quality defects in medicinal products (http://www.ema.europa.eu/)

15) European Medicines Agency. PSURs for centrally authorised veterinary medicinal products. Procedure on PSUR submission and evaluation of non-marketed products (Doc. Ref. EMEA/CVMP/227/01) (http://www.ema.europa.eu/)

16) European Medicines Agency. SOP/V/4023 - Annex I: Addresses of national competent authorities for PSUR submission (http://www.ema.europa.eu/)

17) European Medicines Agency. VeDDRA List of Clinical Terms for Reporting Suspected Adverse Reactions in Animals and Humans to Veterinary Medicinal Products. (Doc. Ref. EMA/CVMP/10418/2009) (http://www.ema.europa.eu/)

18) European Parliament and the Council. Directive 2001/82/EC of 6 November 2001 on the Community Code Relating to Medicinal Products for Veterinary Use, as amended by Directive 2004/28 EC, in European Commission: The Rules Governing Medicinal Products in the European Union – Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use (http://ec.europa.eu/health/documents/eudralex/index_en.htm)

19) European Parliament and the Council. Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, in European Commission: The Rules Governing Medicinal Products in the European Union – Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use (http://ec.europa.eu/health/documents/eudralex/index_en.htm)

20) The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (http://www.vichsec.org/):

- VICH Topic GL 24 on Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs) (http://www.vichsec.org/en/topics.htm)
- VICH Topic GL 29 on Pharmacovigilance of Veterinary Medicinal Products: Management of Periodic Summary Update Reports (PSURs) (http://www.vichsec.org/en/topics.htm)

21) Heads of Medicines Agencies (HMA)
PSUR synchronisation / PSUR work share initiative on PSUR assessment of the Heads of Medicine Agencies, The Heads of the Medicine Agencies>Veterinary Medicines>Heads of Agencies>about HMA>Working Groups>PSSG – PSUR synchronisation Sub Group, (http://www.hma.eu/236.html)

# 5. Annexes and References concerning Electronic Reporting

## 5.1 Overview of Guidelines and reference documents relative to Electronic Reporting of pharmacovigilance information

1. Operational Guidelines
    - Schemas, see also Annex 6. Schemas for the guidance on the Electronic Data Interchange (EDI) of safety data for VMPs in the EEA
    - Guidance for Marketing Authorisation Holders on registration options, reporting/transmission options and access to data. (Doc.Ref. EMEA/290696/2007)
    - Procedure to be followed by all EDI partners in case of prolonged failure of an EDI Partner's database (Doc.Ref. EMEA/32385/2007)
    - Procedure to be followed by all EDI partners in case of prolonged failure of the EudraVigilance Gateway (Doc.Ref. EMEA/31235/2007)
    - Procedure to be followed by all EDI partners in case of failure of EVWEB (Doc.Ref. EMEA/31065/2007)
    - Procedure to be followed by all EDI partners in case of prolonged failure of an EDI Partner's Gateway (Doc.Ref. EMEA/32394/2007).

These reference documents are available on the EVVet website:
http://eudravigilance.emea.europa.eu.int/veterinary

2. Technical Guidelines
    - Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the European Economic Area (EEA) including message and transmission specifications
    - XML schema Definition (XSD) for safety message
    - XSD for EVetMPD
    - EV Veterinary 2.2 Message processing and Business rules (Doc.Ref. EMEA/34509/2006)

These reference documents are available on the EVVet website:
http://eudravigilance.emea.europa.eu.int/veterinary

3. Reference documents and standard lists
    - VeDDRA List of Clinical Terms for Reporting Suspected Adverse Reactions in Animals and Humans to Veterinary Medicinal Products (EMA/CVMP/10418/2009, latest version)
    - List of Species and Breeds for Electronic Reporting of Suspected Adverse Reactions in Veterinary Pharmacovigilance (EMEA/CVMP/553/03, latest version)
    - CVMP List on Additional Controlled Terminology for electronic submission of Reports on Adverse Reactions to Veterinary Medicinal Products (EMEA/556/04, latest version)
4. Tutorials
    - EVWEB Getting Started in EudraVigilance
    - EVWEB Safety Report
    - EVWEB Product Report
    - EVWEB Queries

- EVWEB Acknowledgements
- EVWEB MAH Simplified Electronic Reporting Form

These reference documents are available on the EVVet website:
http://eudravigilance.emea.europa.eu.int/veterinary

5. VICH guidelines

- VICH Topic GL30 Guideline on Pharmacovigilance of Veterinary Medicinal Products – Controlled Lists of Terms
- VICH GL35 Pharmacovigilance of Veterinary Medicinal Product: Electronic Standards for Transfer of Data
- VICH Topic GL42 Guidelines on Pharmacovigilance of Veterinary Medicinal Products - Data Elements for Submission of Adverse Event Reports

These reference documents are available on the VICH website: http://www.vichsec.org/

## 5.2 EudraVigilance Veterinary

1. Description of the system

At the core of EudraVigilance Veterinary System is a database. The system offers the following main features:

- A large reference pharmacovigilance database (the central database) that is built by importing and consolidating data from multiple sources, including information on veterinary medicinal products (EudraVigilance Veterinary Medicinal Product dictionary (EVVetMPD)) and adverse events,
- A fully automated safety message and product message processing mechanism, using XML-based messaging,
- Extensive query and tracking capability, both from scientific and administrative business perspectives.
- A fully integrated organisation and user management in the EudraVigilance community synchronised with the Eudra Gateway profile management (for registration see further),

2. The central database

The central database is administered by the Agency and contains:

- Information on pharmacovigilance events reported in relation to veterinary medicinal products authorised in the EU
- Information on VMPs
- Various lookup lists of standard terms to be used in reports

3. VeDDRA and other controlled terminology lists

The Veterinary Dictionary for Drug Regulatory Authorities (VeDDRA) terminology, List of Species and Breeds, and additional controlled terminology lists are an integral part of the EU system for electronic reporting of adverse reactions to veterinary medicines, EVVet. The provision of these lists and terminology facilitates systematic coding and analysis of reported adverse events to VMPs. These lists are updated annually by the VeDDRA sub-group of the CVMP Pharmacovigilance Working Party (PhVWP-V) which also includes delegates from veterinary pharmaceutical industry. The latest version of these standard lists is available at the Agency's website, see Annex 5.1 Overview of Guidelines and reference documents relative to Electronic Reporting of pharmacovigilance information, and comments for consideration at the annual meeting of the VEDDRA sub-group should be submitted by email to veddra@ema.europa.eu by 31 March of each year.

VeDDRA has a four level hierarchical structure, SOC – System Organ Class being the highest, followed by HLT – High Level Term, PT – Preferred Term and LLT – Low Level Term.

- The relation between SOC and LLT is mono-axial i.e. a specific LLT will only be available in one specific SOC. Where similar LLTs exist in other SOCs, an LLT may contain a cross-reference to the location of the other terms.
- In order to achieve medically relevant groupings for analysis of suspected adverse reactions, the relation between PTs and LLTs covers two different concepts, allowing an LLT to be either a synonym or a sub-classification of a particular PT (Example: PT 'Anaphylaxis' includes the LLTs 'Anaphylaxis' and 'Anaphylactoid reaction').
- The convention is that SOC and HLT terminology should be plural, with PT and LLT being in singular unless it does not make medical sense (Example: SOC: Cardio-vascular system disorders, HLT: Cardiac/heart disorders, PT and LLT: Cardiac disorder NOS).
- Any PT term must be available as LLT, too.

- The use of 'NOS – not otherwise specified' should be limited to the minimum, and ideally restricted to PT and LLT-level.
- Ideally VeDDRA should only contain terms that have actually been reported as adverse reactions. Terms that are not used within a period of three years will be made non-current.
- The selection of VeDDRA terms to describe an adverse event should be at LLT level, although analysis will normally use the PT level terms. There are a number of situations where there could be more than one choice at LLT level, sometimes with different results at SOC level. However, it is not the intention to restrict the choices available, but to encourage a standard approach so that the results of analysis will be consistent and valid.

4. Registration to EVVet - organisation and user management

The EVVet organisation and user management feature contains information on all partners of the Agency that have a legal obligation to report serious adverse drug events for medicinal products authorised in the EU.

In principle all MAHs in the EU need to register to EudraVigilance Veterinary in order to ensure compliance with the reporting requirements for the 15-day third country reports that should be sent directly to the central database. It is considered however to the discretion of the competent authority to allow specific MAHs that have a history of no or very limited reporting to postpone the registration until necessary and in any case when third country reports would be due.

During the registration process, each registering organisation must specify an organisation identifier (ID), which is a precondition to exchange safety, acknowledgement and medicinal product report messages in an electronic data interchange (EDI) environment. This organisation ID is used in a message to indicate the sender and the receiver and allows the Eudra Gateway to identify correctly the two unique partners in the EDI process. Access and visibility rights are also controlled via the organisation and user management directory. Access policy is described in Part III Chapter 10. Access to EudraVigilance Veterinary Data. Guidance on the actual registration process can be found on the EudraVigilance Veterinary Website, see Annex 5.1 Overview of Guidelines and reference documents relative to Electronic Reporting of pharmacovigilance information.

5. Routes to exchange safety, acknowledgement and VMP report messages.

The Agency has implemented an electronic regulatory submission environment, the Eudra Gateway, which follows the ICH M2 Gateway Recommendation for the Electronic Standard for the Transfer of Regulatory Information (ESTRI-Gateway). The purpose of the Eudra Gateway is to operate a single, common, European Economic Area (EEA)-wide Gateway for receiving regulatory submissions in a fully automated and secure way including all aspects of privacy, authentication, integrity and non-repudiation of all transactions in pharmacovigilance.

The Eudra Gateway provides a single point of contact between MAHs and competent authorities in the EEA. By doing so, the Eudra Gateway is considered a hub and all the connections for the MAH, the Agency and NCAs, are known as spokes or endpoints. Safety and acknowledgement messages are routed through the hub to the desired spoke.

The simplicity of this design allows for the secure transmission of all safety and acknowledgement messages to every participant without the expense and complexity that would be needed to establish a connection between each and every endpoint.

Technical Specifications for a local gateway to operate Electronic Data Interchange (EDI)

This chapter describes the computer software and communications standards used by the Eudra Gateway. Senders will be required to adopt hardware, software and data communications configurations to meet these standards.

The Sender's EDI system must comply with the following standards for the Eudra Gateway certification:

- S/MIME compatible email system using POP/SMTP or direct connection via HTTP(s) or FTP

- Support for digitally signed MDN's
- X.509 digital certificate support
- EDIINT/AS1 compliance certification or AS2 interoperability
- Direct transmittal of XML documents

The Agency does not mandate any particular product for the EDI communication. If the Sender's product adheres to the above standards and is fully interoperable with the Eudra Gateway, then the Sender will receive certification from the Agency to use it. It is the direct responsibility of the Sender to conform to the Eudra Gateway, as the Eudra Gateway is a certified interoperable product.

Communications via the Sender's and the Receiver's Gateway will take place over the Internet.

Each EDI Partner is responsible for its own costs of obtaining and maintaining the services of Internet access from an Internet Service Provider (ISP). These costs will include initial hook up charges such as hardware and software components required for connectivity, monthly Internet access rates and any other expenses that may arise from these activities.

Procedural and testing specifications

To assure the successful operation of EDI, each new EDI partner who wishes to transmit Safety Messages electronically via Gateway will undergo a staged test procedure which includes the following phases:

i) **Communication test** to assure successful Gateway to Gateway communication. The successful completion of the communication testing between the EMEA and the EDI Partner will be certified by the Agency so that the EDI Partner can move into the subsequent stages of testing. The process of establishing the connection requires several steps.
   - Document Transport Choice
   - Exchange of Profile Information
   - Exchange of Public keys for encryption
   - Testing the Connection

ii) **Development and validation testing** of EDI partners to the EudraVigilance pre-production environment at the discretion of the EDI Partner. Once the EDI Partner has completed this test phase they will notify the Agency/other potential EDI Partners that they are ready to move into the XML test phase.

iii) **XML Test phase** includes the sequential transmission of messages containing animal SARs as well as human SARs.
   This is an example of a test plan recommended by the Agency which may be followed by the EDI partners. Alternative test plans may be proposed by an EDI partner and will be discussed on an individual basis.

| | |
|---|---|
| Step 1 | Send 2 messages, the first containing one case of an animal SAR and the second containing a case of a human SAR. |
| Step 2 | Send 2 messages each with multiple mixed cases (human and animal). |
| Step 3 | Send 1 message with multiple mixed follow-up cases of cases sent in steps 1 and/or 2. |
| Step 4 | Send 10 messages each with 5 or more mixed cases. Include cases that would be considered as follow-ups to cases that were received first from a competent authority (cases where the Worldwide unique case registration number (R.05) is different to the Sender's report identification number (R.01) |

To enable thorough and realistic testing, the EDI-PARTNERs should ensure that the cases resemble closely the cases normally dealt with. The EDI-PARTNERs should aim to code as much of the information as possible using the majority of the available fields in EudraVigilance Veterinary. The main emphasis of the testing, however, will be on checking the correct implementation of the standard terminology fields; therefore the content of the free-text fields is

not of particular significance. The EDI-PARTNERs should also send in parallel the corresponding original "paper" version of the cases by fax or email (on Common EU Reporting Form for MAHs format) (see Annex 2.1 EU Template for MAHs for reporting adverse events).

The EDI-PARTNER should notify the Agency following completion of each individual step. The Agency will then check the messages received and the acknowledgments sent.

The successful completion of the testing between the Agency and the EDI Partner will be certified by the Agency so that the EDI Partner can move into production. The currently established regulatory reporting mechanism will remain unaffected during the test phase.

iv) **Production pilot testing** with continuous submission of SARs to the production environment of EudraVigilance and parallel submission of paper reports for an agreed period of time or a certain number of reports (e.g. 20). The Agency may decide to shorten this period or extend it depending on the outcome of the production pilot testing. During the test phase the currently established regulatory reporting mechanism will remain unaffected.
Any technical changes which may have a direct effect on the generated XML file or the technical method communication must be communicated immediately in writing between the EDI Partners. Major technical changes may require the re-initiation of the test phases as described above.

EVWEB

The EudraVigilance System also provides interactive tools to allow for a 'manual' creation of safety and acknowledgement message as well as medicinal product report generation and administration by a user via a web interface, called EVWEB. This component is made available by the Agency to registered parties that do not have their own ESTRI Gateway and pharmacovigilance system established.

EVWEB allows the creation, sending and receiving of safety and acknowledgement messages in compliance with the data elements specified in the guideline on data elements for the electronic submission of adverse event reports related to veterinary medicinal products authorised in the European Economic Area (EEA) including message and transmission specifications (see Annex 4. References)

It also allows the saving of all messages locally. The same principles apply for VMP report messages.

The two main functionalities, that support the secure exchange of safety and acknowledgement messages, are integrated:

- **The WEB Trader component of EVWEB**:
  The WEB Trader provides a mechanism to securely send and receive safety and acknowledgement messages, in a semi-automatic way. It provides its users with an inbox, where incoming messages can be located, viewed and further processed e.g. stored at the users local computer. The outbox displays all safety and acknowledgement messages that have been created by WEB Trader users and sent to one or several receivers of the EudraVigilance community. Tracking functions are also available that allow the monitoring of the status of a transmitted message.

- **The Message Posting function of EVWEB:**
  This allows web trader users to upload Safety and Acknowledgement Messages that have been generated by the sender using his local pharmacovigilance system, to the EudraVigilance Gateway, from where the messages will be re-routed to the specified receiver.

EVWEB also provides access to all relevant standard terminology such as VeDDRA in the latest version, the EVVetMPD and other standard terminology.

The creation of follow-up reports is possible and query functions permit restricted or full access to the adverse events stored in the EVVet database.

EVWEB also has a medicinal product section, that allows the insert, update or nullification of VMP and substances information in the EVVetMPD.

From a technical point of view, an EVWEB user needs to have a computer with Internet Explorer version (See web site for the supported versions) available and an Internet connection, preferably ADSL or faster.

EVWEB is being used by the majority of competent authorities in the EEA for electronically exchanging pharmacovigilance information.

The Web application furthermore contains extensive query tools to query the central database to provide either counts of reports or listings of reports based on specific search criteria.

6. EudraVigilance Veterinary Medicinal Product Dictionary (EVVetMPD)

The dictionary contains the essential information of the products for which adverse events have been reported. The population of the EVVetMPD is necessary to permit the correct identification of veterinary medicinal products, related to adverse events reported as well as data analysis and signal detection.

The EVVetMPD has been designed to support the collection, reporting, coding and evaluation of veterinary medicinal product data in a standardised and structured way.

The EVVetMPD provides:

- Integrated standard terminology to standardise active ingredients, excipients, pharmaceutical forms, routes of administration, concentration ranges, units of measure and country codes.
- A hierarchical data structure with a standardised approach to capture veterinary medicinal product information in adverse events taking into account the possible vagueness of the reported pharmacovigilance data by the primary source.
- A hierarchical and multi-axial data structure to support scientific data analysis of medicinal product information related to adverse events and grouping of medicinal product data based on ingredients, strengths and pharmaceutical forms.

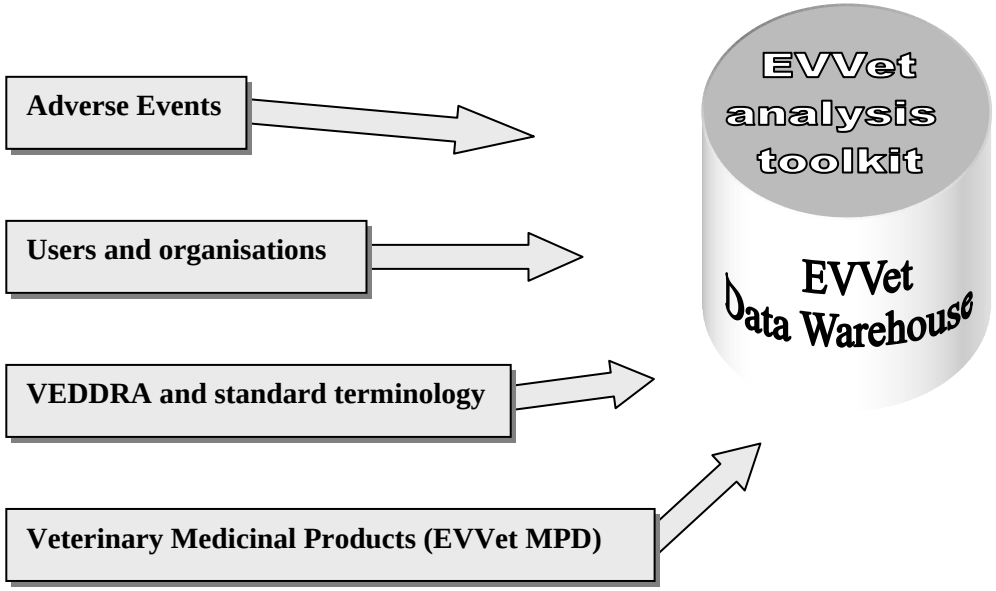
In addition, the EVVetMPD capabilities provide:

- A standardised XML Schema to support the collection and exchange of structured medicinal product information.
- Multi-lingual approach that takes into account the international nature of product data in the area of pharmacovigilance.
- Inclusion of synonyms (alias) for harmonised data mapping of veterinary medicinal product data, taking into account terminologies in existing databases.

7. Eudra Data Warehouse

The Eudra Data Warehouse has been designed to allow users to analyse safety data collected in EVVet consequently allowing better-informed decisions about the safety profile of veterinary medicinal products. It provides a range of general query tools for analysis of the scientific as well as administrative data and more specific tools for signal detection. The user has additional scope to customise the queries, including the possibility to automate the creation of specific reports at pre-defined intervals or time points.

The following illustration displays the components of the Eudra Data Warehouse:




The way users interact with the Eudra Data Warehouse is through a Graphical User Interface (GUI), which is available via a common web browser. This is an Internet application that can be accessed from any place, requiring only an Internet connection and valid account credentials.

### 5.3 Overview of Registration and transmission options to EVVet for MAHs

This section provides an overview of the different registration options for MAHs to EVVet. The various routes of communication, which depend on the type of registration, are further explained as well as the different levels of access to the data. This section should be read in conjunction with the schema in Annex 6. Schemas for the guidance on the Electronic Data Interchange (EDI) of safety data for VMPs in the EEA. Further detailed information on the actual registration process can be found on the EudraVigilance Veterinary Website: http://eudravigilance.emea.europa.eu.int/veterinary.

A MAH in the EEA being a company or a firm, can have a headquarter (HQ) which is the highest level in the organisation ('headquarter level') and linked to it one or several affiliates in the different Member States ('affiliate level'). If a MAH has no affiliates it should register itself HQ.

For MAHs the organisation representative in the EudraVigilance Registration Process must be the 'Qualified Person Responsible for Pharmacovigilance' (QP) (as defined in EU legislation) of the headquarters in the EEA.

Please note that for the email address of the QP generic entries such as administration@abc.com'or info@yahoo.co.uk are not accepted.

Please also note that only the QP at 'headquarter level' will be able to register new users (see arrows in schema further below from QP to all users). New users can be located at the level of the HQ, the nominated affiliates and/or the nominated third party service providers, when relevant.

The QP can delegate the functions related to registration of new users with EudraVigilance to a trusted 'Deputy' within the same organization. The QP should register the trusted 'Deputy' with EudraVigilance Veterinary as a user in the first instance. The delegation and the registration of the deputy can be performed simultaneously.

Clinical Research Organisations (CROs), which do not qualify as a MAH, as well as IT vendors, can not become a registered organisation in the EudraVigilance community. However, CROs or IT vendors may be registered by a MAH as 'Third Party Service Providers' acting on behalf of these organisations by providing services related to EudraVigilance.

Choice of transmission mode

During the registration process the MAH needs to identify for the Transmission Mode for the Headquarter, one of the following two options:

The MAH will send directly via

- **Local Gateway**: This is applicable, if Electronic Data Interchange (EDI) transmissions will be done via a Gateway solution. For further information on Local Gateway, see Part III section 2.1 EudraVigilance Veterinary.

or

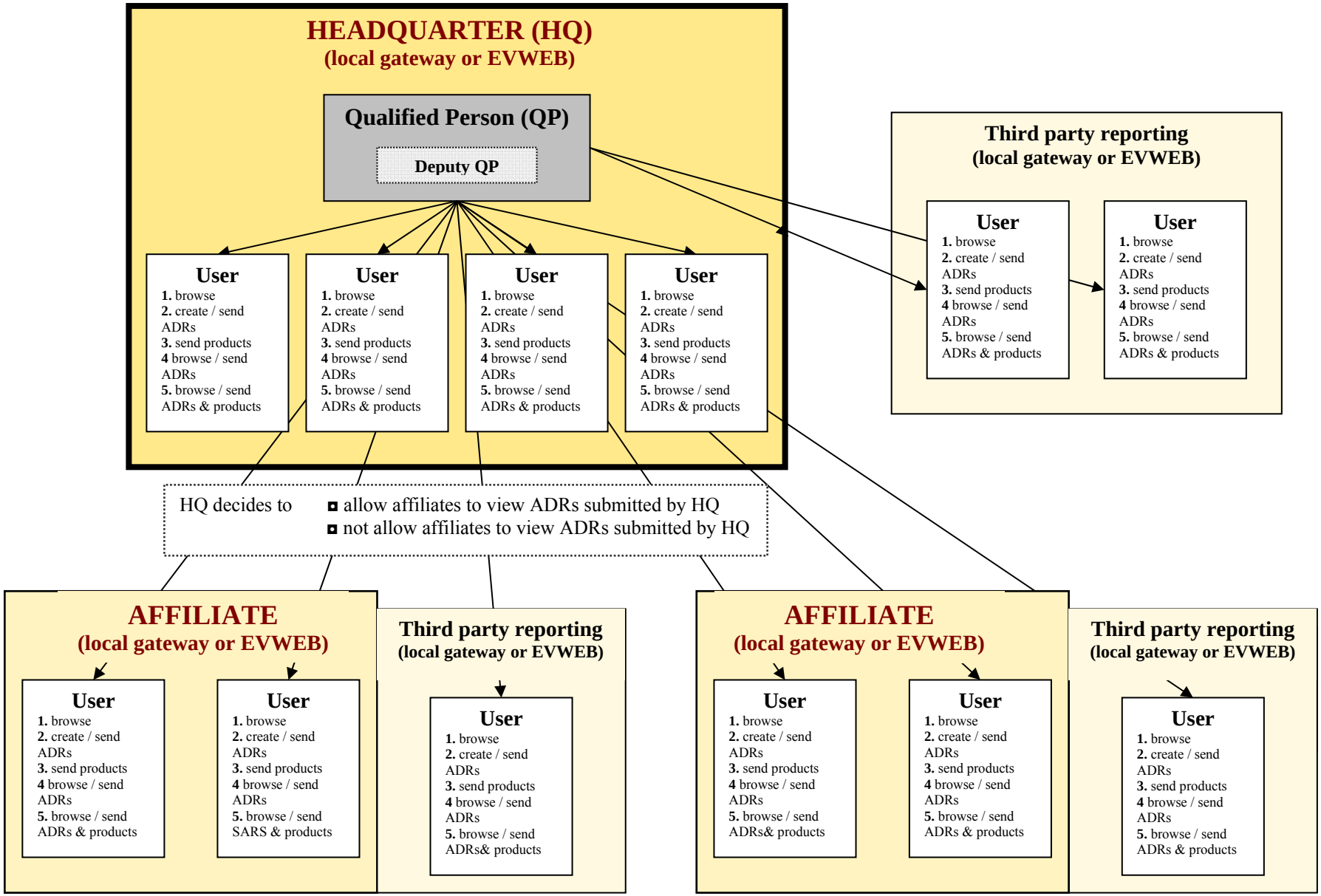
- **WEB Trader**: This is applicable if EDI transmissions will occur via the WEB Trader component of EVWEB. For further information on WEB Trader, see Part III section 2.1 EudraVigilance Veterinary.

If the MAH intends to use a Third Party Service Provider to perform the EDI transmissions on their behalf, a contact name and the contact details for the Third Party Service Provider must be also completed. The Transmission Mode that the Third Party Service Provider will be using i.e. either the Local Gateway or the WEB Trader, must be also indicated.

The SARs created within the HQ or by its Third Party Service Provider will all carry the same sender ID (organisation ID) and the name of the QP. It will not be possible to distinguish the different HQ users or its Third Party Service Provider's users from the XML of the safety message.

In addition, the MAH may choose to allow for EDI transmission via affiliate organisations who at their level also may choose to allow for EDI transmission via a Third Party Service Provider (see Table further below). The affiliate organisations will receive their separate organisation ID, so that safety messages created by the affiliate's users or its Third Party Service Provider user's will carry the organisation ID of the affiliate and the sender name of local QP of the affiliate.

Please note that it is possible to use different options for the transmission mode at HQ level and Third party Service Provider level and affiliate level (e.g. at HQ level a Local Gateway while at affiliate level a WEB Trader). However all users within one organisation will use the same transmission mode chosen for the organisation.

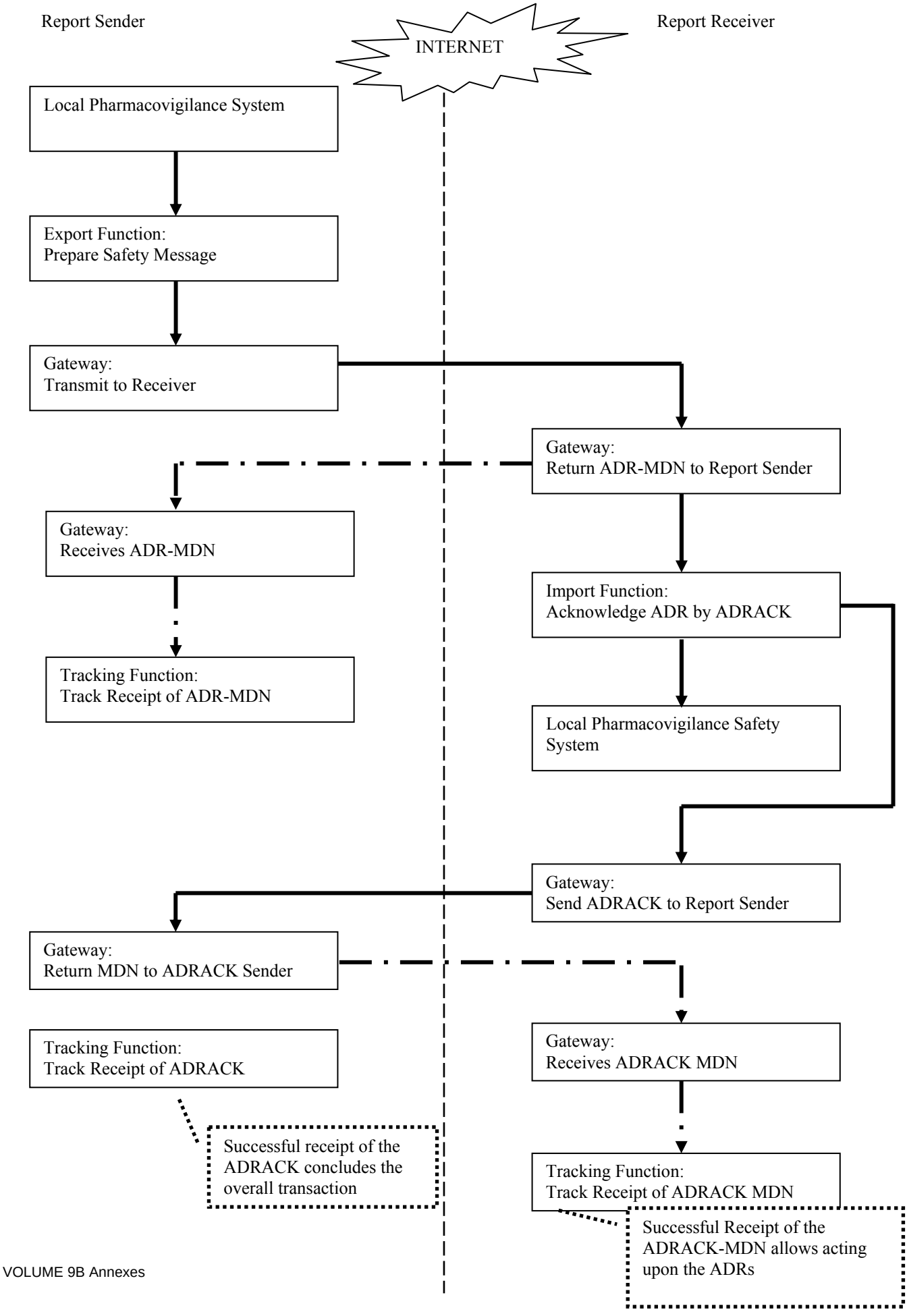

HEADQUARTER (HQ)
(local gateway or EVWEB)
Qualified Person (QP)
Deputy QP
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
Third party reporting
(local gateway or EVWEB)
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
HQ decides to
allow affiliates to view ADRs submitted by HQ
not allow affiliates to view ADRs submitted by HQ
AFFILIATE
(local gateway or EVWEB)
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send SARS & products
Third party reporting
(local gateway or EVWEB)
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs& products
AFFILIATE
(local gateway or EVWEB)
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs& products
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products
Third party reporting
(local gateway or EVWEB)
User
1. browse
2. create / send ADRs
3. send products
4 browse / send ADRs
5. browse / send ADRs & products

User Access rights to be determined by the QP

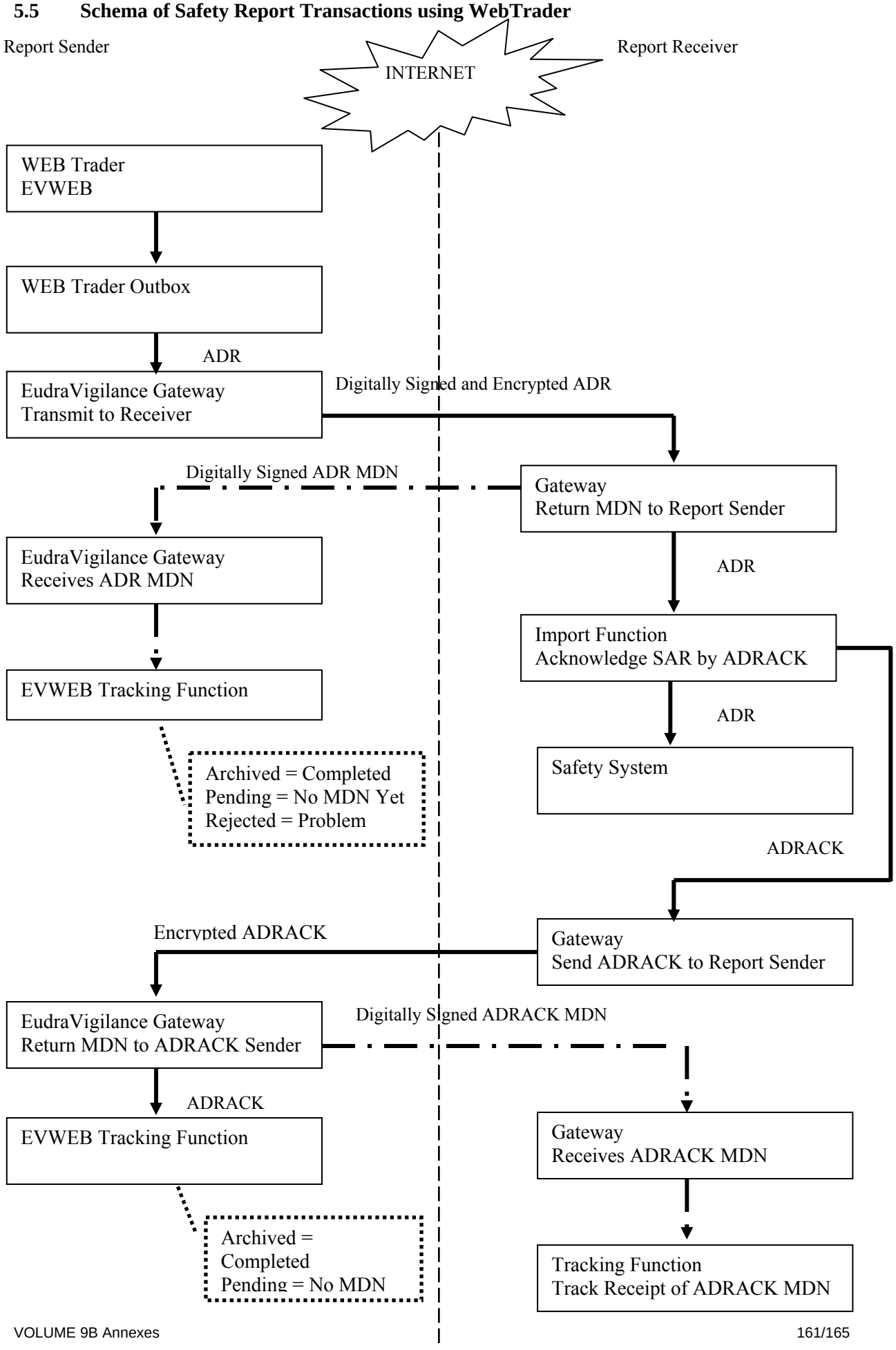
Access rights are set in two ways by the QP of the MAH:

1. The MAH must first decide whether visibility or access rights would be provided to the affiliates or the Third Party Service providers for the EDI information being submitted by the HQ to EVVet. Please note that different affiliates will not be able to access each others Safety Reports via EVWEB.
   The QP will have full access to all Safety Reports sent by HQ and/or its affiliate organisations. At present this access to the Safety Reports in EVVet is however only limited to the messages being sent by the particular MAH to EVVet. All other messages in EVVet involving medicinal products from a MAH will not be accessible if these messages did not originate from the particular MAH. Also, when a Safety report is being sent by a MAH to a competent authority (CA), and this CA forwards the message to the EVVet central database (after including its causality assessment), this Safety Report will not be available to the MAH. When a Safety Report is being sent by a MAH directly to the EVVet central database and to the CA, the follow-up message from the CA to the EVVet central database will still not be visible to the MAH. The MAH will be informed about the causality assessment concluded by the CA, when and if considered relevant by the CA
2. The QP will also decide the specific additional access rights for all their individual users; these access rights determine the features of the system the individual will be able to use:
   i) **Browse EudraVigilance Veterinary**:
   This allows the individual user to access EVVet through EVWEB and to perform queries on a read only basis.
   ii) **Create and Send ADRs**:
   This applies to individual users of organisations at 'headquarter level' or 'affiliate/subordinate level' that are using the WEB Trader transmission mode for the EDI process. The user can create and send Safety Reports using EVWEB. In addition, the user can receive Safety Messages with one or several Safety Reports, store the Safety Messages locally and generate Acknowledgement Messages.
   iii) **Send Medicinal Product Report**:
   This applies to individual users of organisations at 'headquarter level' or 'affiliate/subordinate level' independently if they are using the WEB Trader or Local Gateway Transmission Mode. The user can create and send a Medicinal Product Reports and Medicinal Product Messages using EVWEB.
   iv) **Browse and Send ADRs**:
   This allows the individual user to access EudraVigilance to perform queries. The 'Browse and Send ADRs' functionality allows the user also to create and send Safety Reports via the WEB Trader. In addition, the user can receive Safety Messages with one or several Safety Reports, store the Safety Messages locally and generate Acknowledgement Messages.
   v) **Browse and Send ADRs and Medicinal Product Reports**:
   This allows the individual user to access EudraVigilance to perform queries.
   This status also allows the user to create and send Safety Reports and Medicinal Product Reports via the WEB Trader. In addition, the user can receive Safety Messages with one or several Safety Reports, store the Safety Messages locally and generate Acknowledgement Messages.

## 5.4 Schema of Safety Report Transactions using Gateway



## 5.5 Schema of Safety Report Transactions using WebTrader



## 6. Schemas for the guidance on the Electronic Data Interchange (EDI) of safety data for VMPs in the EEA

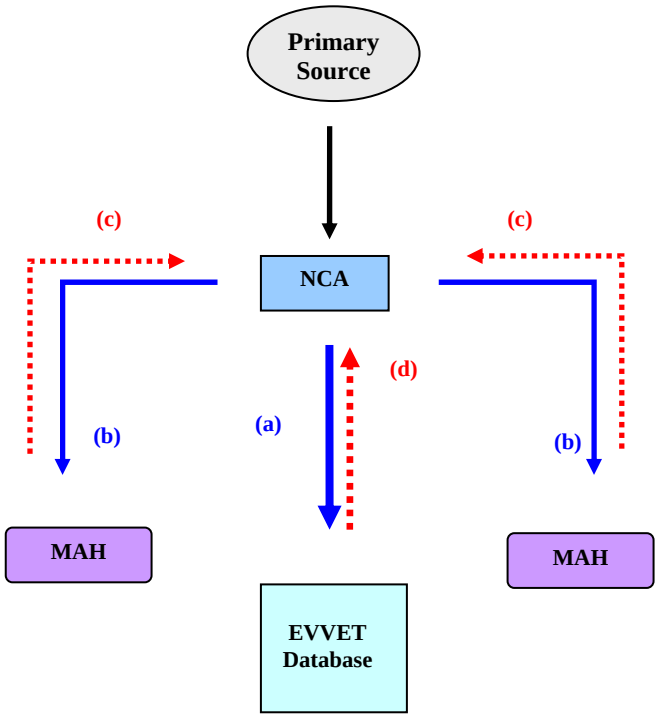
This document (version 1.1 dated 6 December 2008) provides a schematic representation of the reporting procedures and actions allowing an efficient and quick electronic distribution of safety information in accordance with the relevant legislative requirements. These schemas focus on the requirements with regard to distribution of expedited event reports (situation I, II, III) while excluding the follow-up with regard to analysis (scientific and regulatory).

**EXPEDITED ADVERSE EVENT REPORTS**

- Situation I: The primary source (veterinarian or health care professional, owner, breeder) reports directly to the national competent authority (NCA)
  For adverse events having occurred in the EEA and are directly reported from e.g. veterinarians to the NCA, the NCA will input the data into the EVVet database and will send the adverse event reports to all MAHs whose products have been included in the adverse event reports.
- **Situation II: The primary source (veterinarian or health care professional, owner, breeder) reports directly to the MAH**
  For adverse events having occurred in the EEA and communicated first by e.g. a veterinarian to a MAH, the MAH sends the case, within 15 days to the Member State on whose territory the adverse event occurred. The Member State on whose territory the adverse event occurred is responsible for forwarding the SAR to the EVVet central database.
- **Situation III: Third country reporting**
  The MAH should send adverse events reporting for third country reports directly to the EudraVigilance Veterinary database.

## 6.1 Expedited event reports (situations I – II – III)

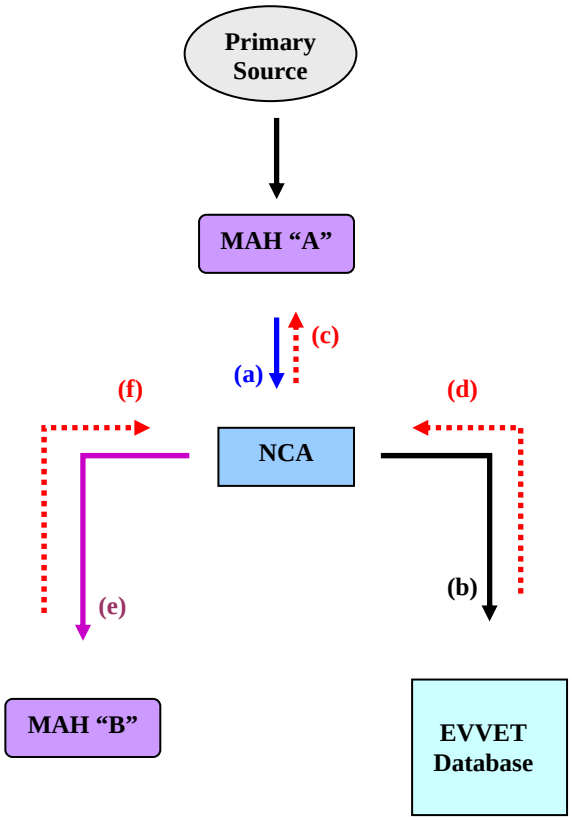
| | |
|---|---|
| **SITUATION I** | **Primary source (veterinarian or health care professional, owner, breeder) reports directly to the NCA on whose territory the adverse event occurred. (Applies to all authorised VMPs in the EU)** |




| ACTION | PERFORMED BY |
|---|---|
| 1. The national competent authority sends the message within 15 days to<br>- Eudravigilance veterinary (EVVet DB) **(a)**<br>- the MAH(s) of the suspect drug (s) **(b)** | NCA |
| 2. The MAH (s) checks the reports and sends an acknowledgment to the competent authority **(c)** | MAH |
| 3. The NCA checks the acknowledgements received from EV vet DB and MAH(s) and stores them locally **(d)** | NCA |

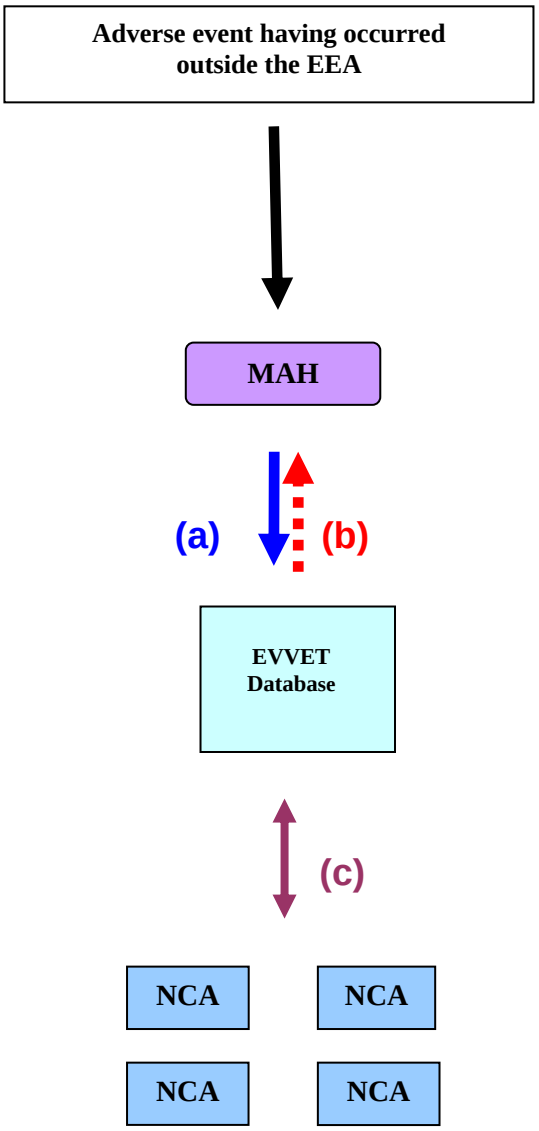
Any follow-up reports from the MAH(s) will follow the situation IIa or IIb.

| SITUATION II | Primary source reports directly to the MAH (Applies to all authorised VMPs in the EU) |
|---|---|




| ACTION | PERFORMED BY |
|---|---|
| 1. The MAH (A) reports within 15 days **(a)** to the NCA on whose territory the adverse event report occurred | MAH |
| 2. The NCA checks the report, adds the NCA's assessment and sends the report within 15 days **(b)** to EV Vet DB where it automatically becomes available to all NCAs including the RMS for MRP and DCP products | NCA |
| 3. The NCA sends an Ack to the reporting MAH **(c)** | NCA |
| 4. The MAH (A) checks and stores the Ack | MAH |
| 5. The NCA checks and stores the Ack received from EV Vet DB (d) | NCA |
| 6. If a further VMP(s) is used as concomitant medication, and is suspected of having interacted with any of the other VMP(s) administered concurrently, or it is suspected of having caused the adverse event:<br>The NCA transmits the adverse event report to MAH of the VMP given concurrently **(e)**. Hereby the NCA also informs the MAH of the other VMP(s) that the case has been entered into EVVetDB where it automatically becomes available to all NCAs including the RMS for the other VMP(s). | NCA |
| 7. The MAH(s) for the other VMP(s) send an Ack to the NCA. (f) | MAH (s) for other products |
| 8. The NCA stores the Ack received from MAH for the other VMP(s). | NCA |

| SITUATION III | **MAH becomes aware of adverse event having occurred in a third country (suspected serious unexpected adverse events, human reactions or suspected transmission of infectious agent)**<br>**(Applies to all authorised VMPs in the EU)** |
|---|---|




| ACTION | PERFORMED BY |
|---|---|
| 1. The MAH reports within 15 days of becoming aware of the report to the EudraVigilance Veterinary DB (a). | MAH |
| 2. The report(s) become available (c) to the Agency and all competent authorities of the Member States. ⟷ | |
| 3. The MAH (A) checks and stores the received Ack from the EVVet DB (b) | MAH |