Guidance

Pharmacovigilance of Veterinary Medicinal Products in Great Britain

Explanation of what pharmacovigilance means and who is responsible.

What is pharmacovigilance

The World Health Organization has defined pharmacovigilance 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 veterinary medicinal products.

Adverse events may be undesirable side effects, such as adverse reactions, or a medicine may not work as expected, known as a lack of efficacy. Adverse events may be seen in the animal being treated, in other animals, the person handling the medicine or in the environment.

Veterinary pharmacovigilance legislation

Statutory Instrument 2013 Number 2033, the Veterinary Medicines Regulations 2013 (as amended), hereinafter referred to as the VMR 2013 (as amended), sets out the legal framework for the pharmacovigilance of veterinary medicinal products (VMPs) in GB.

Although Part 8 of Schedule 1 of the VMR 2013 (as amended) contains the majority of pharmacovigilance provisions in the legislation, you can find other requirements directly relevant to pharmacovigilance in other Schedules and Parts.

This guidance applies to all products authorised in GB. Products authorised in Northern Ireland (NI) are required to follow the European Union (EU) acquis. Notwithstanding, specifically for reporting of adverse events cases occurring in NI, this guidance should be

followed and these reports should continue to be submitted to the VMD.

Who is responsible for pharmacovigilance

The VMD is the regulatory authority of the UK for veterinary pharmacovigilance.

We monitor the safety profile of the VMPs available on our territory and act where necessary, including checking that Marketing Authorisation Holders (MAHs) fulfil their pharmacovigilance obligations. We are responsible for the pharmacovigilance of all Marketing Authorisations (MAs) for VMPs in the UK, this includes UK-wide, GB-only and NI-only MAs. MAHs are legally responsible for MAs held in the UK.

We use internationally agreed Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) terminology and other related terminology to exchange adverse event information with MAHs and other interested parties. You can find information about these terminologies on the website of the European Medicines Agency .

We also, where appropriate, use definitions and guidelines from the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

The VMR 2013 (as amended) set out the obligations placed upon MAHs for the establishment and maintenance of a pharmacovigilance system. It describes MAHs complying with good veterinary pharmacovigilance practice (in paragraphs 56 and 60A) which is the minimum standards for monitoring the safety and efficacy of veterinary medicinal products authorised in the United Kingdom.

Each MAH must ensure that it has an adequate pharmacovigilance system in place. Where appropriate, a risk management system must also be in place. This assures that the MAH takes responsibility and liability for its products on the market and can take appropriate action, when necessary.

This guidance has been prepared by the VMD and is specifically related to pharmacovigilance concerning veterinary medicinal products. It should be noted that this guidance will be regularly reviewed and updated.

The VMR 2013 (as amended) also details legal obligations for some products which do not have an MA. Guidance on this is available in Guidance VI Pharmacovigilance for other products.

Guidance

Guideline I Pharmacovigilance systems, including risk management

1. The Marketing Authorisation Holder

The obligations of the Marketing Authorisation Holder (MAH) for pharmacovigilance associated with their veterinary medicinal products are defined in the VMR 2013 (as amended) Schedule 1 Part 8 paragraph 56.

The MAH must ensure that it:

- has a suitable pharmacovigilance system in place for collecting, collating, and evaluating information in relation to suspected adverse events in respect of any veterinary medicinal product for which it holds an authorisation
- has established and maintained one or more pharmacovigilance system master files (PSMF) describing in

detail the pharmacovigilance system with respect to its authorised veterinary medicinal products

- has adequate resources available and that training is provided
- takes responsibility and liability for its veterinary medicinal products on the market and continuously evaluates, by appropriate means, the benefit-risk balance of their veterinary medicinal products (VMPs)
- can take appropriate action to address any risk presented, when necessary

The MAH must designate one qualified person responsible for pharmacovigilance (QPPV) for each PSMF it holds, who must be permanently and continuously at the disposal of the MAH. This person is ultimately responsible for all aspects of the pharmacovigilance system.

Usually, the QPPV will be designated to a single pharmacovigilance system and respective PSMF. It is acceptable for the same QPPV to provide services for more than one MAH, for a shared or for separate pharmacovigilance systems (e.g. in the case of subcontractor QPPV) or, if required, to fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorisation holder.

The MAH must ensure that the QPPV can fulfil their responsibilities and activities by providing the following:

- appropriate resources, including sufficient trained personnel
- documented procedures
- communication mechanisms, including access to all sources of relevant information
- authority over and access to the PSMF
- an adequate and effective quality management system for the performance of its pharmacovigilance activities

The MAH must also implement mechanisms to keep the QPPV informed of:

- emerging safety concerns

- any other information affecting the evaluation of the benefit-risk balance of their veterinary medicines

This information may be from ongoing or completed clinical trials and other studies the MAH is aware of, including those carried out by organisations with whom the MAH has contractual arrangements, and which may be relevant to the safety of the veterinary medicine.

The MAH must ensure that the QPPV has the authority to:

- implement changes to the MAHs pharmacovigilance system to promote, maintain, and improve compliance
- provide input into the preparation of regulatory action in response to emerging safety concerns, for example, variations, urgent safety restrictions, and, if necessary, 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 to cover, for example, non-availability of personnel, adverse event database failure, or failure of other hardware or software with impact on electronic reporting and data analysis.

If an MAH acquires a Marketing Authorisation (MA)for a veterinary medicine from another MAH, it should be ensured that the previous MAH provides all available pharmacovigilance information relating to the medicine, including any available sales data. The transfer of pharmacovigilance activities and data should be outlined in an appropriate pharmacovigilance agreement.

If someone other than the MAH becomes responsible for the distribution of a veterinary medicine, the MAH must inform the VMD by means of a suitable variation. Suitable pharmacovigilance contracts must be in place to ensure the MAH is informed of any adverse events reported to the distributor.

2. The Qualified Person Responsible for Pharmacovigilance

The obligations of the Qualified Person for Pharmacovigilance (QPPV) are defined in the VMR 2013 (as amended) Schedule 1 Part 8 paragraph 56B.

The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance so that they can be responsible for and perform the tasks of the post. If the QPPV is not a veterinarian, they should have access to a person qualified in veterinary medicine to assist with technical aspects of adverse event reports. The assistance should be appropriately documented within the PSMF. MAHs must notify the VMD of changes to the name and contact details of the QPPV, including out-of-office hours details, or back-up procedures to ensure business continuity and continued fulfilment of pharmacovigilance obligations.

The QPPV:

- oversees 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, collated, and made accessible at one or more locations
- oversees the preparation for the VMD of the reports referred to in Part 8 of Schedule 1 of the VMR 2013 (as amended). Detailed guidance for the preparation of these reports is included in:
    - guideline III Adverse event reporting
    - guideline IV Signal management, including benefit-risk reports
    - guideline V Post-marketing surveillance studies
- oversees the conduct of continuous overall pharmacovigilance evaluation during the post-authorisation period
- maintains the PSMF and monitors the pharmacovigilance system to ensure continuous improvement through the use of

audits, routine monitoring, and an appropriate corrective and preventative action procedure

- answers fully and promptly any request from the VMD for more information. This information, including volumes of sales or prescriptions of a veterinary medicinal product (VMP), aids the evaluation of the benefits and the risks of a VMP
- provides the VMD with any other information relevant to the evaluation of the benefits and risks of a VMP. This information may come from ongoing or completed post-marketing surveillance studies, or from the actual use of a VMP. It may reveal evidence relating to the validity of the withdrawal period, or lack of efficacy, or an adverse environmental event
- liaises with the VMD in relation to any pharmacovigilance inspection carried out by the VMD

The QPPV should have oversight of the pharmacovigilance system in terms of structure and performance. They should be able to guarantee the pharmacovigilance system components and processes, either directly or through supervision. The oversight should include the functioning of the pharmacovigilance system, including:

- quality control and assurance procedures
- standard operating procedures (SOP)
- database operations
- contractual arrangements
- PSMF preparation and reporting
- adverse event reporting
- signal management and benefit-risk evaluation
- compliance data, for example in relation to the quality, completeness, and timelines for adverse event reporting and submission of benefit-risk reports
- post-marketing surveillance studies
- communication to stakeholders
- deviations and Corrective and Preventive Action (CAPA) plan management
- audit reports
- pharmacovigilance training of personnel

The role of the QPPV involves extensive tasks, depending on the size and nature of the pharmacovigilance system, and the number and type of veterinary medicines for which the MAH holds MAs. The QPPV may delegate specific tasks, under supervision, to appropriately qualified and trained individuals, for example, an expert on the safety aspects of certain veterinary medicines. The QPPV must keep system oversight and overview of the safety profiles of all veterinary medicines. Such delegation should be documented in the PSMF. In case of absence of the QPPV, an adequately qualified person must undertake their responsibilities, the back-up arrangements in place should be described in the PSMF.

The MAH should maintain high level organisation charts providing an overview of the pharmacovigilance units and organisations and illustrating the relationships between them. The charts should show the main reporting relationships with management and clearly show the position of the QPPV within the organisation. If the tasks of the QPPV are outsourced to a third party those arrangements should be described in the PSMF and included in a service agreement.

3. Quality Management System Supporting the pharmacovigilance system

The requirements for a quality management system (QMS) supporting the pharmacovigilance system are defined in the VMR 2013 (as amended) Schedule 1 Part 8 paragraph 56 and 56B.

The pharmacovigilance system should be supported by a robust and effective quality management system. A QMS is a set of policies, processes, procedures, and records that helps coordinate and direct an organisation’s activities to meet internal and regulatory requirements and improve its effectiveness and efficiency on a continuous basis.

An MAH’s QMS should cover organisational structure of the MAH, responsibilities, established processes supported by written procedures, the management of resources for the pharmacovigilance system including sufficient trained personnel, as well as compliance management and record management.

While there must be compliance with the legal requirements, the implementation of a quality system should be adapted to the respective organisation. The quality management system shall be described in the pharmacovigilance system master file.

3.1 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 quality management system should include detailed procedures, documented in the PSMF. The following list indicates the topics that should usually be covered by these written procedures:

- maintenance of the PSMF
- the collection and processing of adverse events, including data entry and data management, quality control, coding, classification, review, and reporting. The processes should ensure that reports of different types and from different sources are captured:
    - organised data collection schemes, unsolicited, clinical trials, literature
    - GB and non-GB, veterinarians and other health care professionals, animal owners, sales and marketing personnel, and other MAH personnel, licensing partners, regulatory authorities, others
- the follow-up of reports for missing information and for information on the progress and outcome of the cases
- management of duplicate reports
- reporting adverse events to the VMD

- preparation, processing, quality control, review, and submission of the annual benefit-risk report
- global pharmacovigilance activities applying to all products:
    - signal detection and review
    - continuous monitoring of the benefit-risk balance
    - communication with the VMD and animal health care professionals regarding changes to the benefit-risk balance of products and requests for information
- interaction between safety issues and product defects, specifically product defects that could lead to pharmacovigilance issues
- responses to requests for information from the competent authority
- handling of urgent safety restrictions and safety variations
- meeting commitments to the competent authority in relation to a marketing authorisation
- management and use of databases or other recording systems
- management of contracts and agreements
- audits of the pharmacovigilance system
- pharmacovigilance staff training
- archiving of all relevant documents

Care should be taken to ensure that quality control and review are appropriately addressed in the various processes and reflected in the relevant procedures.

Copies of the global and GB procedures should be available within two working days after receipt by the MAH of a request from the VMD.

A list of written procedures should be available and should comprise the procedural document reference number, title, effective date, and document type (for all SOPs, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified.

3.2 Performance indicators

Key Performance Indicators (KPIs) are important because they provide a value to compare against current performance. An MAH should implement KPIs relating to their pharmacovigilance activities that are achievable and measurable, for collection at defined intervals to demonstrate how effectively the MAH is achieving its key objectives.

It is recommended to re-evaluate KPIs at specific periods to determine whether it's necessary to make changes to the KPIs so they are up to date, achievable, relevant, and in line with the MAH's objectives.

A list of KPIs, including the reason they were chosen, if applicable, and a description of how to use them should be included in Annex IV of the PSMF.

3.3 Audits

Pharmacovigilance audits should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the pharmacovigilance system. Audit evidence consists of records, statements, or other information, which are relevant to the audit criteria and verifiable.

MAHs should use a risk-based approach to develop an audit programme covering:

- all pharmacovigilance processes and tasks
- the quality system for pharmacovigilance activities
- interactions with other departments, as appropriate
- pharmacovigilance activities conducted by affiliate organisations or activities delegated to another organisation (e.g. regional reporting centres, pharmacovigilance service providers, and third-party distributors)

The risk approach should also account for changes that have occurred since the previous audit, the importance of the processes being audited, and the results of previous audits. The QPPV may be an important source of information relevant to the risk assessment.

It is recommended that audits are conducted by individuals who have no direct involvement in, or responsibility for, the area being audited. The findings of the auditors should be documented in an audit report and should be communicated to relevant personnel, including the auditee and those responsible for the pharmacovigilance system, in a timely manner. Based on the audit findings, the marketing authorisation holder shall ensure that an appropriate plan detailing corrective and preventative actions is prepared and implemented.

The MAH shall place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the PSMF. Once the corrective and preventive actions have been fully implemented, the note may be removed.

The MAH should ensure that a list of all scheduled and completed audits is kept in Annex IV to the PSMF. The dates and results of audits and follow-up audits should be documented.

3.4 Corrective and Preventive Action Plan

MAHs should have processes for managing Corrective and Preventive Action (CAPA) plans implemented in response to any deviations detected in daily operational work, during audits conducted by the MAH, or during a pharmacovigilance inspection.

CAPA plans should be documented in writing and should include the following:

- a root cause analysis
- clear corrective and preventive actions
- a timeline for completion of the actions
- requirements for communication to relevant stakeholders, as appropriate.

If major changes to the pharmacovigilance system are required as part of a CAPA plan it is recommended that a change management process is followed to ensure all relevant stakeholders are consulted.

The MAH should periodically follow up on of the actions implemented as part of a CAPA to ensure their effectiveness.

Documentation relating to CAPA should be retained by the MAH for an appropriate period of time in line with their internal procedures.

3.5 Pharmacovigilance 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, technical veterinarians, regulatory affairs, quality assurance, or clinical trial staff. Additionally, all members of an MAH should receive information about what to do if they become aware of a safety concern.

The QPPV should maintain oversight of PV training conducted and required using documented training plans and records. It is expected that personnel will receive training relevant to their role on entering the company and at defined timepoints to ensure continuous development. It is recommended that a system is implemented to monitor the training outcome and ensure the understanding of personnel. Information on training plans and records for pharmacovigilance activities and a reference to their location should be kept in Annex IV to the pharmacovigilance system master file.

3.6 Document management system

The MAH should have a document management system for the storage, management, and control of all documents relating to pharmacovigilance activities. The document management system should be described in Section D of the PSMF.

The document management system should include a database for the compilation of adverse event reports, a description of which should be included in the PSMF. The VMD is flexible as to whether an MAH has an electronic database, depending on the number of reports the MAH receives. However, we would prefer all MAHs to have some form of electronic storage for pharmacovigilance data, for example spreadsheets.

Systems should be in place to ensure the security, integrity, and confidentiality of adverse event data and to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period. The length of time for which pharmacovigilance reports are archived should be documented. The VMD would expect this to be at least for the life of the product plus some time to allow for expiry of the product.

Electronic databases used as part of pharmacovigilance activities should be designed and maintained to suit their intended purpose. These systems should be subject to appropriate checks, qualification, and/or validation activities to prove their suitability. Evidence of the validation status of the systems used should be available upon request.

MAHs may use a third party database, with appropriate functionality, as their electronic database for recording adverse events. In that case the VMD would expect this database to be supported by a local record of adverse events maintained by the MAH, for example through the use of a spreadsheet, unless otherwise justified.

3.7 QMS requirements for pharmacovigilance tasks contracted by the MAH

An MAH may transfer pharmacovigilance tasks and functions, including the role of the QPPV, to another person or organisation. The MAH remains responsible for the quality and integrity of all pharmacovigilance tasks carried out. The MAH must have detailed, up-to-date, and clearly documented contractual arrangements with the other persons or organisations involved. They must provide information on such arrangements to the VMD on request. The third party may be subject to inspection depending on the tasks and responsibilities delegated to them.

Pharmacovigilance agreements should be prepared with the aim of enabling compliance with the legal requirements by each party and should contain sufficient detail to ensure that the requirements are met. It is the responsibility of the MAH to decide what provisions need to be included in these agreements, particularly considering the content required in agreements may vary depending on the parties involved. Some provisions which the MAH may wish to consider in agreements are outlined below, however, this list is not intended to be exhaustive, and the MAH should use their judgement when deciding what information should be included in agreements:

- agreed definitions
- the roles and responsibilities of each party
- the types of safety information which should be collected and exchanged (e.g. suspected adverse events, lack of efficacy reports, product quality complaints etc.)
- timeframes for the exchange of safety information between parties and case confirmation and/or reconciliation provisions
- contact details of relevant individuals within each party
- how the transfer of outstanding safety information to the MAH will be handled should the agreement be terminated
- mechanisms for oversight of the third-party by the MAH (e.g. in process compliance measures and the right of the MAH to audit the third-party)
- provisions stating that the third party may not subcontract any task assigned to it by the MAH without the MAH’s written consent

MAHs who co-market a VMP must have arrangements that include measures to avoid the duplicate submission of adverse events to the VMD.

Where pharmacovigilance tasks have been contracted/subcontracted out by the MAH to a third party, those arrangements shall be set out in detail in the PSMF.

4. The pharmacovigilance system

All MAHs are required to have an appropriate system of pharmacovigilance in place as outlined in the VMR 2013 (as amended) Schedule 1 Part 8 Paragraph 56 and 56B. The MAH should ensure that the pharmacovigilance system is:

- fit for purpose
- describes the roles and responsibilities of all parties involved in the system
- supported by an appropriate QMS
- contains systems and processes for monitoring the benefit-risk balance of the MAH's VMPs, and for managing any risks identified in relation to those products
- is monitored to ensure that, if necessary, an appropriate corrective or preventive action plan is prepared and implemented to improve the operation of the system
- is clearly documented in the PSMF

5. Requirements for the PSMF Summary and the PSMF

When applying for an MA, the Applicant should submit a Summary of the PSMF in accordance with paragraph 2(2)(g), in Part 1 of Schedule 1 of the Veterinary Medicines Regulations 2013 (as amended) and, where appropriate, a description of the risk management plan.

The name and contact details of the QPPV should be provided in section 8.3 of the MA application 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.

The MAH must clearly document the pharmacovigilance system in the PSMF and should have the full PSMF available for inspection when required.

5.1 PSMF Summary

The PSMF Summary should be provided in Part 1 of the MA application and should include:

- the pharmacovigilance system master file reference number
- the pharmacovigilance system master file location
- name, contact details, and place of operation of the QPPV
- a signed statement from the marketing authorisation holder and the QPPV that the QPPV has the necessary means to fulfil the tasks and responsibilities required by the applicable GB legislation
- the type of record management system used for adverse events reports including the name of the database, if applicable

Upon a change in any of the information in the summary of the applicant's PSMF, the relevant variation not requiring assessment must be submitted to the VMD.

5.2 Content of the PSMF

The MAH must maintain, and make available on request of the VMD, a PSMF that describes the global pharmacovigilance system and reflects the global availability of safety information for UK authorised products.

The marketing authorisation holder may, where appropriate, use separate pharmacovigilance systems for different categories of VMP. Each such system shall be described in a separate PSMF. For each VMP, the MAH must not have more than one pharmacovigilance system described in a PSMF.

The PSMF should be an accurate representation of the pharmacovigilance system that has been established and the MAH must assign a unique PSMF reference number to every pharmacovigilance system covering a UK authorised product.

When pharmacovigilance activities are shared between MAHs it is advised that the partners agree on how to maintain the relevant sections within their own PSMF Accessibility of the PSMF to all the applicable MAHs, and its provision to regulatory authorities should be defined in written agreements.

The PSMF should describe the pharmacovigilance system that is in place at the current time. A system should be in place to review and update the PSMF, as appropriate, to ensure up to date and accurate information. The sections in the main part of the PSMF should contain information that is fundamental for the description of the pharmacovigilance system, whereas the corresponding Annexes should include supplementary information for each section that may change frequently. The content should be indexed and follow the structure described.

The main part of the PSMF should be version controlled, any alteration to the content of the PSMF made within the last five years should be recorded in the logbook, indicating:

- the section that was changed
- information regarding the changes that were made
- the date of the change
- the person that was responsible for the change
- where appropriate, the reason for the changes made

Changes to the information in the Annexes do not need to be tracked in the form of a logbook and version control should be adjusted to the type of information. For example, information in the Annexes of the PSMF that is being regularly updated may include outputs from controlled systems (such as electronic document management

systems or regulatory databases). The information and superseded versions of such content may be managed outside of the PSMF content itself, provided that the history of changes is maintained and available.

The main part of the PSMF should contain the following sections:

Section A: Information on the PSMF, including:

- PSMF reference number
- PSMF location

Section B: QPPV, assistant veterinary surgeon and back up procedures, including:

- information on the QPPV including name, contact details, and a signed statement from the MAH and the qualified person confirming that the qualified person concerned has the necessary means to fulfil the tasks and responsibilities required by the applicable GB legislation
- documentation regarding arrangements for the assistance of a veterinary surgeon, if applicable, including the contact details
- a description of back-up arrangements that apply in the absence of the QPPV

Section C: Marketing Authorisation Holder information including:

- a detailed description of the organisational structure of the MAH, including a parent company or group of companies associated
- the position of the QPPV within the organisation

Section D: A description of the document management system including:

- information regarding the database used for recording adverse event reports, for example paper records, spreadsheets, a database developed in-house, or a proprietary database, including the name of the database if applicable. If the database is capable of assisting the compilation of safety reports and performing electronic reporting to the VMD this should be described. The location

where the adverse event database is kept, the person or group responsible for the operations and management of the database, and a summary of the assessment of its fitness for purpose should be described.

- information regarding any additional systems and databases used for pharmacovigilance purposes, for example, signal detection, contract management, sales data, document life-cycle management, CAPA management; brief functional descriptions of these should be provided.

Section E: Quality Management System for pharmacovigilance activities, including:

- a description of the processes used for pharmacovigilance activities
- a description of the training management system in place
- A description of the system used for documenting or archiving information
- a description of the system for monitoring the performance of the pharmacovigilance system
- a description of the responsibilities for quality assurance auditing of the pharmacovigilance system including, where appropriate, auditing of subcontractors. The process for risk-based planning should be described and the rationale for the risk-based schedule should be documented.
- a list of audits associated with unresolved critical or major findings
- a description of the CAPA plan management and change management in place

Section F: A description of the contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities, where applicable

The PSMF shall contain the following Annexes:

Annex I: a logbook containing records of all changes to the main part of the PSMF

- any alteration to the content of the PSMF made within the last five years should be recorded in the logbook, indicating:
    - the section that was changed
    - information regarding the changes that were made
    - the date of the change
    - the person that was responsible for the change,
    - where appropriate, the reason for the changes made

Annex II: additional information regarding the QPPV, assistant veterinary surgeon, and associated back-up arrangements:

- curriculum vitae including information on qualifications and training of the QPPV and, if applicable, the assistant veterinary surgeon
- a description of the tasks and responsibilities of the QPPV
- list of the pharmacovigilance activities that have been delegated by the QPPV to third parties

Annex III: additional information on the marketing authorisation holder:

- a list of all VMPs registered in GB and covered by the PSMF, including the international non-proprietary name (INN) of the active substances, if applicable, and the authorisation number
- a list of reference numbers for other PSMFs held by the same MAH, where applicable
- the name of the local representative for the purpose of receiving reports of suspected adverse events in GB, including their contact details and responsibilities, where applicable
- a list of the sites where pharmacovigilance activities are carried out

Annex IV: further details about the quality management system:

- a list of documents, policies, procedures, and processes used for pharmacovigilance activities which should include the procedure reference number, the title, the effective date, and document type (SOPs, work instructions, manuals etc.).

Procedures belonging to service providers and other third parties should be clearly identified.

- a list of all scheduled and completed audits including outstanding critical and major findings
- a list of performance indicators and how to use them, as applicable
- information on training plans and training records
- a list of risk management measures, including Risk Management Plans (RMPs) held by the MAH, safety related changes to the product literature, and the outcome of risk minimisation measures

Annex V: further information on contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities:

- a list of the activities or services subcontracted by the MAH to third parties to fulfil pharmacovigilance obligations and information on who the activities or services are subcontracted to, including the name and address of any subcontractors, where applicable
- a list of the tasks of the QPPV that have been totally or partially outsourced and the information on who the activities or services are subcontracted to, including the name and address of the subcontractor(s), where applicable
- a list of existing contracts and agreements with third parties, where applicable, including the products and territories concerned

Annex VI: GB specific information

The VMD is prepared to accept the PSMF produced in line with the EU regulations. In this case the PSMF should include an additional annex covering GB specific information, this may include, but is not limited to:

- a signed statement from the MAH and the qualified person confirming that the qualified person concerned has the necessary means to fulfil the tasks and responsibilities required by the applicable GB legislation

- a list of all VMPs marketed in GB, and covered by the PSMF, including the INN of the active substances, if applicable, and the authorisation number
- a list of contracts and agreements with third parties specific to veterinary medicinal products marketed in GB, not already included in Annex V
- a list of completed and scheduled audits, including outstanding critical and major findings, specific to veterinary medicinal products marketed in GB, not already included in Annex IV
- a list of UK specific written procedures covering pharmacovigilance activities, where applicable
- a list of any risk management measures, including RMPs held by the MAH, safety related changes to the product literature, and the outcome of risk minimisation measures specific to a VMP marketed in GB, not already included in Annex IV
- the name of the local representative for the purpose of receiving reports of suspected adverse events in the UK, including their contact details and responsibilities, where applicable

Where appropriate, information may be provided in the form of charts or flow diagrams.

After the system as described in the PSMF has been formally terminated, MAHs should maintain an electronic version of the PSMF for a reasonable length of time.

Upon request, the MAH must provide a copy of the PSMF to the VMD within seven days of receipt of the request.

6. Risk Management Plans

A VMP is authorised on the basis that, at the time of authorisation, the benefit-risk balance 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 MA is granted; it is recognised that safety information is relatively limited due to many factors including the limited representation of target animals, for example the 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. This is particularly true for novel therapies and for products authorised under 'exceptional circumstances' to cover an as yet unmet medical need. In these situations, it may be necessary for the MAH to develop an RMP in relation to a specific VMP or group of related VMPs.

GB legislation recognises that the MAH may need to develop an RMP for inclusion in the MA application before an MA can be granted in accordance with paragraph 2(3)(k), Part 1 of Schedule 1 of the VMR 2013 (as amended). Requests for the provision of an RMP could also be made following the assessment of pharmacovigilance data as described in the VMR 2013 (as amended) Schedule 1 Part 8 paragraph 61.

An RMP is defined as a set of targeted pharmacovigilance activities and interventions designed to identify, characterise, prevent, or minimise risks relating to VMPs. The content and requirements of the RMP will be assessed by the VMD and agreed with the MAH prior to implementation, the following list describes elements that may be required as part of the RMP:

- a description of any known and potential risks and any areas lacking data, including a summary of any specific safety concerns relating to the VMP
- a description of any specific activities required that complement routine pharmacovigilance and that address the specific safety issues, for example through the implementation of post-marketing surveillance studies, data collection questionnaires, or specific sampling
- the RMP may also propose and evaluate potential risk minimisation activities for each specific safety issue should the data collected confirm the need for additional actions

Data generated through an RMP should be provided to the VMD within the timeframe specified in the agreed RMP. This data would be

assessed and the need for further actions determined as appropriate. Once actions outlined in the RMP have been successfully completed, the plan would be terminated.

Guideline II Inspections

1. Monitoring of compliance by the VMD

Compliance monitoring relates to activities carried out by the VMD to ensure that a system of pharmacovigilance is in place within Marketing Authorisation Holders (MAHs). Methods used include examination of the Pharmacovigilance System Master File (PSMF), written procedures and safety reports, and monitoring prompt responses to requests for information. Deficiencies identified during compliance monitoring may lead to an inspection request. The aim of this process is to support companies to achieve compliance before regulatory action becomes necessary.

1.1 Qualified Person for Pharmacovigilance (QPPV)

The VMD will maintain a list of QPPVs. This list will include business address and contact details, including out of hours contact. MAHs should inform the VMD promptly of any changes in the name or contact details of the QPPV. Failure to inform the VMD of QPPV changes may be considered as non-compliance.

1.2 Availability of pharmacovigilance data

The VMD will monitor, through assessment of the PSMF and when inspections are carried out, that pharmacovigilance data are collated and accessible by the MAH at least at one location.

1.3 Expedited adverse event reporting

Requirements for expedited reporting of adverse events are given in section 2 of Guideline III Adverse event reporting. Methods available to the VMD for monitoring of compliance with expedited reporting of adverse events include:

- monitoring adverse event reports received from MAHs against other sources to determine complete failure to report
- monitoring the time between receipt by the MAH and submission to the VMD 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 Guideline III Adverse Event Reporting
- checking interim and final reports of post-marketing surveillance studies to ensure that all qualifying adverse event reports have been submitted to the VMD within 30 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 to confirm that procedures are in place to follow up reports

1.4 Benefit-risk reports (BRRs) and signal notifications

MAHs should continuously monitor the benefit-risk balance of their products and submit an annual BRR to the VMD, as outlined in section 4 of Guideline IV Signal management, including benefit-risk reports.

One of the key responsibilities of MAHs is to immediately notify the VMD of any change in the benefit-risk balance of their veterinary medicinal products (VMPs). Any failure to do so may pose a significant threat to public or animal health. If a signal is identified suggesting a new risk or change of the benefit-risk balance of a product, the MAH must notify the VMD within 30 calendar days of it being identified. If an urgent safety signal is identified, the MAH should notify the VMD without delay and no later than the next working day (see section 2 of Guideline IV Signal management, including benefit-risk reports).

The VMD places great importance on compliance with BRR reporting. Non-compliance may include:

- complete non-submission of the BRR, late submission, or submission of a BRR that does not cover the correct time frame
- incorrect format of the document
- omission of information required in the BRR
- failure to inform the VMD of a change in the benefit-risk balance of a VMP within the specified timeframes
- previous requests from the VMD not addressed: submission of a report where previous requests from the VMD have not been addressed, for example, close monitoring of specific safety issues

1.5 Requests for information from the VMD

No fixed time frames are laid down in UK legislation or guidelines for responding to a request for information from the VMD. 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 VMD will ensure that requests for

information from MAHs have a clear deadline when needed and this deadline should be appropriate to the complexity and urgency of the issue. The VMD 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.

1.6 Submission of safety variations

As with responding to requests for information from the VMD, deadlines for submission of safety variations will depend on the urgency and potential public or animal health impact of the pharmacovigilance issue. In general, any variation requested should be submitted to the VMD within six months. Should the VMD require a variation to be submitted within a different timeframe the VMD will liaise with the MAH regarding the appropriate deadline. Failure of MAHs to submit the variation application within the deadline may be considered as non-compliance.

1.8 Post-marketing surveillance studies

Because of the objectives of post-marketing surveillance studies there is considerable potential for safety signals to arise or changes in the balance of benefits and risks of products to be identified. Therefore, reporting and submission to the VMD of interim and final study reports from such studies has an important role in protecting public or animal health. Where appropriate, the VMD will scrutinise protocols prior to the initiation of post-marketing surveillance studies. The VMD checks that relevant adverse event reports are submitted from those studies and monitors the submission of interim and final study reports. Guidance on post-marketing surveillance studies is available in Guideline V Post-marketing surveillance studies.

2. Pharmacovigilance Inspections

The VMD inspects all MAHs to ensure that they have the personnel, systems, and facilities in place to comply with their pharmacovigilance obligations as described in the VMR 2013 (as amended) Schedule 1 Part 8 paragraph 60A. Any MAH with a product authorised in GB can be subject to a pharmacovigilance inspection by the VMD, which may also include any of their partners or service providers.

2.1 Types of inspection

Pharmacovigilance inspections are scheduled according to the VMD's risk-based approach, largely based on complexity and size of an organisation, products authorised, compliance history, and additional risk factors such as:

- the MAH has recently been, or is involved in, a merger or takeover process
- the MAH has changed their system significantly, for example, new database system, contracting out of reporting activities etc

Inspections will generally be routine but can also be targeted to MAHs suspected of being non-compliant.

2.2 Routine inspections

The MAH is notified of these inspections in advance. These may be inspections of the general pharmacovigilance system, or 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. This provides practical evidence of the functioning

of the pharmacovigilance system of the MAH and their compliance with their regulatory obligations.

Where the pharmacovigilance system of a MAH has not been inspected previously, an inspection of the system will be performed within four years of placing the first VMP on the GB market. Where the system has previously been inspected, re-inspection will take place at intervals. If no critical findings are identified the frequency of inspection will be decided using the risk-based approach.

If an inspection results in a critical finding it is likely the MAH will be subject to a triggered re-inspection within 12 months, with a focus on the actions that were agreed following the last inspection.

2.3 Targeted inspections

Targeted inspections may be conducted when triggers are identified and the VMD determines that inspection is the appropriate course of action. Triggers which may result in a targeted inspection include:

- delays in carrying out, or failure to carry out, specific obligations or follow-up measures relating to the monitoring of product safety and efficacy
- delays in reporting
- incomplete reporting
- submission of poor quality or incomplete BRRs
- inconsistencies between reports and other information sources
- failure to communicate change in benefit-risk balance
- previous inspection experience
- information received from other authorities
- poor follow-up to requests for information from the VMD

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

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

2.4 Remote inspections

Routine and targeted inspections may be conducted by inspectors remotely. These inspections are conducted through a combination of review of requested documents, including evidence to support pharmacovigilance activities, and a method for interviews with relevant personnel. Logistical aspects of the inspection will be arranged with the MAH prior to the inspection. Should any significant issues be identified, that cannot be adequately reviewed during the remote inspection, it may be necessary to schedule an on-site inspection of the MAH's pharmacovigilance system.

2.5 Inspection conduct

Inspection requests are prepared by the pharmacovigilance Inspector. As part of the inspection notification a number of documents will be requested. You must acknowledge you have received the notification and provide the requested documentation within the timeframe stated in the letter. Details of the relevant contact person for future correspondence about the inspection should be provided. If this is not the QPPV they should be made aware by the MAH of the inspection and be contactable during the inspection.

The inspection team will ask for additional documentation during the inspection. It is expected that any documents listed in the PSMF will be readily available for inspection. This includes procedure documents (such as standard operating procedures, working instructions, and guides), as well as outputs from pharmacovigilance activities such as safety meeting minutes, documented product safety reviews, audit risk assessments, and agreements in place with third parties and service providers.

The MAH should ensure access to internet and teleconference facilities, if required, throughout the inspection; as well as prompt access to printing and copying facilities, and access to all electronic documentation and systems including the safety database.

At the closing meeting the inspector will provide feedback and discuss any deficiencies and actions required with the MAH.

Each inspection will result in an inspection report. The inspection report will be made available to the MAH. Where an inspection reveals non-compliance the MAH will be required to prepare a corrective action plan to correct the non-compliances and avoid recurrence. The MAH may be required to provide 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 actions.

The results will be used to help MAHs improve compliance and may also be used as a basis for enforcement action.

3. Regulatory Action

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.

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

- MAHs may be assisted to comply with the legislation through the provision of advice and guidance
- non-compliant MAHs may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved
- a formal warning may be issued reminding MAHs of their pharmacovigilance regulatory obligations

- an Improvement Notice may be issued
- the Marketing Authorisation (MA) may be suspended
- the MA may be revoked

Guideline III Adverse event reporting

1. Introduction

The obligations of the Marketing Authorisation Holder (MAH) for recording and reporting adverse events associated with their veterinary medicinal products (VMPs) for which Marketing Authorisations (MAs) are held are defined in the VMR 2013 (as amended) Schedule 1 Part 8 paragraph 57-59.

The term adverse event used in this guidance is as defined in VICH GL24: “adverse event” means any observation in animals that occurs after any use of a VMP, whether or not considered to be product-related, that is unfavourable and unintended.

The VMR 2013 (as amended) includes this definition and defines human adverse event, adverse environmental event, and lack of efficacy which are referred to in this guidance. These definitions can also be found in the Glossary. For authorised VMPs, independent of the authorisation procedure, adverse event reports received from any source should be reported, regardless of whether or not the product was used in accordance with the authorised Summary of Product Characteristics (SPC) and/or any other conditions laid down for marketing of the product in accordance with applicable legal requirements.

The MAH is expected to validate all adverse events reported by all sources to ensure, prior to reporting to the VMD, that the minimum information required is included in the report, minimum information is covered in section 3.1 of this guidance. 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 VMD. All

available information relevant to the evaluation of the adverse event should be provided in the adverse event report.

2. Requirements for expedited reporting

The MAH should report all adverse events occurring worldwide for their VMPs which are authorised in the UK, or the equivalent products authorised elsewhere, to the VMD within 30 calendar days of being made aware of them.

The date the MAH becomes aware of a report which fulfils the minimum information should be considered day 0.

The clock for expedited reporting starts, day 0, as soon as the minimum information 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.

The expedited reporting of adverse events should occur regardless of whether the adverse event is categorised as serious or non-serious.

If a seriousness category is required for an adverse event report then this should be based on the definition of a serious adverse event as per VICH GL24: “any adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect. For animals managed 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.”

Electronic reporting of adverse events is mandatory for MAHs, save in exceptional circumstances with prior or simultaneous notice. The VMD should be informed of these circumstances as soon as possible by e-mailing adverse.events@vmd.gov.uk. For pharmacovigilance requirements for other products including submission routes see Guideline VI Pharmacovigilance for other products. This includes Animal Test Certificate holders, medicines for small animals exempt

from authorisation, Autogenous Vaccine Authorisation holders, and extemporaneous preparation manufacturers.

Requirements for electronic reporting are covered in section 3.2 of this guidance.

The electronic reporting solutions are available using the Veterinary Medicines Digital Service (VMDS). Any MAH not signed up to VMDS can e-mail adverse.events@vmd.gov.uk to register.

Where there are no appropriate fields in which to record specific details, the information should be provided in the case narrative as appropriate.

MAHs should not report adverse events that are likely to have already been reported by other MAHs, for example a report from another MAH found in the database of a different regulatory authority.

2.1 Reporting of adverse events in respect to animals

All reports of animal adverse events should be recorded by the person responsible for pharmacovigilance and reported to the VMD within 30 days. This includes adverse events occurring in animals exposed to the treated animal or in offspring of a treated animal (see sections 4.5 and 4.6).

2.2 Reporting of human adverse events

A human adverse event is defined as a reaction that is noxious and unintended and that occurs in a human being following exposure to a VMP. All reports of human adverse events should be recorded by the person responsible for pharmacovigilance and reported to the VMD within 30 days.

2.3 Reporting of lack of efficacy

Lack of efficacy is defined as the apparent inability of an authorised VMP to have the expected efficacy in an animal, whether or not the product was used in accordance with the Summary of Product Characteristics (SPC).

All reports of lack of efficacy should be recorded by the person responsible for pharmacovigilance and reported to the VMD within 30 days.

It is important for MAHs to identify if the report involves a possible batch quality problem. If an adverse event involves a batch quality problem, or any other product defect related issue, then it must be reported via pharmacovigilance reporting pathways and should also be reported to the VMD via the product defect report form. Batch quality problems or other product defect related issues that did not result in an adverse event do not need to be reported via pharmacovigilance reporting pathways, but should be reported via the product defect report form.

2.4 Reporting of adverse events following off-label use

Off-label use relates to situations where the VMP is used outside the terms of the MA.

The MAH should collect any available information on adverse events following off-label use related to their VMPs and report this to the VMD within 30 days in the same way as for other adverse event reports.

Examples of off-label use include using the VMP in a non-authorised species, or for a sub-category of animal within that species that the product is not authorised for, for an unauthorised indication, or at a dose that is different to the doses specified in the product literature.

Adverse events may be reported subsequent to off-label use of VMPs following prescribing under the provisions of the cascade.

Reports of off-label use without an adverse event occurring reported to the MAH should be recorded but do not need to be reported to the VMD.

2.5 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 veterinary medicinal products 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 medicine has been respected, this information may cast doubt on the validity of the withdrawal period and consequently should be investigated and reported to the VMD. If the case meets the minimum information required for adverse event reports, then it should be recorded and reported within 30 days even if the information about whether the recommended withdrawal period has been respected is unknown.

In circumstances where these reports cast doubt on the appropriateness of the recommended withdrawal period of the given veterinary medicinal product, the reports should be recorded and reported to the VMD within 30 days of receipt.

2.6 Reporting on adverse environmental events

An adverse environmental event means an event where a non-target organism, population or ecosystem is adversely affected as a result of exposure to a VMP, its active substances or its metabolites present in soil, water or animal remains.

Any suspected adverse environmental event related to VMP exposure should be recorded by the MAH as soon as it comes to their attention.

Reports of potential adverse environmental events arising from the use of a VMP should be submitted to the VMD within 30 days of receipt.

2.7 Reports published in peer-reviewed worldwide literature

Adverse event reports from worldwide literature are considered to be reports the MAH can reasonably be expected to be aware of. The MAH is therefore expected to monitor the scientific literature regularly to identify adverse events concerning their products that qualify for reporting.

The MAH should report to VMD published adverse events associated with the use of its veterinary medicinal products in accordance with the requirements for adverse event reporting described above.

Contractual arrangements may be made with a person or organisation to perform literature searches and/or report relevant individual adverse event reports to the VMD. 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 adverse events described in the worldwide scientific literature to ensure that the MAH can comply with their reporting obligations.

It is recommended that MAHs search the scientific literature regularly as part of their ongoing signal detection procedures, this should be at least once a year. A risk-based approach is advised covering active substance, type of product, the stability in number and incidence of adverse event reports, and stability of the pharmacovigilance profile. Rather than performing a product specific search, it is recommended to begin literature searches based on the active substance which should then be narrowed down to the individual product. Search terms for ‘adverse events’ should not be too restrictive and other terms should be considered, for example adverse reaction, side effect, toxicity, and idiosyncratic effect.

The MAH is expected to consider reports from products other than their own if the event of interest is related to the active substance and/or if the specific product cannot be identified.

The choice of databases and search criteria will be reviewed during pharmacovigilance inspections. It is preferable to ensure that a variety of databases and search engines are searched, including, for example CAB Abstracts, Google Scholar, Medline, PubMed, and Scopus; the choice remains at the discretion of the MAH.

Data on resistance to a VMP from a literature search and/or other sources would be expected to be considered in the ongoing signal management and benefit-risk assessment of a product.

2.8 Reporting on adverse events from post-marketing surveillance studies

Any adverse event following administration of an authorised VMP should be recorded by the person responsible for pharmacovigilance and reported to the VMD within 30 days. This includes adverse events occurring during post-marketing surveillance studies.

See Guideline V Post-marketing surveillance studies for further guidance on these studies.

2.9 Reporting on adverse events from the Internet

MAHs should review any reports submitted through their websites and determine whether they should be reported within 30 days.

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

Non-spontaneous adverse event reports and pharmacovigilance information may originate from an ever-increasing number of online resources. The main sources of such information that VMD is currently aware of are discussed below.

2.9.1 MAH hosted websites and social media accounts

Most MAHs have an active presence on the internet in the form of websites and social media accounts, and many MAH hosted websites have ‘contact us’ forms. These may be used by reporters to notify MAHs of adverse events. All adverse events identified via company websites or social media accounts should be followed-up by the MAH and reported to the VMD within 30 days if the information fulfils the criteria for a valid adverse event report.

MAHs maintaining a presence on social media and/or the internet are encouraged to make use of these media to inform product users how to report adverse events, by providing relevant contact information and/or facilitating adverse event reporting by providing forms and details on the minimum information required to report an adverse event.

2.9.2 Groups of animal owners on the internet

Various breed organisations or associations of individuals and interest groups have their own websites or social media groups on the internet, these often include the capacity to communicate with each other through discussion boards, threads, and chat rooms. Often these discussions may include information from owners regarding adverse events.

As there are many websites and social media groups, and some of these are not public access i.e. private or closed, MAHs would not be expected to have awareness of these adverse events. However, if the MAH becomes aware of potential adverse events during active searches set up by the MAH, reasonable effort should be made to follow up on the reports to obtain at least the minimum reporting criteria so that the events can be submitted as per reporting requirements and further actions undertaken if required, such as additional review.

In cases where the minimum criteria for a valid adverse event report have not been met despite efforts to investigate the potential event it is recommended that the MAH keeps a record of this data, for example a reference to the concerned site, in line with the Quality Management Systems of the MAH.

2.10 Reports from other sources

If an MAH becomes aware of an adverse event report from sources other than those mentioned above, for example the lay press or other media, reasonable attempts should be made to obtain the minimum information that constitutes an individual adverse event and to follow-up the report. The approach taken by the MAH for reports from other sources would be expected to be like the approach for reports identified on websites and in social media.

3. Required information for adverse event reports

3.1 Minimum information for adverse event reports

An adverse event report must contain the minimum information below to be considered valid:

- an identifiable source or primary reporter
- animal or patient details: as a minimum species should be known (animal species or human)
- VMP concerned: name and MA number
- adverse event details

For the VMP concerned the MAH must use up to date MA numbers, and this must match the UK country of occurrence. For example, a case occurring in GB must be submitted with a veterinary medicinal product MA number for GB. If this does not match, for example with an imported product, then this needs to be clearly indicated in the narrative.

If a single MA number is split into two separate MA numbers at any time, MA numbers submitted in adverse event reports must be aligned with these updates at the earliest opportunity.

For adverse event reports occurring outside of the UK, the MA number should map to the equivalent VMP available in the UK. This should be done by ensuring the equivalent UK MA number is entered into XML field B.2.1.1). All up to date local country MA numbers will also be requested as part of the annual benefit-risk report (BRR).

The original words and/or phrases used by the reporter should be provided in the adverse event report even if they are also coded using the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) List of Clinical Terms for reporting adverse events in animals and humans.

The use of internationally agreed standard terminology lists is crucial in harmonising the exchange of pharmacovigilance information. An MAH should use VeDDRA terminology to code clinical signs in adverse event reports, and the latest version should be used in line with specified implementation dates. The VeDDRA lists are revised regularly and are available on the EMA website.

Reporter details such as initials and geographic location are important to avoid duplication of reports. All reporter details obtained should be recorded by the MAH, however MAHs need to comply with the relevant data protection laws, for example the General data Protection Regulation (GDPR) and privacy legislation, whenever this information is transmitted. An MAH should not transmit any identifiable confidential information from the reporter when submitting an adverse event report to the VMD. Usually only the initials (last name initial +/- first name initial if known) and the first two letters of the postcode should be included in any adverse event report submitted.

In addition to this the narrative of adverse event should not contain identifiable confidential information, such as specific animal names (for example pedigree or racehorse names identifiable to one individual), veterinarian details, veterinary referral centre details, or diagnostic laboratory details.

3.2 Minimum information for electronic adverse event reports

MAHs must report all adverse events occurring in the UK electronically, unless in exceptional circumstances with prior or simultaneous notice to the VMD.

Electronic reporting must be made using the VICH Extensible Markup Language (XML) format as per VICH guidelines 35 and 42, using terms from the controlled list of terms and vocabulary list as per VICH guideline 30.

As well as the minimum information for reporting as per section 3.1, electronic adverse event reports have additional mandatory data fields that must be completed. As per section 3.1, in addition to the minimum information for electronic reporting, all information relevant for the evaluation of the report should be requested and reported.

All mandatory VICH XML fields for electronic transmission as per VICH guideline 42:

- Regulatory authority name, Street address, City, State/county, Post code, Country (using appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists)
- Mandatory only for MAH submitting the adverse event report: Business name, Street address, City, State/county, Post code, Country (using appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists)
- Primary Reporter: last name and country code are mandatory, if last name not provided then WITHHELD can be entered in the last name field (and should be transmitted as WITHHELD rather than 'W')
- Primary Reporter Category +/- Other Reporter Category if applicable (controlled list)
- Unique Adverse Event Report Identification Number (using controlled list of Regulatory Authority identifier codes if applicable)
- Original Receive Date (VICH GL35 data type description - "YYYYMMDD")
- Date of Current Submission (VICH GL35 data type description - "YYYYMMDD")
- Type of Submission (controlled list)
- Reason for Nullification Report (if applicable)
- Number of Animals Affected
- Species (controlled list, select human for human adverse events)
- Measured, Estimated, Unknown Weights (mandatory if minimum or maximum weight specified, unknown if not available from reporter, controlled list precision categories)
- Measured, Estimated, Unknown Age (mandatory if minimum or maximum age specified, unknown if not available from reporter, controlled list precision categories) and applicable Age Units

- Registered or Brand Name (mandatory for MAH's products)
- Registration Identifier (for MAH's products, unless cannot be determined due to insufficient information from the reporter, then "Cannot be Determined" is entered)
- Anatomical Therapeutic Chemical Classification for VMPs (ATCvet) code (for MAH's products, from WHO list)
- Units for Value for the Interval of Administration (if interval of administration specified)
- Active Ingredient(s) (for MAH's products, unless cannot be determined due to insufficient information from the reporter, then "Cannot be Determined" is entered)
- Units for Strength Numerator and Denominator (if strength is specified)
- Narrative of AE (adverse event narrative)
- Adverse Clinical Manifestation (from the controlled list of VeDDRA terms)
- Date of Onset of AE (VICH GL35 data type description - "YYYYMMDD")
- Duration Time Unit (if duration is specified)
- Serious AE (completed by MAH, Yes or No)

The Unique Adverse Event Report Identification Number (sometimes known as AERID or the worldwide case number) is electronically assigned by the first organisation to send an adverse event report.

This number consists of:

- country of occurrence code (3 characters using appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists)
- the MAH's organisational ID (MAHORGID, 8 characters)
- remaining free text (up to 47 characters, which can include a routing ID)

This number must not be changed for any future transmissions. This avoids the creation of duplicate reports.

The original receive date is the first communication of an adverse event from the primary reporter to the MAH or regulatory authority. This applies to date of receipt by any personnel of the MAH or an

organisation having a contractual arrangement with the MAH. This date is fixed and cannot be changed in future.

If an MAH does not have a MAHORGID, or suspects a duplicate report,a change to AERID, or original receive date has occurred, then they should contact the VMD via e-mail at adverse.events@vmd.gov.uk.

3.3 Additional information for adverse event reports

As well as collecting the minimum information for a valid report, MAHs are also expected to record all information relevant for the evaluation of the report, provided by the sender or obtained during the processing of the case, and include this in the adverse event report.

Reasonable effort should be made to fill out all relevant data fields, and any additional information that does not fit in a data field of the chosen submission method should instead be included in the narrative of the adverse event. Further guidance on data elements of VICH XML data is available in VICH guideline 42.

The adverse event narrative should serve as a complete and comprehensive summary, presented in a logical time sequence in chronological order. It should contain all known relevant clinical information, including any information that supports or negates an association between a product and an adverse event. The opinion of the primary reporter and attending veterinarian (if not the primary reporter) regarding causality should be recorded. The use of abbreviations and acronyms should be avoided.

4. Guidance on particular types of reports

All electronic adverse event reports should be completed using the guidance from VICH guidelines 35 and 42, using terms from the controlled list of terms and vocabulary list as per VICH guideline 30. All reports should have appropriate VeDDRA terms added from the Combined VeDDRA list of clinical terms following the Guidance notes on the use of VeDDRA.

Guidance on certain types of adverse event reports has also been included in the following sections.

4.1 Follow-up adverse event reports

The MAH is expected to follow-up adverse event reports with reasonable effort to obtain further pertinent information. Follow-up reports to incomplete adverse event reports should be submitted by the MAH to the VMD, particularly in cases where only the minimum information was submitted initially or when the investigation of the adverse event is completed.

Initial adverse event reports must be submitted within 30 days, there is no specific deadline for follow-up reports and therefore they should be submitted within reasonable time frames. If further information is expected then it may be appropriate to delay submission of a follow-up until that information is obtained, rather than sending multiple follow-up reports in rapid succession.

Only follow-up reports containing clinically relevant information should be submitted, for example new VeDDRA terms, additional clinical details in the narrative, or post-mortem examination or laboratory results. Follow-up reports do not need to be submitted for non-clinically relevant information such as a change or addition of a causality assessment, and ‘no further information expected’ or ‘case closed’ follow-up reports.

If an accidental follow-up submission is made to the VMD that does not contain clinically relevant information, then VMD should be informed by e-mailing adverse.events@vmd.gov.uk.

In some instances, an MAH may submit a follow-up to a case where the originator is the VMD or another MAH. The VMD's version of the adverse event report must always reflect all products present, and therefore MAHs should refrain from sending follow-up reports which have been amended to suit their VMPs only.

Follow-up reports to another MAH's case should not be sent when the only update is to provide a best guess for a VMP in the adverse event report that has been partially added, unless that information has been provided directly by the original reporter (for example in situations where a reporter has contacted multiple MAHs).

Any VMD comments in the narrative (which are often labelled as National Competent Authority comments or NCA comments) should be retained within the case. If an amendment or further detail is required in response to the comment, then this should be added after the comment rather than editing or replacing the comment.

If an MAH adds a comment to the narrative of an adverse event report involving multiple MAHs, they should specify who is commenting in the comment.

4.2 Human adverse event reports

Information about any human adverse events to VMPs, whether occurring in conjunction with the treatment of animals, the handling of a VMP or following exposure through the environment, should be reported to the VMD. There should be one report per human involved in the adverse event.

Asymptomatic human events should be recorded but not transmitted to the VMD.

The adverse event narrative is very important and should contain all known relevant information, including how the exposure occurred, for example accidental or routine use, the degree of exposure, the volume injected or splashed, the course of events, medical diagnosis, and any other information that supports or negates an association between a VMP and an adverse event.

Minimum information for a valid report should be obtained (see sections 3.1 and 3.2), in addition reasonable attempts should be made to obtain all relevant information regarding the adverse event. In particular information regarding the following is useful for a full evaluation and should be provided in the relevant data fields and/or adverse event narrative when known:

- patient details including patient identification (as appropriate according to GDPR and privacy legislation, such as the initials of the patient)
- details of medical doctor/physician, or Poison Centre, if consulted (initials and first 2 digits of postcode)
- route of exposure, such as respiratory (inhalation), oral, or cutaneous, and duration of exposure
- reason for exposure: accidental exposure or deliberate misuse (deliberate misuse would be considered off-label use)

4.3 Adverse event reports involving lack of efficacy

If an adverse event report includes lack of efficacy (sometimes referred to as LEE) or partial lack of efficacy, then this should be VeDDRA coded with an appropriate lack of efficacy VeDDRA low level term (LLT), with a relevant death VeDDRA LLT added if required. No other clinical signs relating to the lack of efficacy should be coded using VeDDRA.

In lack of efficacy reports following use of euthanasia products, these events should be coded using only the VeDDRA LLTs ‘Lack of efficacy - NOS’ and ‘Unrelated death’; as the death was unrelated to the lack of efficacy.

Electronic reporting using VICH XML format involves the optional selection of ‘Type of Information in Report’. This has terms for ‘Safety Issue’, ‘Lack of Expected Effectiveness’, ‘Both Safety and Lack of Expected Effectiveness’, and ‘Other’ (see tab d. Type of Information of the VICH GL 30 Vocabulary Lists). If a case contains a lack of

efficacy VeDDRA term then the Type of Information should be selected as ‘Lack of Expected Effectiveness’ or ‘Both Safety and Lack of Expected Effectiveness’ as applicable.

Historical adverse event reports submitted using a different XML format may not have the option of selecting both a safety and a lack of efficacy information type, and therefore they may transmit as just safety. Therefore, it is important that information regarding lack of efficacy is clearly included in the narrative as well as the VeDDRA coding.

If a case contains both lack of efficacy and other adverse events that do not fall within the remit of lack of efficacy, events that are grouped under the appropriate lack of efficacy VeDDRA LLT term should be clearly identified as such within the narrative.

4.4 Adverse event reports involving off-label use

Information should be provided in adverse event reports if the product has not been used according to the product literature i.e. off-label use.

‘Use according to label’ should be selected as ‘No’ even if the product was deliberately prescribed not according to label.

If there were mistakes in prescribing, storing, the preparation, or the administration of a product, the event should be reported as off-label use.

Human cases of accidental exposure are not considered off-label use; only deliberate use of a VMP on a human is off-label use. Off-label use relates only to treated animals, not to human accidental exposure.

For electronic reporting the appropriate ‘Explanation for Off-Label Use’ should be selected as per tab bb. XML Locator Codes of the VICH GL 30 Vocabulary Lists (from T95028 to T95037).

The following terms are available: Overdosed, Underdosed, Treatment regimen Off-Label, Indication Off-Label, Storage condition Off-Label, Product expired, and Other off label issue.

As well as filling out the relevant fields, all details regarding off-label use should be added to the case narrative, especially in adverse event reports where more than one type of off-label use has occurred, or more than one product has been added but the off-label use only occurred for one product.

If there is an appropriate VeDDRA LLT from the 'Medication and product use errors' system organ class (SOC) available then this should be added to the report. Examples include overdose, underdose and intentional misuse.

The VeDDRA guidance provides details on how the terms within this SOC should be used.

VeDDRA LLT 'Intentional misuse' should be added when there is deliberate use of a VMP or a medicinal product for human use in animals for a purpose not consistent with applicable legal or medical guidance. This VeDDRA also applies to intentional use of a VMP in humans, unless permitted by legal provision.

4.5 Adverse event reports involving more than one species

If more than one species is involved in the same adverse event, separate reports should be submitted for each species, although it should be indicated that the reports are linked (see section 4.14 on linked reports). This applies when more than one animal species is involved, or when an animal and a human are involved.

4.6 Adverse event reports 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, with all information regarding the exposure and the treated animal included in the narrative. The patient details should be for the untreated animal exposed, and the administration route details should reflect the route by which the affected animal was exposed, such as oral route if the contact was by licking or grooming, or cutaneous route if there was dermal contact between the treated and untreated animal.

4.7 Adverse event reports involving offspring exposed through a parent

4.7.1. Abortion

A report should be submitted relating to the parent. The animal details should be those of the parent. The ‘Number of Animals Affected’ recorded should relate to the parent. The number of aborted offspring should only be stated in the case narrative and should not be counted as number of animals died. The VeDDRA LLT ‘Abortion’ should be added, unless the product is indicated for reduction or prevention of abortion (for example by preventing the transmission of a pathogen to an offspring), in which case an appropriate lack of efficacy VeDDRA LLT should be selected.

4.7.2 Stillbirth

A report should be submitted relating to the parent. The animal details should be those of the parent. The number of stillbirth offspring should be counted as the number of animals died. The VeDDRA LLT ‘Abortion’, as well as the relevant parent-offspring VeDDRA LLT, should be added.

4.7.3. Adverse events in offspring only

The ‘Number of Animals Treated’ should be the parent. The ‘Number of Animals Affected’ should be the number of affected offspring.

The animal details should relate to the offspring, and the narrative should include information on the parent treated. The VeDDRA LLT ‘Offspring-only event’ should be added, along with any VeDDRAs relevant to the adverse events noted.

4.7.4. Adverse events in parent and offspring

In reports involving adverse events where an unidentified parent was treated, and it is suspected that the treated parent and offspring are affected by this treatment, a single report should be submitted relating to both the parent and the offspring. The animal details to be recorded should be those of the parent. The number of parent and offspring affected should be recorded in the ’Number of Animals Affected’ field and any details regarding exposure route should be recorded in the case narrative. The relevant VeDDRA low level term ‘Parent-offspring event’, ‘Father and offspring event’ or ‘Mother and offspring event’ should be added, along with any other VeDDRAs relevant to the adverse events noted. If the parent or offspring died this should be recorded in the number of animals died.

4.8 Adverse event involving validity of the withdrawal period

For these adverse event reports the relevant VeDDRA LLT from the ‘Residue investigations’ high level term (HLT) category should be selected, for example ‘Residues in milk’ or ‘Residues in meat/offal’.

Electronic reporting using VICH XML format involves the optional selection of ‘Type of Information in Report’. For these adverse event reports ‘Other’ can be selected.

The report should contain all mandatory information and all other clinically relevant information obtained, in particular it should contain details about:

- the source of the report
- the withdrawal period applied
- date of first exposure
- dates of sample collection and detection of the residues
- the level of residues detected
- the location of the case
- animal weight
- the analytical method used to determine the residues
- the steps taken by the MAH to investigate the matter

4.9 Adverse event involving adverse environmental events

For these adverse event reports the VeDDRA LLT ‘Environmental incident’ should be selected.

Electronic reporting using VICH XML format involves the optional selection of ‘Type of Information in Report’. For these adverse event reports ‘Other’ can be selected.

The report should contain all mandatory information and all other clinically relevant information obtained, in particular it should contain details about:

- the location
- the ecosystem, animal, or plant involved, as appropriate
- the nature of the suspected adverse environmental event
- the suspected veterinary medicinal product

4.10 Adverse event involving suspected infectious agent transmission or suspected reversal to virulence

4.10.1 Suspected infectious agent transmission

For these adverse event reports the VeDDRA LLT ‘Suspected infectious agent transmission’ should be selected.

4.10.2 Suspected reversal to virulence

For these adverse event reports the VeDDRA LLT ‘Suspected reversal to virulence’ should be selected.

4.11 Adverse event reports involving suspected diagnoses

If an adverse event report involves a list of suspected diagnoses, then these should not be individually VeDDRA coded. However, following appropriate examination by a veterinarian if there is only one suspected diagnosis, especially when relevant investigations have been performed or the diagnosis is a diagnosis of exclusion, then the diagnosis should be VeDDRA coded with an appropriate LLT.

4.12 Adverse event reports published in peer-reviewed worldwide literature

Electronic reporting using VICH XML format involves the optional selection of ‘Type of Information in Report’. For these adverse event reports ‘Other’ can be selected.

Details of the publication such as title and authors should be included in the adverse event narrative.

4.13 Adverse event reports from post-marketing surveillance studies

Electronic reporting using VICH XML format involves the optional selection of ‘Type of Information in Report’. For these adverse event reports ‘Other’ can be selected.

The adverse event report should clearly indicate that this is a report from a post-marketing surveillance study, this can be provided in the adverse event narrative.

4.14 Linked adverse event reports

For electronic reporting, the relevant ‘Explanation for Linkage’ should be selected, as per tab cc. Explanation for Linkage of the VICH GL 30 Vocabulary Lists, bearing in mind the definitions for each term.

The AERID (worldwide case number) of the linked adverse event report should be included in the narrative.

4.15 Adverse event reports involving death

If an adverse event report involves death then an appropriate death VeDDRA LLT should be selected.

If a post-mortem examination has been carried out, then the VeDDRA LLT ‘Necropsy performed’ should be added. Findings from the post-mortem examination should also be individually VeDDRA coded with the relevant LLTs. ‘Necropsy performed’ should not be added for lack of efficacy only adverse event reports as these should only contain lack of efficacy VeDDRAs and a death VeDDRA if relevant.

4.16 Adverse event reports involving product defects or counterfeit products

If an adverse event report involves a product defect, then the VeDDRA LLT ‘Product defect NOS’ should be selected.

If an adverse event report involves a suspect or confirmed counterfeit product then the relevant counterfeit product VeDDRA LLT should be selected.

4.17 Adverse event reports involving anaphylaxis

4.17.1 Anaphylaxis

Anaphylactic shock is an acute allergic, potentially life-threatening, Type 1 hypersensitivity reaction resulting from the generalised release of potent vasoactive substances from mast cells and basophils. The clinical signs of anaphylaxis can vary between species. The table in section 4.17.2 summarises the clinical signs that may be seen, however this list is not exhaustive.

An appropriate anaphylaxis LLT should be VeDDRA coded if the adverse event report contains clinical signs from this list. In addition, if

the reporter’s own words when reporting include anaphylaxis then this should be VeDDRA coded.

4.17.2 Table of clinical signs of anaphylaxis in different species

Species	Clinical signs
Dog	Excitement, urticaria, pruritus, angioedema, vomiting, defecation, dyspnoea, collapse, convulsions
Cat	Pruritus, angioedema, salivation, vomiting, dyspnoea, incoordination, collapse
Rabbit	Tachypnoea, dyspnoea, pallor, collapse, defecation, urination, loss of consciousness, collapse, convulsions
Horse	Shivering, sweating, incoordination, coughing, dyspnoea, diarrhoea, colic, collapse
Cow and sheep	Urticaria, restlessness, pruritus, angioedema, defecation, urination, coughing, dyspnoea, cyanosis, bloat, collapse

Pig	Dyspnoea, cyanosis, pruritus, collapse, vomiting, diarrhoea

5. Reporting following suspension or withdrawal of the MA

Reporting requirements remain following suspension of the MA of a VMP for pharmacovigilance or commercial reasons: see relevant sections of this guideline and Guideline IV Signal management, including benefit-risk reports.

Where an MA is withdrawn or revoked, the former MAH is encouraged to continue to report in line with guidance to, for example, facilitate review of delayed onset adverse events and retrospectively notified cases. It may be appropriate to continue submission of benefit-risk reports after withdrawal or revocation of the MA. This should be addressed and agreed on a case-by-case basis with the VMD.

Guideline IV Signal management, including benefit-risk reports

1. Signal management process

1.1 Signal management process overview

Signal management is performed to detect potential safety signals and investigate the possibility of a previously unidentified potential risk, a change in the status of a known risk, or provide reassurance about the absence of a risk of a product or active substance.

A veterinary adverse event signal is information that arises from one or more sources which may suggest a new potentially causal association, or a new aspect of a known association, between an adverse event or set of related events and one or more veterinary medicinal products (VMPs) or active substances. The signal may involve a previously unknown event or could involve an event reported with a higher frequency than what is expected in a population. It may warrant further investigation and, when necessary, action. A signal does not always mean that a VMP has caused the suspected adverse event. Assessment of the signal is required to determine whether or not there is a causal relationship.

Signals may also be identified in relation to lack of efficacy or development of resistance.

Signals may originate from sources such as spontaneous reports, clinical, non-clinical or epidemiological studies, and published literature. They may be identified where:

- a sudden increase in the number of adverse events in a short period is observed
- an increase in the frequency of a particular clinical sign or Veterinary Dictionary for Drug Related Affairs (VeDDRA)

Preferred Term (PT) is recorded, compared with the expected frequency for that sign
- an increasing trend of a particular clinical sign or VeDDRA Preferred Term is noted over time
- new, previously unidentified, clinical signs or VeDDRA PTs are identified
- a potential impact on, or risk to public or animal health, or welfare is suspected

New information that may be relevant to the signal management process may include the severity, time to onset, duration or outcome of an adverse event, the country in which the event occurred, or clinical information such as gender, age, breed, cause of death or off-label product use.

Signals can relate to an active substance, a particular VMP, or a group of related active substances or VMPs. They may also relate to a specific strength or formulation of a VMP.

Multiple spontaneous adverse event reports are usually required for the threshold to be met for a signal. If a single report contains detailed information regarding an adverse event of significant seriousness or severity and/or involved multiple animals, it may be considered to meet the threshold, but this would only be applicable in very rare and specific circumstances where there is considered to be a significant risk to human, animal, or environmental health or welfare.

1.2 Signal management process requirements

Both the VMD and MAHs are responsible for detecting and managing signals.

The obligations of the Marketing Authorisation Holder (MAH) for signals associated with their VMPs for which Marketing Authorisations (MAs) are held are defined in the VMR 2013 (as amended) Schedule 1 Part 8 paragraph 56 and 59.

The VMR 2013 (as amended) defines the terms benefit-risk balance and signal management process which are referenced in this guidance and can also be found in the Glossary.

The signal management process is a process for performing active surveillance of pharmacovigilance data for VMPs and active substances, assessing that data, and determining whether there is any change to the benefit-risk balance of those products or active substances.

The process should include signal detection and analysis, validation, prioritisation, assessment and confirmation, and subsequent recommendation of proposals for action if required. The order in which these steps are taken may depend on the data available to the MAH. A risk-based approach should be utilised.

The benefit-risk balance is an evaluation of the positive effects of a VMP in relation to risks to human or animal health (relating to the quality, safety, or efficacy of the product), risks of undesirable effects on the environment, or any risk relating to the development of resistance.

MAHs should continuously monitor the benefit-risk balance of their VMPs via a documented signal management process, whether the reports derive from the UK or any other country. This allows for any emerging issues that may affect the benefit-risk balance to be promptly detected.

Both documentation detailing internal signal management processes and evidence that these processes have been followed should be promptly provided to the VMD upon request, whether in relation to an inspection or at any other time.

At a minimum the process should be able to identify:

- a sudden and unexpected increase in the number of adverse events
- an unexpected increase in the frequency of a known clinical sign
- a new clinical sign
- reports in scientific literature of any of the above

The MAH must record and submit the results of this signal management process on an annual basis to the VMD via a benefit-risk report (BRR) (see section 4).

Additionally, if a validated signal suggesting a new risk or change of the benefit-risk balance of the product is identified during the process, the MAH must notify the VMD promptly and within 30 calendar days of

it being identified. If an urgent safety signal is identified, the MAH should notify the VMD without delay and no later than the next working day (see section 2). Where the process identifies the necessity for a variation in an authorisation, the MAH must also promptly submit an application for such a variation.

The MAH is obliged to inform the VMD of any valid signal identified by any regulatory authority in any country where the product is marketed which might influence the evaluation of the benefit-risk balance of the product concerned.

Notification of a validated signal, urgent safety signal, or signal identified by another regulatory authority should be carried out via completion of the signal and regulatory actions section of the BRR template (see section 4.7).

1.3 Signal detection and analysis

MAHs should utilise all relevant post-marketing pharmacovigilance data which they could reasonably be expected to be aware of, including:

- data collected within a pharmacovigilance database, such as:
    - spontaneous reports obtained via direct reporting to the MAH from all reporters, including those received via sales representatives or other company employees,
    - spontaneous reports obtained as part of an enquiry or product defect concern,
    - spontaneous reports that the MAH is aware of reported on social media or other media sources,
    - spontaneous and solicited reports received from other MAHs, manufacturers, or regulatory authorities,
    - reports from routine searches of published literature.
- post-marketing clinical trials, post-marketing surveillance studies or other observational studies
- new toxicology and international safety data updates
- sales data

Increasing the number and variability of data sources, and additional focused data analysis of certain product groups or patient demographics may additionally benefit the signal detection process.

Signals may be detected via qualitative review of individual spontaneous adverse event reports or using semi-quantitative and quantitative statistical analysis methods. A combination of both methods is generally preferable, although the method(s) used may depend on the volume of reports received by, and the size of, the MAH.

When a large number of adverse event reports are received or multiple data sources are integrated, it is recommended to use statistical methods and data mining algorithms based on 2X2 contingency tables producing disproportionality analysis.

Essentially, this provides a measure of the risk (for a particular product/active substance/product group) of an event being reported versus other events, compared to a reference risk (that observed for all products/active substances in the database or for all other products in that product group).

Frequently used measures of association include proportional reporting ratio (PRR), reporting odds ratio (ROR), relative risk reduction (RRR), and information coefficient (IC). The individual approach of an MAH is considered best selected depending on the database available.

1.4 Signal prioritisation

Signals should be prioritised according to their likelihood of having a significant impact on individual, population, environmental, or public health. Prioritisation should take into consideration the benefit-risk balance of a product or its active substance and those most likely to lead to risk minimisation measures or regulatory actions, particularly those that might need to occur in a timely fashion.

All events that occur in humans and all events related to lack of efficacy should be prioritised.

The VMD has included in section 1.4.1 a list of Medically Important Terms (MITs) which includes VeDDRA PTs that are considered significant medical concepts and should be used for signal prioritisation. This is a non-exhaustive list and subject to update. Some MITs are species-specific.

Prioritisation should additionally consider the frequency of the event, severity of the event, population risk (determined by the size of the exposed population), type of medicinal product/active substance, the length of time the product has been on the market, and the amount of known pharmacovigilance data over the lifecycle of the product.

In certain situations, signals that may be linked to topical public concerns or media attention may need to be prioritised, if there may be a benefit to the release of prompt communications.

Signal prioritisation should be carried out throughout the signal management process.

1.4.1 List of Medically Important Terms (MITs)

This section provides a list of MITs at the level of VeDDRA PT. This list will be regularly updated and therefore MAHs should always ensure that the latest version is being used. It is intended to be used as guidance for prioritisation and analysis of data during the signal management process, however, absence of an event from this list does not exclude that event from analysis.

PTs	Species
All	Human
Abdominal pain	Horse
Abomasitis	Ruminant, Camelid

Abortion	All
Acute mastitis	Ruminant, Camelid, Horse
Aggression	All
Anaphylaxis	All
Anorexia	Horse
Apnoea	All
Ataxia	Horse
Bee systemic disorder NOS	Bee
Birth defect	All

Blindness	All
Bone marrow hypoplasia	All
Cardiac arrest	All
Cardiac insufficiency	All
Circulatory shock	All
Coagulopathy	All
Collapse NOS	All
Coma	All
Convulsion	All

Deafness	All
Death	All
Diabetes mellitus	All
Disseminated intravascular coagulation	All
Dyspnoea	All
Epileptic seizure	All
Fish asphyxia	Fish
Fish body deformity	Fish
Haemolytic anaemia	All

Haemorrhagic gastroenteritis	All
Heart block	All
Hepatic failure	All
Hypersensitivity reaction	All
Hypocalcaemic condition	Ruminant, Camelid
Hypomagnesaemic condition	Ruminant, Camelid
Impaired hearing	All
Impaired vision	All
Immune mediated thrombocytopenia	All

Increased coagulation time	All
Ketosis	Ruminant, Camelid
Laminitis	Horse
Loss of consciousness	All
Lying down	Horse, Ruminant, Pig, Camelid
Metastatic neoplasia	All
Metritis	All
Moribund	All

Multi-organ failure NOS	All
Myoglobinuria	Horse
Paralysis	All
Paresis	All
Perinatal mortality	All
Recumbency	Horse, Ruminant, Pig, Camelid
Renal insufficiency	All
Reticulitis	Ruminant, Camelid

Stillbirth	All
Suspected infectious agent transmission	All
Thrombocytopenia	All

1.5 Signal validation

An initial validation step should be carried out to determine whether more detailed analysis is justified.

As far as possible, it should be ensured that the signal is not based on duplicate reports.

There should always be a temporal association (the event must have occurred after exposure to the product occurred).

Signals related to adverse event terms (or clinical signs that can be considered covered by the wording) already present in the product information, should generally be counted as non-valid signals. However, if a signal highlights an additional aspect of a current association that may warrant alteration of the wording (for instance regarding the reversibility or expected duration of an event) or to the frequency category, it may be a valid signal.

Signals involving MITs (see section 1.4.1) that are already present in the product information should also be considered valid, however may only warrant a limited assessment (such as calculation and comparison of incidence).

1.6 Signal assessment and confirmation

Once a signal has been validated, further evaluation should be carried out to determine whether or not there is a possible causal association, or new aspect of a known association between the product and event, and whether the evidence is strong enough to consider further action.

Assessment should involve review of all data available, including spontaneous reports, literature reports, pre-clinical trials and clinical studies, toxicology and epidemiological updates, international regulatory data, and sales data. All previously reported cases including the same events and products/active substances should be reviewed. In some cases, it is recommended to additionally review any previously reported cases involving similar events and similar products/active substances.

The evaluation should provide clinical context to the report and take into consideration other knowledge of an association (previous or concurrent reports, previous signals, previous analysis via Periodic Safety Update Reports (PSURs)/BRRs for example).

How strong the evidence is may also depend on the total number of reports, the source of the reports (such as if they are from one or different sources, the quality of the source, and if the data is incomplete or vague), and the availability of supportive laboratory data. The potential for over-reporting should also be taken into consideration, for example due to increased media attention, or a known significant increase in sales volumes.

The following list contains considerations that should be made when assessing signals:

- total number of cases (excluding duplicates)
- increase in the number of reports (incidence)
- clinical relevance (seriousness, severity, outcome, reversibility, relationship to signalment)
- dose-adverse event relationship
- drug-drug interaction
- the consistency between reports (for instance in terms of time to onset, pattern of events, outcome, dosages involved)
- plausibility of the pharmacological/biological mechanism linking the product and event, or a lack of alternative causes
- dechallenge/rechallenge data
- supportive relevant investigation/laboratory data

- clinically similar events occurring in additional reports
- other potentially impacting clinical variables such as concurrently administered products, medical history
- potential for over-reporting, for example due to increased media attention, or a known increase in sales volumes

Following assessment of a signal, a conclusion should be made as to whether or not there is good enough evidence to suggest a potential causal association between the product/active substance and event, in order to determine whether action needs to be taken.

1.7 Recommendations for action

If a potential causal relationship between a product/active substance and event is considered unlikely or there is not strong enough evidence at that time, the benefit-risk balance is considered to remain the same and no action is required at that time. A record of assessed signals that have been determined not to meet the threshold for further action should be maintained for review during subsequent signal assessment and potential re-assessment upon obtaining further information.

If a potential causal relationship is considered possible, it should be determined whether further information is required to provide additional evidence, or whether the benefit-risk balance can be considered to have been altered.

If further information is required, one of the following recommendations for action should be proposed by the MAH, with an explanation of the reasoning behind the proposal:

- close monitoring
- post-marketing surveillance study

Close monitoring requires in-depth assessment of all new or updated adverse event reports pertaining to the signal. A summarised assessment of these reports and subsequent evaluation of the additional information received should be provided within the

subsequent benefit-risk report. The VMD may also request additional information to be provided prior to the due date for the subsequent BRR. If this occurs then the reason for the requirement and the time by which, or the period during which, the requirement must be complied with.

If the benefit-risk balance is considered altered; the MAH should propose risk minimisation measures or other relevant actions as appropriate.

The benefit-risk balance may be improved either by increasing the benefits, for example including further explanation of how best to use the product, or by reducing the risks by risk minimisation measures, for example 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, the feasibility of those measures 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 VMD:

- variation of marketing authorisations (MAs) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse events or other sections of the product literature
- direct provision of important safety information to veterinarians and other health-care professionals and animal owners, for example through letters, bulletins, via electronic media etc
- 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 implements an urgent safety restriction, the MAH shall give the VMD prior or simultaneous notification. Urgent safety restrictions may also be initiated by the VMD
- suspension or withdrawal of the MA of a VMP, in the event that, the overall benefit-risk balance is considered unfavourable and proposed risk minimisation measures are

considered inadequate. Relevant stakeholders should be informed as appropriate

Such actions may be taken voluntarily by MAHs. However, it is recommended that any such intended measure be discussed at an early stage with the VMD.

If the resulting action requires a variation to an MA, the MAH must promptly submit an application for such a variation, alongside data to support the proposed variation. The VMD will assess, and accept or reject the variation, based on the benefit-risk balance.

The MAH should also inform the VMD of any prohibition or restriction imposed by the regulatory authority of any country in which the VMP is marketed within 30 calendar days of the receipt of such information, if no equivalent measure has been already taken in GB.

2. Urgent safety signals

Urgent safety signals are those containing new information affecting the benefit-risk balance of a VMP which require rapid implementation of risk minimisation/safety measures.

These signals may be identified from studies, spontaneous reports, published literature, or be related to regulatory actions proposed by other regulatory authorities.

Urgent safety measures may need to be taken in the event of a risk to human or animal health, or to the environment, and may take the form of an urgent safety restriction, risk management plan, batch recall or suspension/withdrawal of a product. It may be necessary to provide safety information communications to relevant stakeholders.

An urgent safety restriction is an interim change to the product literature or distribution category, for example, therapeutic indications, dosage information, contraindications, or warnings.

The VMD should be informed of a potential urgent safety signal, or any urgent regulatory actions proposed by other regulatory authorities

without delay and at the earliest available opportunity (no later than the next working day).

The MAH should provide a detailed description of the signal, including information on the source, incidence, and clinical details, alongside an evaluation of the urgency and potential impact. Any proposed actions, or those that have already been taken should also be detailed. Any emerging information following this initial notification should be promptly provided to the VMD.

The VMD will assess the information provided and discuss the implementation of actions with the MAH.

Urgent safety measures including any related safety communications can be proposed and implemented by the MAH, however the VMD should be informed of these with prior or simultaneous notice. Urgent safety measures may also be proposed by the VMD at any time where there is a significant concern that the benefit-risk balance has altered.

3. Notifying VMD of a signal

3.1.1 Validated signals suggesting a change to the benefit-risk balance

The VMD should be notified without delay of all validated signals which following assessment, suggest a new risk, change to the benefit-risk balance, or require further investigation.

The VMD should be notified of these signals using the Signal notification option on the BRR template within 30 calendar days of conclusion of an internal signal management process, or no later than the next working day for urgent safety signals. Valid signals identified by any regulatory authority in any country where the product is marketed which might influence the evaluation of the benefit-risk balance of the product concerned should also be reported in this way.

Signals should be accompanied by a proposal by the MAH to either obtain further information (via close monitoring or a post-marketing surveillance study), perform a regulatory action (change to product

literature via variation, risk management plan (RMP), product recall, suspension of product, withdrawal of product) or for there to be no further action taken at that time.

A separate signal notification document must be provided for signals with different MA numbers, even if the signal is applicable across, for example, all strengths of the same product.

3.1.2 Validated signals that do not suggest a change to the benefit-risk balance

All validated signals, including those which, following assessment, are deemed to not suggest a new risk or change to the benefit-risk balance, or that do not require further investigation, should be submitted annually via the BRR template on the ‘Signals and regulatory actions’ tab. Applicable signals that have been assessed via other regulatory authorities should also be included within this section.

Non-validated signals should be recorded by the MAH but should not be submitted to the VMD.

Multiple signals (adverse event terms) for the same MA number can be reported within the same annual BRR.

3.1.3 Submission of signal notifications

The signal notification should be submitted using the BRR template via VMDS.

Multiple BRR template signal documents can be submitted per VMDS submission as long as only one template is submitted per MA. If further information is requested, or the MAH wishes to submit further documentation, then this can be added to the submission as a separate document.

Signal documents should be submitted to the VMD via the Veterinary Medicines Digital Service (VMDS). Any MAH not signed up to VMDS can e-mail adverse.events@vmd.gov.uk to register.

Once signed in to the VMDS account, the MAH should select the relevant group. Non-urgent 'standard' signal notification submissions should be sent to PHV Signals, and urgent safety signals should be sent to PHV Urgent Safety Signals.

The Excel document should be named using the applicable MA number (with an underscore rather than forward slash separation), the year of submission, type of signal (Signal for 'standard' signals and Urgent for urgent signals) and number describing the order of signals submitted, separated by underscores: MAnumber_YYYY_Signal_x or MAnumber_YYYY_Urgent_x.

Number 1 should be used for the first signal for that product of that type submitted in that year, and 2, 3, 4 etc used for subsequent signals. For example, the first standard signal document for a product with an MA number 09285/8019 being submitted in the year 2024, would be named 09285_8019_2024_Signal_1. The second would be 09285_8019_2024_Signal_2. And if subsequently the first urgent signal was submitted for the same product within the same year, the document would be named 09285_8019_2024_Urgent_1.

It is not anticipated that additional documents other than the Excel signal document will be submitted. If further documentation is considered necessary, use the same naming convention as described above, following by underscore 2, 3, 4 for subsequent additional documents. For example, a second document submitted for the above described urgent signal should be named 09285_8019_2024_Urgent_1_2.

Queries related to urgent safety signal submission or requests for assistance with VMDS in relation to urgent safety signals should be sent via the VMDS secure messaging group Adverse Events or by e-mail to adverse.events@vmd.gov.uk.

Queries related to all other (non-urgent) signal notification submissions should be directed either via VMDS to the PSUR Queries group or via e-mail to psur.queries@vmd.gov.uk.

3.1.4 Content of signal notifications

For signal notification only the ‘Benefit-risk statement’ and ‘Signals and regulatory actions’ tab need to be completed. MAHs do not need to complete the other tabs as these are only for use when submitting the annual BRR.

The following information should be completed by MAHs in the first tab of the BRR template (further details on completion of these fields can be found within section 4.2):

- Brand name
- Marketing Authorisation Holder
- Marketing Authorisation Number
- If marketed since the last BRR, the date first marketed
- If withdrawn from the market since the last BRR, the date withdrawn from the market
- Type of submission – here signal notification should be selected from the dropdown menu

For the field ‘Type of submission’, ‘Signal notification’ or ‘Urgent signal notification’ should be selected from the dropdown menu.

No fields on the ‘Benefit-risk statement’ tab of the template below the ‘Type of submission’ should be completed for a signal notification, these fields should only be completed for annual BRRs (see section 4 of this guideline).

The following information should be completed by MAHs in the ‘Signals and regulatory actions’ tab of the BRR template:

- signal VeDDRA preferred Term (or non-VeDDRA term if no suitable preferred Term)
- species as per tab F. Species of the VICH GL30 Vocabulary Lists
- date first detected

- current status – ‘Ongoing’ should be selected from the dropdown menu unless the signal has already been closed by another regulatory authority
- date closed (for closed signals)
- source of signal (such as MAH database, regulatory authority database, literature report)
- country (in which the signal was detected), using appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists
- evaluation and brief summary of the findings, information that should be considered for inclusion within this section may include:

    - brief description of event outcome
    - observed patterns of event development
    - details of other products
    - reversibility
    - supporting lab data
    - assessment of the causal relationship
    - details of regulatory procedures ongoing at the time of submission e.g. variations or signal processes, including those involving other regulatory authorities
    - details of the source
    - event incidence
    - for urgent signals in particular, an evaluation of the urgency and potential impact
    - proposed action
    - proposed action details

For the proposed column, one of the following actions will need to be selected:

- close monitoring
- post-marketing surveillance study
- variation, including change to the product literature
- product/batch recall
- suspension
- withdrawal

- risk management plan
- no further action required
- other

Only select 'Other' if no other option applies.

If close monitoring is proposed, the period over which the product will be closely monitored should be specified, alongside any details of additional monitoring processes that will be put in place.

If a post-marketing surveillance study is proposed then details regarding the scope, objectives, and timelines should be provided.

If a variation is proposed, details of this should be provided. If the variation proposed involves a change to the product literature, then details of the section of the product literature affected and proposed wording should be provided.

If a product/batch recall is proposed, details of the batches affected and whether they have been distributed should be provided.

If a suspension or withdrawal is proposed, details should be provided including dates if applicable.

If a risk management plan is proposed, details should be provided e.g. details of communications disseminated to specified stakeholder groups and a proposed timescale, or details of a restriction.

If the MAH proposes that no regulatory action should be taken, an explanation of why this has been proposed should be provided.

It is expected that for the majority of signals reported during the reporting period, an action will be proposed, as a potential change to the benefit-risk balance will have been identified.

The VMD will contact the MAH for further information if required.

Final actions should be completed for ‘Closed signals’ only (where ‘Closed’ was selected for ‘Current status’). The majority of signals

reported during the reporting period (as opposed to in the annual BRR) will be ongoing at the time of reporting and may require discussion with the VMD.

4. Benefit-risk reports

A BRR is an important document provided by the MAH to the VMD post-authorisation on an annual basis. The document is intended to provide an update on the worldwide benefit-risk balance of a product, including validated signals detected. This evaluation should determine whether further investigations need to be carried out and/or whether regulatory action is required.

BRRs are required for all products authorised in the UK regardless of whether or not a product has been marketed. Electronic copies of the BRR template should be submitted in Excel format to the VMD using the Veterinary Medicines Digital Services (VMDS).

4.1 Benefit-risk report submissions

Following the placing of a VMP on the market in the UK, an MAH must submit a BRR once in the course of every year during the period of validity of the authorisation.

BRRs should be submitted regardless of whether the product was marketed or whether there were any signals detected throughout the year. They should cover the period of time since the data lock point (DLP) in the preceding BRR (or for first submission of a BRR, the final PSUR) and there should be no gaps in, or overlapping, of data.

The DLP should be no earlier than 60 calendar days prior to the submission date.

It is recommended that the DLP date be on the last day of a month.

Any validated signals noted after the DLP but prior to submission of the BRR should be included in the subsequent BRR, unless they meet the criteria for an urgent safety signal.

Submission dates for BRRs should align with the grouped active substance recommended due dates of submitting annual statements available on the European Medicines Agency's website.

For new Anatomical Therapeutic Chemical Classification System for veterinary medicinal products (ATCvet) codes which are not included in the list, or if there are any queries regarding ATCvet codes, MAHs should contact psur.queries@vmd.gov.uk.

The BRR should be submitted to the VMD no later than the applicable submission due date for the product.

In exceptional circumstances, MAHs can request to change the submission dates (and DLP) for the annual BRR by contacting psur.queries@vmd.gov.uk with a proposal for an alternative date, and an explanation of the reason for the request. Where possible, alternative dates should be the last day of a month.

BRRs should also be submitted immediately on request by the VMD on an ad hoc basis. The DLP and submission date for these ad hoc requests will be proposed by the VMD depending on the urgency of the issue and should be agreed with the MAH.

BRRs should be submitted as one completed Excel document per MA as per the BRR template BRR template.

The Excel document should be named using the applicable submission category date, MA number (with an underscore rather than forward slash separation) and document number 1 separated by underscores: YYYYMM_MAnumber_1. For a product with a submission category date of 31-AUG and an MA number 09285/8019 being submitted in the year 2024, for example, the name of the document would be 202408_09285_8019_1.

Multiple BRR template documents can be submitted per VMDS submission as long as only one template is submitted per MA. If further information is requested or the MAH wishes to submit further documentation, then this can be added to the submission as a separate document.

Additional documents should be named using the applicable submission category date, MA number and subsequent document

number (this would be 2 if two separate documents are submitted, and 3 if three separate documents are submitted and so on). For the 2nd document submitted for a product with a submission category of 31-AUG and an MA number 09285/8019 being submitted in the year 2024, for example, the title of the document would be 202408_09285_8019_2. The corresponding BRR document would have been named 202408_09285_8019_2.

Note that validation rules apply, so documents named using spaces or forward slashes rather than underscores, or other characters will be rejected automatically.

BRRs should be submitted to the VMD via the Veterinary Medicines Digital Service (VMDS). Any MAH not signed up to VMDS can e-mail adverse.events@vmd.gov.uk to register.

Once signed in to the VMDS account, the MAH should select the relevant group: PSUR Submission.

Queries related to BRR submission should be directed either via VMDS to the PSUR Queries group or via e-mail to psur.queries@vmd.gov.uk.

4.2. Content of benefit-risk reports

All BRRs should be completed in English; and all declarations and signals must take into account all adverse events arising in the UK and outside of the UK regardless of the route of authorisation.

It is strongly recommended that, before submitting the BRR, the MAH should make sure that all adverse event reports have been submitted electronically where required and duplicate detection performed.

For pharmacovigilance data to be correctly attributed to the right product in the VMD databases, one BRR template must be submitted per MA number. The MAH must use up to date MA numbers. If a product authorised in the UK has multiple MA numbers, one BRR template must be submitted for each MA number and the information contained in the BRR template must pertain to that specific MA.

The following sections will provide details on how to fill out the BRR template.

4.3 Benefit-risk statement

The first tab in the BRR template is the benefit-risk statement.

For an annual BRR submission MAHs should complete:

- Brand name
- Marketing Authorisation Holder
- Marketing Authorisation Number
- If marketed since the last BRR: date first marketed
- If withdrawn from the market since the last BRR: date withdrawn from the market
- Type of submission – here Annual benefit-risk report should be selected from the dropdown menu
- Data Lock Point
- Period of report from
- Period of report to
- Dose factor
- Dose factor justification
- Have you sent an additional dose factor justification document? (Yes/No)
- Benefit-risk statement

4.3.1 Brand name

This should be identical to the name of the VMP as stated in the national MA and associated documentation.

4.3.2 Marketing Authorisation Holder

This should be identical to the business name of the MAH as stated in the national marketing authorisation and associated documentation.

4.3.3 Marketing Authorisation Number

This should be identical to the MA number as stated in the national MA and associated documentation, unless the MA number has been updated since initial authorisation, in which case the current MA number must be used.

The authorisation number is preceded by ‘Vm’ for VMPs and ‘Vh’ for registered veterinary homeopathic medicines. An MAH’s unique 5-digit company number forms the first part of the MA number.

Enter only the authorisation number itself within the Excel spreadsheet, without Vm or Vh preceding it.

As one BRR template should be completed per MA number there should only be one MA number entered in the MA number field.

4.3.4 If marketed in the UK since last BRR: date first marketed

Only complete if the product has first been marketed in the UK since the last annual BRR submission. Enter the date in the format DD/MM/YYYY. Leave blank if this does not apply.

The product should also be included in the ‘Worldwide authorisation status’ tab.

4.3.5 If withdrawn from UK market since last BRR: date withdrawn from the market

Only complete if the product was withdrawn from the UK market since the last annual BRR submission. Enter the date in the format DD/MM/YYYY. Leave blank if this does not apply.

The product should also be included in the ‘Worldwide authorisation status’ tab.

4.3.6 Annual benefit-risk report or signal notification

Select ‘Annual benefit-risk report’.

4.3.7 Data lock point

The DLP should be entered DD/MM/YYYY, and must be within the 60 calendar days prior to the submission due date.

4.3.8 Period of report from

The start date of the reporting period covered by the annual BRR.

4.3.9 Period of report to

The end date of the reporting period covered by the annual BRR.

4.3.10 Additional information

A brief explanation of the justification for the dose factor should be provided. If more extensive information needs to be provided, such as calculations, this can be submitted alongside the BRR as a separate document.

For sales data where the split between GB and NI data is estimated, enter a brief explanation for the split.

If a single MA covers multiple presentations of a product that cannot be effectively expressed in litres/kilograms e.g. 2 separate collar sizes, the number of each unit type making up the sales volume should be stated, and whether this is an estimated figure or not. A brief justification for the dose factors used should additionally be entered here.

4.3.11 Additional dose factor documentation

Select ‘Yes’ or ‘No’ from the dropdown menu as applicable for 'Have you sent an additional dose factor justification document?'

See section 4.6.2 of this guidance for further details on submission of dose factor information.

4.3.12 Benefit-risk statement

The MAH should select ‘Yes’ or ‘No’ from the dropdown menu as applicable in response to the statement, 'The benefit-risk balance of the product remains the same and no action is required.'

If a MAH selects ‘No’ as a signal has been noted that alters the benefit-risk balance of the product or further information is required to determine this via close monitoring or a post-marketing surveillance study, then this should be detailed in the ‘Signals and regulatory actions’ tab of the BRR.

4.4 Backlog line listings

Any non-serious UK cases not previously submitted to the VMD i.e. since last PSUR DLP, can either be submitted electronically or should be included in a line listing in the relevant tab ‘Backlog line listings’ of the BRR template.

All worldwide cases not previously submitted to the VMD should also be added to this tab, these should not be submitted electronically.

In subsequent BRRs this tab does not need to be completed as all adverse events should be sent electronically within 30 calendar days of receipt by the MAH to the VMD.

Guidance on the required information for adverse event reports, and particular types of reports can be found in section 5 of Guideline III Adverse event reporting.

The following fields must be completed if the information is available.

Country (3 character country codes ISO 3166)

The country where the adverse event occurred should be entered in 3 character country code format using the appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists.

Unique Adverse Event Report Identification Number (Worldwide Case Number)

The Unique Adverse Event Report Identification Number (sometimes known as AERID or the worldwide case number) is electronically assigned by the first organisation to send an adverse event report.

This number consists of:

- country of occurrence code (3 characters using appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists)
- the MAH's organisation ID (MAHORGID,8 characters)
- remaining free text (up to 47 characters, which can include a routing ID)

Original Receive Date

The date of first communication of an adverse event report from the primary reporter to the MAH or regulatory authority. It should be entered in the format DD/MM/YYYY.

Date of First Exposure

The date of first exposure/treatment with the product involved in the adverse event. It should be entered in the format DD/MM/YYYY.

Date of Onset of Adverse Event

The date of onset of the adverse event. It should be entered in the format DD/MM/YYYY.

Number of Animals Treated

The number of animals treated or humans exposed.

For human exposure cases, this will always be 1 as there should only ever be one human per adverse event report.

Species

Species should be entered as per VICH GL30. Enter 'Human' for human adverse event reports.

Breed

Breed should be entered if known, using the most relevant available breed from VICH GL30.

Enter N/A for human adverse event reports.

Age

This should be entered in years.

Number of Animals Affected

The number of animals/humans affected in the adverse event report, including indirectly exposed animals, for example, those treated during pregnancy or lactation, co-mingled, or via infectious spread.

This should always be entered as 1 for human adverse event reports.

Number of Animals Died

The number of animals/humans for which the outcome of the adverse event was death.

Use According to Label

For animal cases, this should be entered as ‘Yes’ for use in accordance with the MA, or ‘No’ for use outside the terms of the MA.

For human adverse event reports, N/A should be entered unless the case involves deliberate misuse by a human which has led to adverse events in a human, in which case enter ‘No’.

Other products administered

List all other products that have been added to the products section of the case, separated by commas. Brand names or active ingredients of products can both be added.

VeDDRA Low Level Terms

Add all VeDDRA LLTs that have been added to the case, separated by commas.

Narrative of Adverse Event

A description of the adverse event should be provided. The recommended content of adverse event narratives is covered in Guideline III Adverse event reporting.

4.5 Worldwide authorisation status

Provide the authorisation status per country, including the authorisation number and whether the product is marketed in that country or not at the time of BRR submission

This should be completed for all countries, including the UK.

If the product was first marketed, or withdrawn from the UK market at any point during the reporting period, add the product in this tab and ensure the applicable dates have been completed on the ’Benefit-risk statement’ tab.

The MAH should complete the following fields:

Country (3 character country codes ISO 3166)

The country where the product is authorised should be entered in 3 character country code format using the appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists.

Brand Name

This should be identical to the name of the VMP as stated in the MA for the applicable country.

Marketing Authorisation Number

This should be identical to the MA number as stated in the MA for the applicable country.

Marketed

Select ‘Yes’ or ‘No’ from the dropdown menu depending on whether the product is currently marketed in the applicable country.

4.6 Sales data

Each BRR should contain the number of doses/amount of product sold in the UK and in other countries, if applicable. The UK sales data should be provided per calendar year and should be split into GB and NI data. If accurate sales data for GB and NI separately are unknown, an estimate should be provided and this should be clearly stated. Third country sales data should be provided as a total for the reporting period covered by the BRR, split by country.

Sales data should be provided for each pack size covered by the MA.

Queries related to selection of the appropriate sales volume unit, pack unit size or dose factor should be directed to psur.queries@vmd.gov.uk.

4.6.1 Sales volume units

The following should be used for sales volume units:

- 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 vials

If a single MA covers multiple presentations of a product e.g. 5ml and 10 ml syringe sizes, the sales volume should be expressed in litres. Selecting a unit e.g. syringes would not be appropriate.

If a single MA covers multiple presentations of a product that cannot be effectively expressed in litres/kilograms e.g. 2 separate collar sizes, details should be provided (see section 4.6.2 of this guideline).

4.6.2 Dose factor

The dose factor is a positive numerical value which provides an estimate of the number of treated animals using the sales data. It should equal the average number of animals of a target population which can be treated by one package of a given pack size of a product, regardless of the formulation. It should be calculated independently of reported adverse events. A separate dose factor should be calculated and submitted for each marketed pack size. Dose factors for pack sizes that are not marketed at the time of BRR submission do not need to be included.

If multiple pack sizes contain the same amount of individual units e.g. a tub of 250 tablets and a pack of 50 blister strips containing 5 tablets per strip, only one pack size (and therefore dose factor) need be submitted.

As much as possible, it should be kept consistent across reporting periods to allow comparability of incidence calculations, and ideally be

kept consistent between reference and generic products. Any changes to the dose factor should be highlighted and justified within the related BRR.

The calculation of an appropriate dose factor will depend on factors such as the type of product, target species, production status, formulation, indication and treatment regimen, and should be determined by the MAH. Any suggestions for methods for calculation should only be used if deemed representative of the conditions of use of the product.

For VMPs that are administered as a single dose, where the pack unit amount is 1 dose, the number of doses equals the number of animals treated and the dose factor would be 1.

Examples include flea collars, and some vaccines, long-acting injectable preparations, wormers and flea spot-ons.

For VMPs where one unit of product is administered for the entire course of treatment for an individual animal, the number of units again equals the number of animals treated (1 unit = 1 animal treated), and therefore the dose factor would be 1.

Examples include VMPs for topical use, such as shampoos, pastes, eye preparations or ear preparations. For other single dose administration VMPs, a general suggested formula is to divide the package volume by the single dose amount (e.g. 1 dose or 10ml).

For single dose administration VMPs where there is a range of doses that could be administered as per the SPC, the dose factor should be calculated using the maximum dose in this range; divide the package volume by the single maximum dose amount (e.g. 1 dose or 10ml).

If an active substance concentration is applicable to the product:

1. Multiply the concentration of the active substance (in mg/ml or mg/mg) as stated in the product literature by the package volume (ml, g)
2. Multiply the weight of the target species (derived from the table provided below) by the maximum dose (in mg/kg or ml/kg) as stated in the product literature
3. Divide the result of step 1 by step 2

For non-single dose administration VMPs where there is a set dose and duration of treatment that should be administered as per the SPC:

1. Multiply the recommended dose based on standard weight (in mg, ml, tablet etc) as stated in the product literature by the duration of treatment (days)
2. Divide the package volume by the result of step 1.

For non-single dose administration VMPs where there is a range of doses and durations that could be administered as per the SPC, the dose factor should be calculated using the maximum dose in these ranges, for example:

1. Multiply the recommended maximum dose based on standard weight (in mg, ml, tablet etc) as stated in the product literature by the maximum duration of treatment (days)
2. Divide the package volume by the result of step 1

For non-single dose administration VMPs where there is a range of doses and durations that could be administered as per the SPC and If an active substance concentration is applicable to the product:

1. Multiply the package volume by the concentration of the active substance (in mg/ml or mg/mg) as stated in the product literature.
2. Multiply the weight of the target species (derived from the table provided below) by the maximum dose (in mg/kg or ml/kg) and by the maximum duration (days) as stated in the product literature
3. Divide the result of step 1 by the result of step 2

For VMPs which are indicated for continuous long-term/lifelong treatment, the maximum estimated dose per animal over a 6-month period should be used (utilising a maintenance dose stated in the SPC if applicable) i.e. maximum estimated dose (mg, ml, g, tablet etc) x 182 days.

For VMPs which are indicated for both short-term and long-term treatment, where there is no defined length of treatment, the maximum estimated dose per animal over a 1-month period should be used i.e. maximum estimated dose (mg, ml, g etc) x 30 days.

In general, where there is a range provided in the Summary of Product Characteristics (SPC) for the dose and/or duration, use the maximum recommended dose and/or longest duration of treatment as applicable. Any other dose/duration should be justified.

For VMPs which are used for multiple animals, and contain multiple doses per package:

1. Multiply volume of a single dose (e.g. litres) by the duration (days) of the treatment
2. Divide the result of step 1 by the estimated dose (e.g. litres)
3. Divide the total pack size (total volume) by the result of step 2.

For dry cow intramammary products, 1 dose is considered equivalent to 4 intramammary syringes, and for lactating cow intramammary products, 1 dose is considered equivalent to 1 intramammary syringe.

For inhalation anaesthetics, a duration of anaesthesia of 45 minutes at the typical rate used for maintenance should be used.

The average weight of the target species or population should be derived from the table below.

If there is a range of weights or production status within a target population e.g. use in newborns as well as adults, an average weight should be determined based on the estimated use within a species group.

If there is a range of species within a target population, an average weight should be determined based on the estimated use within the target population, calculated by estimated species split alongside estimated production status within the individual species.

A brief explanation should be provided, including the estimated percentage of each species use.

If no dose factor is provided by an MAH, the VMD will determine a dose factor based on the product, previous PSURs/benefit-risk reports and other relevant data.

Species, sub-population	Standard weight (Kg)
Dog	20
Cat	5
Rabbit	1.5
Guinea pig	1
Ferret	1.4
Horse	550
Adult cow	550
Beef calf	150
Newborn calf	50
Sow/boar	160
Breeding sow	240
Finishing pig	60
Weaner pig	25
Piglet	2
Adult sheep/goat	60
Breeding sheep/goat	60

Sheep/goat under 12 months	20
Lamb/kid	10
Chicken, broiler	1
Chicken, layer	2
Turkey	10
Turkey, poult	4
Duck	2
Goose	5
Pheasant, Guinea fowl	0.5
Salmon	3

Exposure in pigeons is recommended to be calculated on the basis of 30 pigeons/litre of drinking water. The dose factor should be submitted as a numerical value with up to 4 decimal digits only.

A brief explanation of the justification for the dose factor should be provided within the 'Explanation' field. If more extensive information needs to be provided, such as calculations, this can be submitted alongside the BRR as a separate document. If a separate document is submitted, this should be specified by selecting 'Yes' on the Benefit-risk statement page.

Incidence % should be calculated for signals submitted, using the following formula:

Incidence % = (Number of animals reacted ÷ number of animals treated) x 100

The number of animals treated should be calculated using the dose factor (sales volume x dose factor). The number of animals reacted should include all on and off-label events including lack of efficacy.

4.6.3 UK sales data

The MAH should complete the following fields:

Country (3 character country codes ISO 3166)

The country where the product is marketed should be entered in 3 character country code format using the appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists.

Year, Period, Date period start and Date period end

These are the start and end dates of the period over which the sales data provided applies. As the sales data for the UK must be provided per calendar year, and the reporting period in most cases will not match this calendar year, it is anticipated that the data will often need to be split across 2 date ranges.

Each calendar year would be made up of two time periods. Period 2 would cover the remaining sales data from the previous calendar year and period 1 would cover the sales data from the current calendar year, up to until the reporting period end date.

For example, a product with a BRR reporting period from 01/02/2024 to 31/01/2025 would be entered across 2 rows:

Year	Period	Date period start	Date period end
2024	2	01/02/2024	31/12/2024
2025	1	01/01/2025	31/01/2025

Dates should be entered in the format DD/MM/YYYY.

Number of months

The number of months covered by the period between the date period start and date period end should be entered.

In the example above, period 2 of 2024 covers 11 months and period 1 of 2025 covers 1 month. If the number of months is not a whole number, round to the nearest whole number. Do not use decimals. We encourage DLPs to be on the last day of a month to allow for whole numbers if possible.

Pack unit size

The pack unit size is the total number of units within a package size e.g for a tub of 100 tablets, this would be a numerical value of 100, and for a blister pack of 50 strips with 5 tablets per strip, this would be 250.

Number of pack units

Enter the numerical value of the number of pack units. The pack unit should be equivalent to that used in the dose factor calculation. If no pack units were sold during the period (for a country in which the product is authorised), enter 0. If further explanation of the pack unit is necessary, enter further details within the Explanation field.

Dose factor

This should be entered as a numerical value, with no more than 4 decimal digits. See section 4.6.2 of this guidance for further information on dose factor calculation.

Sales volume

Enter the numerical value of the volume of sales. If no sales occurred during the period (for a country in which the product is authorised), enter 0.

Units

Select the appropriate unit from the dropdown menu, aligning with section 4.6.1 of this guideline.

Estimated

For sales data where the split between GB and NI data is estimated, enter Yes. If specific data can be provided for GI and NI, enter No.

4.6.4 Third country sales data

Country (3 character country codes ISO 3166)

The country where the product is marketed should be entered in 3 character country code format using the appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists.

Year, Period, Date period start and Date period end

These are the start and end dates of the period over which the sales data provided applies.

As the sales data for the UK must be provided per calendar year, and the reporting period in most cases will not match this calendar year, it is anticipated that the data will often need to be split across 2 date ranges.

Each calendar year would be made up of two time periods. Period 2 would cover the remaining sales data from the previous calendar year and period 1 would cover the sales data from the current calendar year, up to until the reporting period end date.

For example, a product with a BRR reporting period from 01/02/2024 to 31/01/2025 would be entered across 2 rows:

Year	Period	Date period start	Date period end
2024	2	01/02/2024	31/12/2024
2025	1	01/01/2025	31/01/2025

Dates should be entered in the format DD/MM/YYYY.

Number of pack units

Enter the numerical value of the number of pack units. The pack unit should be equivalent to that used in the dose factor calculation. If no pack units were sold during the period (for a country in which the product is authorised), enter 0. If further explanation of the pack unit is necessary, enter further details within the Explanation field.

Number of months

The number of months covered by the period between the date period start and date period end should be entered. In the majority of cases, this will be 12, as the period should cover a full year.

However, in some instances, the number of months within the report will be different, due to a discrepancy between the date of authorisation compared to the submission due date for the product. In these scenarios the number of months may be more or less than 12 months. If the number of months is not a whole number, round to the nearest whole number. Do not use decimals. We encourage DLPs to be on the last day of a month to allow for whole numbers if possible.

Pack unit size

The pack unit size is the total number of units within a package size e.g for a tub of 100 tablets, this would be a numerical value of 100, and for a blister pack of 50 strips with 5 tablets per strip, this would be 250.

Number of pack units

Enter the numerical value of the number of pack units. The pack unit should be equivalent to that used in the dose factor calculation. If no pack units were sold during the period (for a country in which the product is authorised), enter 0. If further explanation of the pack unit is necessary, enter further details within the Additional information field on the ‘Benefit-risk statement’ tab.

Dose factor

This should be entered as a numerical value, with no more than 4 decimal digits. See section 4.6.2 of this guidance for further information on dose factor calculation.

Sales Volume

Enter the numerical value of the volume of sales. If no sales occurred during the period (for a country in which the product is authorised), enter 0.

Units

Select the appropriate unit from the dropdown menu, aligning with section 4.6.1 of this guideline.

Estimated

Enter N/A for third country sales.

4.7 Signals and regulatory actions

All validated signals, including those which following assessment are deemed to not suggest a new risk or change to the benefit-risk balance, should be submitted annually via the BRR template. Applicable signals that have been assessed via other regulatory authorities should also be included within this section.

Non-validated signals should be recorded by the MAH but should not be submitted to the VMD.

Signals should be listed within the ’Signals and regulatory actions’ tab of the BRR.

Note that the VMD should be additionally notified of validated signals where there is a potential risk or change to the benefit-risk balance within 30 calendar days, or no later than the next working day for urgent safety signals.

The following information should be completed by MAHs in the ’Signals and regulatory actions’ tab of the BRR template:

VeDDRA preferred term (or non-VeDDRA term if there is no suitable preferred term)

A separate row should be used for each individual VeDDRA PT or non-VeDDRA term.

Species

Species should be entered as per VICH GL30. Enter 'Human' for human adverse event reports.

The same signal affecting a different species should be entered on a separate row (one row per species affected).

Date signal detected

The date the signal was first detected by the MAH's internal signal management processes or by a regulatory authority, whichever occurred first.

Current status

Select ‘Ongoing’ or ‘Closed’ from the dropdown menu.

‘Closed’ should only be selected for any signal where the action has been completed, or for signals where it is proposed or has been agreed by a regulatory authority that there should be no further action.

Date closed

The date that the action taken was finalised. This would be the date that a variation was completed, or a product/batch was recalled/suspended/withdrawn. This should be entered in the format DD/MM/YYYY.

Source of signal

Suggestions for sources include MAH database, regulatory authority database, literature report.

Country

The country where the signal was noted should be entered using appropriate ISO-Country code as per tab A.36 ISO-Country of the VICH GL30 Vocabulary Lists.

Evaluation and brief summary of the findings

This should provide adequate evidence of how the signal was validated and assessed. Information that should be considered for inclusion within this section may include:

- brief description of event outcome
- observed patterns of event development
- details of other products
- reversibility
- supporting lab data
- assessment of the causal relationship
- details of regulatory procedures ongoing at the time of submission e.g. variations or signal processes, including those involving other regulatory authorities
- details of the source
- event incidence
- an evaluation of the potential impact

Proposed action

This is the action that was initially proposed by the MAH or regulatory authority.

Select the appropriate action from the dropdown menu. The options available are:

- close monitoring
- post-marketing surveillance study
- variation, including change to the product literature
- product/batch recall
- suspension
- withdrawal
- risk management plan
- no further action required
- other

Only select 'Other' if no other option applies.

Proposed action details

Provide further details of the proposed action.

If close monitoring is proposed, the period over which the product will be closely monitored should be specified, alongside any details of additional monitoring processes that will be put in place.

If a post-marketing surveillance study is proposed then details regarding the scope, objectives and timelines should be provided.

If a variation is proposed, details of this should be provided. If the variation proposed involves a change to the product literature then details of the section of the product literature affected and proposed wording should be provided.

If a product/batch recall is proposed, details of the batches affected and whether they have been distributed should be provided.

If a suspension or withdrawal is proposed, details should be provided including dates if applicable.

If a risk management plan is proposed, details should be provided e.g. details of communications disseminated to specified stakeholder groups and a proposed timescale, or details of a restriction.

If the MAH proposes that no regulatory action should be taken, an explanation of why this has been proposed should be provided.

Final action

This should be completed for closed signals only (where ’Closed’ was selected for ‘Current status’.

It should be left blank for ongoing actions, such as a post-surveillance study, risk management plan or close monitoring. If these actions

were both carried out as proposed and a resulting final action was also completed within the reporting period (such as a variation or a new decision made that no further action is required as a result of the proposed action), this resulting final action should be entered.

Select from the dropdown menu one of the following:

- variation completed
- product/batch recall
- suspension
- withdrawal
- no further action required
- other

Only select 'Other' if no other option applies.

Final action details

Provide further details of the final action.

If variation, such as a change to the product literature, was initially proposed, and a variation has since been completed, details of the section of the product literature affected and finalised wording should be provided.

If a product/batch recall has been carried out, details of the batches affected, whether they have been distributed should be provided.

If a suspension or withdrawal is proposed, details should be provided including dates if applicable.

If ‘No further action required’ is selected, an explanation should be provided, unless this matches the initial proposed action and therefore an explanation has already been provided within the proposed action details section.

The VMD will contact the MAH for further information if required.

4.8. BRR assessment

If the VMD has any comments or questions related to the BRR submission, the VMD will inform the MAH of these via a BRR assessment report. Responses to questions should be addressed by the MAH within 60 calendar days. Any changes or variations requested should be submitted within 6 months unless otherwise requested or agreed.

Changes may be requested for any section of the product literature.

Requests for changes to the product literature should be made in line with the appropriate GB QRD template.

Guideline V Post-marketing surveillance studies

1. What is a post-marketing surveillance study?

A post-marketing surveillance study is any study carried out after a veterinary medicinal product (VMP) has been authorised. The aim is to:

- identify, characterise or quantify an adverse event
- confirm the safety and/or efficacy profile of a VMP
- measure the effectiveness of risk management measures

These studies can take the form of non-interventional studies, in which a VMP is prescribed in the usual manner in accordance with the marketing authorisation.

2. Why is a post-marketing surveillance study needed

Before authorisation, the number of animals exposed to the VMP is restricted, so experience of adverse events within any specific population of the target species may be limited. Post-authorisation, the number of animals exposed becomes greater, and can reveal other adverse events that were not apparent during the pre-authorisation stage.

A Marketing Authorisation Holder (MAH) may elect to carry out a study to investigate many different aspects of a VMP, including if:

- the concurrent use of a specific product with the VMP results in previously unknown adverse events
- the use of the VMP in a particular breed of animal results in previously unknown adverse events
- the incidence of a particular adverse event is dependent on the characteristics of an animal treated with a specific product, such as age or weight
- the incidence of a particular adverse event is dependent on the existence of another underlying disorder
- the long-term use of a product gives rise to an adverse event

There may be many other reasons for the need for a post-marketing surveillance study. The VMD may require an MAH to carry out such a study, if they determine that there may be signals that require further investigation.

3. How is a post-marketing surveillance study carried out

Only animals treated with a particular VMP in the manner specified in the product literature can be included in a post-marketing surveillance study. The MAH may recruit animals that fit the criteria for the study to

be performed. Once recruited, the animal will be treated as it would normally be treated for the condition it has, but the veterinarian providing that treatment will be required to monitor the animal more closely throughout the treatment.

4. What happens after the study

At the end of the study, the MAH will provide the VMD with the findings, which will determine whether there is or is not evidence of any adverse events. As a result of this, further regulatory action may be required. The VMD may require the MAH to update the product literature to, for example to:

- exclude the use of the VMP in a particular age-range or group of animals
- advise prescribers and end-users to perform closer monitoring of animals in a particular age-range or group of animals
- advise that the VMP is not used at the same time as another specific product

5. What types of studies are not included

Clinical trials in which a VMP is used in a manner not authorised for the species in question.

Guideline VI Pharmacovigilance for other products

1. Introduction

Some products available for use in animals in the UK are authorised via different pathways or do not have a marketing authorisation. The VMR 2013 (as amended) detail pharmacovigilance responsibilities in these situations, and information on this is detailed in this guideline. If you require any further information, please e-mail adverse.events@vmd.gov.uk

2. Animal Test Certificate (ATC) holder responsibilities

ATC holders must:

- name a person responsible for pharmacovigilance on the ATC application form
- record all adverse events in treated animals
- report online via the VMD online reporting form all adverse events occurring in treated animals to the VMD within 30 calendar days of being made aware of them, the ATC number should be included in the report

Adverse events must be reported whether an animal was treated with the test product or control product (even if this is a placebo, such as saline).

If the ATC holder is also an MAH, then they must report adverse events via VMDS in accordance with Guideline III Adverse Event Reporting.

Refer to Animal Test Certificates for further information.

3. Medicines for small animals, exempt from authorisation

The manufacturer or importer of medicines exempt from authorisation because they are intended for use in minor pet species must:

- keep records of all adverse events they are made aware of for 3 years
- provide the VMD with copies of adverse event records on request
- report online via the VMD online reporting form all serious adverse events within 15 days of being made aware of them

If the manufacturer or importer of medicines for small pet animals exempt from authorisation is also an MAH, then they must report adverse events via VMDS in accordance with Guideline III Adverse Event Reporting.

Refer to Exemption from authorisation for medicines for small pet animals for further information.

4. Autogenous Vaccine Authorisation (AVA) holder responsibilities

All adverse events, including lack of efficacy, following use of an autogenous vaccine must be reported to the VMD within 30 days of the AVA holder being made aware of the event. All fields should be filled in as completely as possible, but in particular the report should include:

- a description of the adverse event

- the number and species of animal involved
- the date(s) of administration of the product
- the date(s) that the event occurred
- the clinical signs observed
- the AVA number
- the batch release request number, if available

If the AVA number and/or batch release number are not available then the AVA holder should provide:

- a precise description of the vaccine constituents
- the date the vaccine was produced
- the expiry date of the vaccine

so that the exact product and batch can be identified. This information should be taken from the vaccine container label.

Reports should be submitted using the online reporting form.

If the AVA holder is also an MAH, then they must report adverse events via VMDS in accordance with Guideline III Adverse Event Reporting.

Refer to Specific Manufacturing Authorisations for further information.

4. Products for administration under the cascade

Manufacturers of extemporaneous preparations (ManSA) must report any adverse event, including lack of efficacy, to the VMD within 30 days of being made aware of the event. All fields should be filled in as completely as possible, but in particular the report should include:

- details of the extemporaneous preparation
- ManSA reference numbers

Reports should be submitted using the online reporting form.

If the extemporaneous preparation manufacturer is also an MAH, then they must report adverse events via VMDS in accordance with Guideline III Adverse Event Reporting.

Refer to Specific Manufacturing Authorisations for further information.

Guideline VII Communication

1. Introduction

Communication between stakeholders regarding veterinary pharmacovigilance information is crucial to ensure the appropriate dissemination of this information. All relevant stakeholders must be informed on important changes to authorised veterinary medicinal product (VMP) information in order to safeguard human and animal health and the environment.

Communication to stakeholders regarding veterinary pharmacovigilance issues should be considered when new relevant information arises and needs to be communicated more urgently than through a routine procedure, such as an update to product literature.

2. Objective of communications

The main objective of pharmacovigilance communications is to convey relevant, clear, accurate, consistent messages to the relevant stakeholders so they can be kept up to date and take action when appropriate.

This could include important new veterinary pharmacovigilance information such as:

- new adverse events or changes in severity, characteristics, or frequency of adverse events
- confirmed signals
- new information in the product literature of a VMP, such as a contraindication being added or additional precautions to be taken by the person administering the product to an animal

3. Communication between stakeholders

There should be collaboration and coordination between Marketing Authorisation Holders (MAHs) and the VMD regarding pharmacovigilance communications, as this is crucial for delivering consistent information.

When making an announcement regarding pharmacovigilance concerns to veterinarians or the general public, an MAH must give the VMD prior or simultaneous notice.

This includes any planned communications about safety concerns due to quality issues, including notifications or advice to veterinarians in the event of a product or batch defect or withdrawal of a product from the market for safety reasons.

This includes any format for the announcement, including letters, bulletins, or e-mails.

Information must be objectively presented and must not be misleading.

The MAH does not need to notify VMD when discussing individual adverse events with reporters or when responding to individual enquiries.

4. Freedom of Information requests made to the VMD

The VMD is committed to follow the legislation relating to freedom of information act (FOIA) requests including our commitment not to disclose information where that information is properly covered by one of the FOIA's exceptions. We will deal with data requests on a case-by-case basis and will consult with the data 'owners' where necessary. The VMD will seek the views of those that provided us with the data on what harm will fall if we disclose the information and

decide if it's likely to be actual and reasonably foreseeable on the basis of the MAH's case.

The final decision on whether we release the information rests with the VMD. However, we will take MAH's views into account when we make this decision.

Glossary

1. Adverse event

Any observation in animals that occurs after any use of a veterinary medicinal product, whether or not considered to be product-related, that is unfavourable and unintended. Ref. The Veterinary Medicines Regulations 2013 (as amended), Part 1

2. Adverse reaction

A reaction to a veterinary medicinal product that is harmful and unintended and that occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function.

3. 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.

4. Cascade use

Veterinary medicines are authorised for specific conditions for specific target species, based on assessed data. The conditions of use for each authorised veterinary medicine are listed in its Summary of Product Characteristics (SPC). The VMD's Product Information Database contains the SPCs of all veterinary medicinal products authorised in the UK. Where there is no clinically suitable veterinary medicine authorised in the United Kingdom for the specific condition in the animal being treated, in particular to avoid unacceptable suffering, the veterinary surgeon may use their clinical judgement to treat animals under their care in accordance with the cascade.
Ref. The Veterinary Medicines Regulations 2013 (as amended), Schedule 4.

5. Clinical Trial

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 medicinal product under investigation.

6. Data Lock Point (DLP)

A cut-off date for data to be included in a Benefit-Risk Report.

7. The European Medicines Agency (EMA)

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 medicinal products for human and veterinary use.

8. Expedited adverse event report

Any adverse events occurring worldwide for a marketing authorisation holder's (MAH) veterinary medicinal products which are authorised in the UK, or the equivalent products authorised elsewhere, should be sent via expedited reporting to the VMD within 30 calendar days of the MAH being made aware of them.

Ref. The Veterinary Medicines Regulations 2013 (as amended), Schedule 1, Part 8, paragraph 57.

9. Human adverse event

A reaction that is noxious and unintended and that occurs in a human being following exposure to a veterinary medicinal product. Ref. The Veterinary Medicines Regulations 2013 (as amended), Part 1.

10. International Birth Date (IBD)

The date of the first marketing authorisation for a same or similar product granted anywhere in the world, including any VICH region.

11. International Cooperation on Harmonisation of Technical

Requirements for Registration of Veterinary Medicinal Products (VICH)

A trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration. Ref. VICH.

12. Lack of efficacy

The apparent inability of an authorised veterinary medicinal product to have the expected efficacy in an animal, whether or not the product was used in accordance with the Summary of Product Characteristics (SPC). Ref. The Veterinary Medicines Regulations 2013 (as amended), Part 1.

13. Marketing Authorisation (MA)

A decision by a regulatory authority authorising the placing on the market of the veterinary medicine. Ref. The Veterinary Medicines Regulations 2013 Part 2, Regulation 4).

14. Marketing Authorisation Holder (MAH)

A person or entity who/which holds the authorisation of a veterinary medicine.

15. Off-label use

Off-label use relates to situations where a veterinary medicinal product is used outside the terms of its marketing authorisation.

16. Post-marketing surveillance 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 pharmacovigilance concern relating to an authorised veterinary medicinal product.

17. Pharmacovigilance System Master File (PSMF)

A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised veterinary medicinal products.

18. 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.

19. Regulatory authority

An authority 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 applicable law.

20. Serious adverse event

Any adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect. 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. Ref. VICH GL 24 . See also definition for “Animals managed and treated as a group”.

21. Serious adverse reaction

Any adverse reaction which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect. 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 also definition for “Animals managed and treated as a group”.

22. Signal

Information that arises from one or more sources which may suggest a new potentially causal association, or a new aspect of a known association, between an adverse event or set of related events and one or more veterinary medicinal products or active substances.

23. Summary of Product Characteristics (SPC)

A document that contains the information on the condition of use of a veterinary medicine as developed during the course of the assessment process. Ref. The Veterinary Medicines Regulations 2013, Schedule 1, Part 1, paragraph 3.

24. Veterinary Dictionary for Drug Regulatory Activities (VeDDRA)

A list of standard clinical terms to be used in reporting suspected adverse events in animals or humans after exposure to veterinary medicinal products. Ref. Combined Veterinary Dictionary for Drug Regulatory Activities.

25. Veterinary Medicinal Product

Any substance or combination of substances presented as having properties for treating or preventing disease in animals; or any substance or combination of substances that may be used in, or administered to, animals with a view either to restoring, correcting or

modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis; or any substance or combination of substances that may be used for the purpose of euthanising an animal. Ref. The Veterinary Medicines Regulations 2013 (as amended), Part 1.