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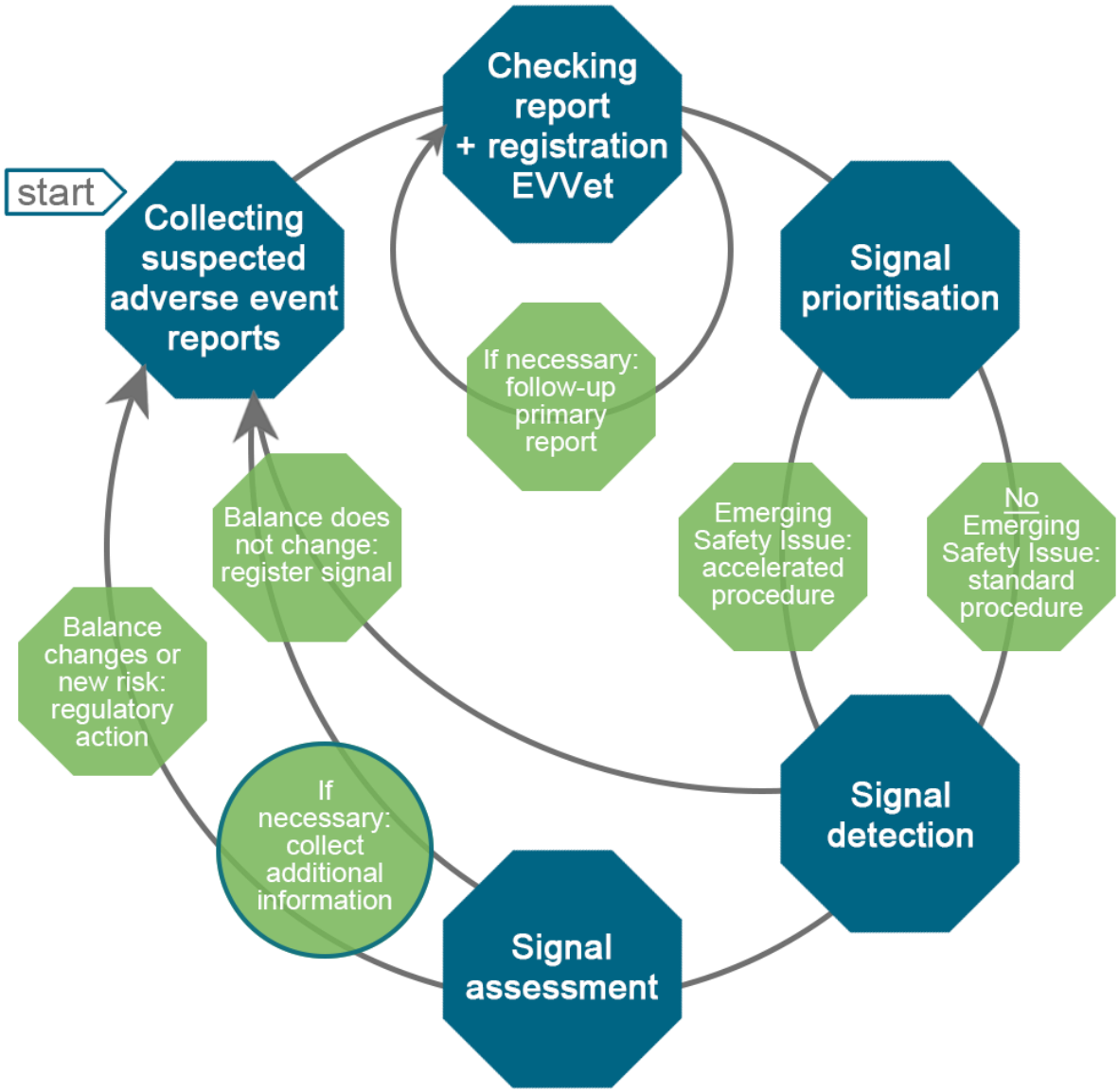

Guidebook Pharmacovigilance

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AUTHOR: ALETTA DE VRIES

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1 Introduction

1.1 Goal of pharmacovigilance

The World Health Organization (WHO) defines pharmacovigilance (or drug monitoring) as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem”. The goal of veterinary pharmacovigilance is to continuously assess the benefit-risk balance of a veterinary medicinal product (VMP), during this process it is evaluated if the benefits (animal health and welfare) outweigh the possible risks (public health, animal health and welfare and the environment).

The moment a VMP is introduced into the industry after authorisation, the available knowledge about the VMP is still limited. The clinical trials which have been carried out for application of the VMP were with a small number of animals, which possibly prevents rare adverse effects from being discovered. In addition, these trials are conducted in a controlled environment or through a field study, again with a relatively small number of animals. After authorisation the VMP will be used in a large number of patients with possibly additional underlying diseases, a therapeutic plan with several other VMPs and the possibility to use the product with animals outside it's authorisation (according to the so-called cascade). Besides assessing the benefit-risk balance, it is therefore an additional important goal of veterinary pharmacovigilance to expand knowledge about a VMP, which enables veterinarians and animal keepers/owners to use the VMP as safe and correct as possible.

1.2 Scope of pharmacovigilance

Veterinary pharmacovigilance applies to all VMPs. A VMP is any substance or combination of substances which has at least one of the following characteristics (VO 2019/6, art. 4(1)):

a) It has properties for treating or preventing disease in animals;
b) It is used for restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;
c) It is used in animals for making a medical diagnosis;
d) It is used for euthanasia of animals.

This does not include supplements or instruments, supplements e.g. are registered and monitored according to the obligations in Regulation (EU) 1821/2003. All VMPs registered in the Netherlands can be found in the Veterinary Medicines Information Bank of the Bureau Diergeneesmiddelen (BD, part of the aCBG). Since Regulation (EU) 2019/6 came into force, the European Medicines Agency (EMA) has also set up the Union Product Database (UPD). This contains all VMPs registered in a member state of the European Union (EU).

The legal obligations for pharmacovigilance of VMPs which are authorized in the Netherlands, are recorded in Regulation (EU) 2019/6 Chapter 4, Section 5 (articles 73 through 81) and Implementing Regulation (EU) 2021/1281. Because the European Regulations are directly applicable, specific Dutch legislation is no longer available about this subject. This has been a deliberate choice in favour of harmonisation of VMP-legislation in Europe. Marketing authorisation holders (MAH) of homeopathic VMPs must comply with the same obligations for pharmacovigilance as the legislation applicable for VMPs (VO 2019/6, art. 2(5)), this also applies to MAHs of VMPs which are exempted from authorisation according to article 5(6) of Regulation (EU) 2019/6. The obligation to comply with pharmacovigilance is an integral part of the authorisation to sell a product in the industry. It is recommended to apply a similar process for other veterinary health products, other than VMPs.

The obligations for pharmacovigilance for every authorized VMP (and for VMPs with an exemption according to VO 2019/6, art. 5(6)) are equal, despite the possibility of different procedures for requesting authorisation (national, decentralized, mutual recognition, centralized).

1.3 Setup of the guidebook

Before 28th January 2022 a Periodic Safety Update Report (PSUR) had to be submitted for every VMP at specified intervals. This was a periodic review of the safety of a VMP. When Regulation (EU) 2019/6 and Implementing Regulation (EU) 2021/1281 came into force at 28th January 2022, the pharmacovigilance process changed drastically, since the choice was made for a continuously signal management process. This signal management process is divided in at least signal detection, prioritisation, validation, assessment and documentation of the outcome (VO 2021/1281, art. 17(1)) and has a risk-based approach. The guidebook will at least shortly address these topics, and a few additional ones, in several chapters based on the Regulation (EU) 2019/6, Implementing Regulation (EU) 2021/1281 and the guidelines for Veterinary Good Pharmacovigilance Practices (VGVP) which have been set up by the EMA (see Appendix V). These guidelines provide additional information about pharmacovigilance if necessary. Every chapter will be concluded with a checklist of items with which the MAH must comply for the components described in that chapter. The complete checklist is included in Appendix II. The guidebook also provides a flowchart to create an overview of the signal management process (see Appendix I).

1.4 Goal of the guidebook

This guidebook helps to conduct veterinary pharmacovigilance in practice. The process of pharmacovigilance is described in a practical way, with references to the original legal acts. To facilitate keeping the guidebook up-to-date, it will solely be offered digitally to the members of Fidin. As part of transparency, the guidebook will also be offered at the website of Fidin. The guidebook will be revised at least once a year, with the aim of keeping it up-to-date.

2 Collecting of adverse event reports

Once a VMP is authorized, the most common adverse events are usually known by the clinical trials which have been carried out during the application process and by studying the pharmacological profile of the active substance. However, it is possible that certain rare adverse events have been missed and while using the VMP in the field new risks could emerge. By continuously monitoring for signals of suspected adverse events, it is possible to identify unknown adverse events. To collect information about suspected adverse events several sources can be used. The main source being spontaneous reports of adverse events by veterinarians (amongst others). This 'spontaneous reporting system' was introduced in the Netherlands in 1994, in 2005 the systems of the member states of the EU were connected to a central database for pharmacovigilance of the EMA (EudraVigilance Veterinary, EVVet) and since 2022 this system was further improved with Regulation (EU) 2019/6 coming into force.

2.1 Suspected adverse events

Until a causality is confirmed between a certain event and the administration of a VMP, you speak of a suspected adverse event. The term 'adverse event' is wider than merely the unintended effects with the animal in which the VMP is administered. The following circumstances are included under the term adverse event (VO 2019/6, art. 73(2)):

a) Unwanted reaction to a VMP in an animal;
b) Lack of efficacy of the VMP;
c) Environmental incidents after administering a VMP;
d) A noxious reaction in humans exposed to a VMP;
e) Exceedance of Maximum Residue Limits (MRL);
f) Suspected transmission of an infectious agent via a VMP;
g) Unwanted reaction in an animal to a medicinal product for human use.

The same procedures apply regarding pharmacovigilance for each type of adverse event as described above, it is also important that every report will be assessed in the same way. In summary, a (suspected) adverse event is every unintended effect with an animal, human or in the environment which occurs after use of a (veterinary) medicinal product. This includes suspected adverse events after use of the VMP in accordance with the SPC and after use outside the directives of the SPC (cascade, off-label) (VO 2021/1281, art. 11). Although the term 'side effect' is a well-known synonym for the term 'adverse event', the term 'adverse event' will be used in this guidebook since this is the terminology used in the legislation.

Suspected adverse events can be reported by animal caretakers and -owners, it is recommended to them to report through the attending veterinarian to increase the usability of the report. Veterinarians are obligated to report suspected adverse events (Regeling Diergeneesmiddelen 2022, art. 5.1). Veterinarians are only obligated to report about suspected adverse events that fall under categories a), b), d) and e) of the above list, a deadline of 15 days has been set by law for reporting adverse events (Regeling Diergeneesmiddelen 2022, artikel 5.1). Veterinarians are advised to report about VMPs directly at the MAH, and to report with the BD about suspected adverse events after administering a medicinal product for humans in an animal through the form at their website.

The MAH of the VMP is also obligated to do something with incoming reports (VO 2019/6, art. 76(2)), this concerns reports by veterinarians as described above and concerns reports of suspected adverse events from other sources. The MAH must register every incoming report regarding all the categories listed above (VO 2021/1281, art. 12(1)), as long as it meets the minimal requirements set for a valid

report (see Chapter 2.3: Minimal requirements of a report). Furthermore the MAH has an obligation to make an effort to follow-up on the report of the suspected adverse event, whereas veterinarians do not have this obligation (VO 2021/1281, art. 12(4)).

2.2 Sources of suspected adverse event reports

The signal management process starts with collecting information on suspected adverse events, for this, several sources can be used. The VGVP Guideline 'Collection and recording of suspected adverse events for veterinary medicinal products' (EMA/306663/2021) divides reports in unsolicited and solicited reports, where solicited reports come from studies which have been set up by the MAH. Spontaneous reports are by far the most important, but reports from scientific literature and surveillance studies are also important. The procedures that are used are described in detail in the Pharmacovigilance System Master File (PSMF) (see Chapter 5.3 Pharmacovigilance System Master File (PSMF)).

All reports concerning suspected adverse events must be registered in EVVet within 30 days (VO 2019/6, art. 76(1) and (2)). Reports of suspected adverse events must be reported in EVVet based on the correct VeDDRA-terms (Veterinary Dictionary for Drug Related Affairs) (EMA/306663/2021).This is a list of English terms composed by the EMA for reporting suspected adverse events. By processing reports according to these terms, harmonisation and standardisation of reports is possible on a national and international level and it is easier to combine multiple reports to a dataset which can be analysed as a whole. This is also the reason it is strongly recommended to always report in EVVet in English (VO 2021/1281, art. 13(2)). The list of VeDDRA-terms is revised periodically and published at the website of the EMA. On this website you can also find the 'guidance notes on the use of VeDDRA terminology for reporting suspected adverse events in animals and humans'.

2.2.1 Unsolicited reports

Spontaneous reports from a veterinarian, other healthcare professional or animal caretaker to the national competent authority (in the Netherlands the BD), the MAH or another organisation (e.g. a wholesaler) are the main source of information. In these reports a suspected adverse event observed in an animal or human is described following exposure to one or multiple VMPs or medicinal products intended for human use. Appendix VIII contains a link to the form which is being used by the BD for collecting reports of suspected adverse events, however MAH are free to create their own form. In doing so, it is important that the form will result in a qualitative report and that at least the four minimal requirements for a valid report are questioned (see Chapter 2.3: Minimal requirements of a report).

Scientific literature is also a possible source for new information about suspected adverse events. For this, the relevant databases and peer-reviewed journals are searched at least once a year (before the deadline of the annual statement in EVVet) (VO 2021/1281, art. 13(2) and art. 18(1)). The procedure used is included in the PSMF and describes at least the search strategy that will be used, including databases used. There should also be a procedure which ensures suspected adverse events found in non-peer reviewed local journals end up with the correct person as quickly as possible (EMA/306663/2021), however it is not necessary to actively search in these journals.

Non-medical sources which could provide reports of suspected adverse events are mainly websites and social media pages which are under the MAH's own management. These must also be monitored actively, because the 30-day deadline for registration in EVVet starts the moment information about the suspected adverse event is posted (and not the moment the MAH notices the post). The MAH can also use their website as a tool to collect reports about suspected adverse events, e.g. by placing a report form or providing contact details for reporting suspected adverse events. If a report of a

suspected adverse event is found on a website outside the MAH's own management (by coincidence), the MAH should make reasonable effort to follow-up and retrieve the information for the minimal requirements for a valid report. The MAH is not obligated to monitor websites outside its own management, this is again about reports founds by chance for which the MAH must make reasonable effort to at least find out the four requirements. (EMA/306663/2021)

2.2.2 Reports based on (surveillance) studies (solicited reports)

After authorisation clinical trials or post-marketing surveillance studies can be carried out at the request of the BD, the EMA or at the instigation of the MAH (VO 2019/6, art. 76(3) and (4), VO 2021/1281, art. 15(1)). The studies can be set up for different reasons, e.g. to expand the authorisation to other target animals or indications for use and to further investigate possible new safety risks.

Studies instigated by the MAH must be reported with the BD or the EMA immediately after initiation (VO 2021/1281, art. 15(2)). The BD and the EMA inform each other if they request a MAH to set up a post-marketing surveillance study (VO 2019/6, art. 76(3) and (4)). The protocol and final report must be submitted to the BD and the EMA within one year after completion of the data collection (VO 2021/1281, art. 15(2)) and must be used in the pharmacovigilance process (VO 2019/6, art. 77(1). VO 2021/1281, art. 11). All relevant documents shall be made in a language customary in the field of medical science (VO 2021/1281, art. 15(6)). All information concerning the study will be saved after finishing the study and kept available for audits and inspections (VO 2021/1281, art. 15(7)).

2.2.3 Reports from third countries

If the VMP is sold outside the EU as well, reports from these third countries must be included in the signal management process (VO 2021/1281, art. 11). This applies to all types of reports mentioned above (spontaneous reports, scientific literature, non-medical sources and (surveillance) studies). Spontaneous reports from third countries must also be registered in EVVet by the MAH within 30 days (VO 2019/6, art. 76(2)), usually these reports come in at the MAH through the local branch or distributor.

2.3 Minimal requirements of a report

A report of a suspected adverse event of a VMP should at least contain the following information (VO 2021/1281, art. 12(2), EMA/306663/2021):

- Identifiable source (including country code reporter);
- Short description of involved animals, humans and the environment:
    - Species (including "human" if applicable);
    - Number of animals or individuals involved;
- Product names of (veterinary) medicinal products;
- Details about the suspected adverse event (clinical symptoms (including abnormal laboratory findings), diagnosis or symptoms in case of a suspected adverse event in humans).

In absence of one or more of these items, the MAH is obligated to follow-up on the report with reasonable efforts to get the missing information to be able to still include the report in the system (VO 2021/1281, art. 12(4)). Furthermore the MAH must follow-up the report to gain additional information (e.g. results from additional diagnostics), to make sure the quality of the report is as high as possible for the assessment of the report and potential subsequent signals (EMA/306663/2021). If it is not possible to (fully) determine the product name, the report will be included in the database based on the active substances (VO 2021/1281, art. 12(3)).

2.3.1 Causality assessment

A first assessment of the presence of a causality in individual reports could be done using the ABON-system. This is a system from former legislation which was designed to assess the causality of individual reports (Eudralex Volume 9B). Despite this system not being incorporated in the new legislation, it is still seen as effective and useful by MAHs. The MAH could consider still apply this system as part of the signal management process, also because the causality assessment is still a mandatory part of pharmacovigilance in some third countries. It is however important to keep in mind, that the BD no longer uses the ABON-system, and advises to leave these field blank in EVVet.

When using the ABON-system, several aspects are taken into account:

- Correlation concerning time and anatomical location of administration of the VMP
- Pharmacology (knowledge about the effects of the VMP)
- Evaluation of clinical and pathological symptoms (=veterinary clinical reasoning)
- Exclusion of other causes
- Completeness and reliability of the information in the report
- Quantitative measurement (dosis-effect relationship)
- Repeatability

Subsequently, based on the points mentioned above, one of the following categories will be assigned to the report:

- Category A: probable
- Category B: possible
- Category O: unclassifiable/unassessable (due to a lack of information)
- Category O1: inconclusive (a correlation cannot be ruled out, but other factors make it impossible to come to a conclusion)
- Category N: unlikely

For marking a report as category A there should be a reasonable relation between the time of administration, time of start and the duration of the suspected adverse event. The suspected adverse event should be consistent (or at least plausible) with the pharmacological and toxicological characteristics of the VMP and there should be no other explanation which is just as reasonable. If one of these criteria is not met, the report should be labelled as either category B, O, O1 or N, in which a category N can only be given if there is another identifiable cause without reasonable doubt.

2.4 Checklist

Collecting of suspected adverse event reports	YES	NO
• Is there a procedure which describes the way it is ensured spontaneous reports are collected and reach the correct person or department?	☐	☐
• Is there a procedure which describes the way it is ensured reports from scientific literature are collected and reach the correct person or department?		
• Is there a procedure which describes the way it is ensured reports from non-medical sources are collected and reach the correct person or department?	☐	☐
• Is there a procedure which describes the way it is ensured results relevant to pharmacovigilance from clinical and surveillance studies after authorisation are collected and reach the correct person or department?	☐	☐

…

Collecting of suspected adverse event reports (continued)	YES	NO
• Is there a procedure which describes the way it is ensured reports from third countries are collected and reach the correct person or department?	☐	☐
• Is there a procedure which describes the way incoming reports are processed, checked for the availability of the four minimal requirements and if necessary will be followed up with the reporter?	☐	☐
• Is there a procedure which describes the way it is ensured reports will be reported in EVVet within 30 days, and if applicable will be registered in the database of the MAH?	☐	☐

3 Signal management

A report about a suspected adverse event is merely a suspicion of a causality between the administration of a VMP and a certain event. After a report has been added to the existing dataset of previously collected reports, there is another check to see if everything is correct and to make sure reports will not be registered in EVVet more than once. Next, the dataset containing a cumulation of reports is checked for an upcoming signal using an algorithm (signal detection). For every emerging signal an assessment is made (signal assessment) if there is a causality, if there are consequences for the authorisation of the VMP and which regulatory consequences are necessary (e.g. changing the package leaflet and SPC-texts). It is important to keep in mind a signal is merely a suggestion of a potential new causal association, which requires more research to determine whether there is really a causality between the event and the VMP (VO 2021/1281, art. 1(c)). During the entire signal management process it should be evaluated whether a signal is of such severity, that quick action is necessary to ensure the safety of a VMP (signal prioritisation).

The process of prioritisation, validation, detection and assessment is the same for every signal. It is important that every signal will be assessed in the same way, regardless of its source. In addition the methodology, extent and frequency of every step in the signal management process are determined based on a risk based approach, in which the type of product, length of time on the market, stability of the pharmacovigilance profile, identified and potential risks and the need for additional information are taken into account. The reasons behind the chosen methodology, extent and frequency are documented in the PSMF. (VO 2021/1281, art. 17(3))

3.1 Signal prioritisation

Based on the impact of the events of a report and the possible risks for animal health and welfare, public health and the environment, reports and signals will be prioritised. Despite the position of signal prioritisation in the flowchart (Appendix I) in this guidebook, it is a component of the signal management process which must be taken into account during every stage. A tool that could be used is prioritisation based on 'Medically Important (MI) terms' according to the VeDDRA-terms. Terms considered as 'Medically Important' are listed in Appendix IV, but can also be found in Appendix 1 of the VGVP-guideline on 'Signal management' (EMA/522332/2020).

Another reason for prioritising are so called Emerging Safety Issues (ESI's). These must be reported within three business days in IRIS (the system for signal management with the EMA) and with the BD (VO 2019/6, art. 58(10)). ESI's are events which require urgent attention and possibly need urgent measures, because:

- They might have a big impact on the benefit-risk balance of the VMP or the active substance;
- Reports are coming in that might have a big impact on animal health and welfare or public health;
- There might be a new association between the VMP and the unwanted effect, or a new aspect of an already known association;
- There might be an indication for a batch mistake, which require urgent actions.

Such an accelerated report consists of the safety risk, source of the report(s), plan of action or actions already taken (including a timeline) and other documents relevant at that moment.

3.2 Signal validation

Signal validation ensures the quality of incoming reports and emerging signals. A part of the signal validation is already executed by checking every incoming reports for the presence of the necessary information (the four minimal requirements, see Chapter 2.3: Minimal requirements of a report). In

addition, the timeline must be correct (e.g. the occurrence of the suspected adverse event after the administration of the VMP), the signal must not be based on double reports and the signal must not already be described in the SPC as a side effect.

3.2.1 Checking for double reports

It must be ensured that reports of suspected adverse events will not be reported EVVet more than once. Only the primary receiver of the report (competent authority or MAH) has access to all the details of the reporter, when the report is forwarded to EVVet these details are anonymised in accordance with the privacy legislation. To check for double reports the initials of the first and last name of the reporter and the first two digits of the zip code are entered in the field available for the last name.

3.3 Signal detection

Individually assessed and validated reports are added to the dataset of previously entered reports for that VMP. Based on this dataset and (statistical) analyses (EudraVigilance uses the Relative Odds Ratio if it concerns a larger dataset) signals could subsequently be detected. Beside EVVet (Data WareHouse), there are other systems available to collect reports and carry out signal detection. A MAH is free in choosing a signal detection system and database (EMA/522332/2020), as long as it is included in the PSMF and the reports in EVVet are done. Depending on the number of reports a MAH receives for a VMP, they could either choose to conduct signal detection after each new reports or periodically. The MAH is obligated to conduct at least one cycle of signal detection in EVVet per year (VO 2021/1281, art. 17(7)). This cycle must be conducted within the last two months before the yearly report will be submitted (see Chapter 4.2 Annual submission regarding the signal management process).

Based on several factors a dataset is made which can be searched per VMP and per target species for possible signals. In the dataset an alert pops up once there are at least five cumulative reports using that VeDDRA-term (three reports for MI VeDDRA-terms). Subsequently, the Relative Odds Ratio (ROR-value) is a tool that can be used to detect and prioritise a signal. If the minimal value of the 95% confidence interval is more than 1 the EVVet result will turn red, if this value is more than 2 the field will become orange. When both fields are filled with these colours, it is possibly a sign of a signal which should be assessed. The ROR-value should be seen as a tool which can be used for signal detection; clinical symptoms that go with the underlying disease and with the pharmacokinetics (e.g. timeline, effect) and -dynamics of the VMP (e.g. the receptor which is targeted by the active substance) should also be taken into consideration. In this step potential causality is also taken into account.

It is important to realise that reports about herds or flocks are often in a single spontaneous report. Because these reports are about a large number of animals, a single report is enough to generate a signal. This is why the number of reports should always be compared to the number of animals involved during signal detection. It is also desirable to analyse every report of a suspected adverse event in a human.

3.4 Signal assessment

A detected signal must be assessed to determine whether there is a change in the benefit-risk balance, a new risk or a change of a known risk, or that there is no change. For this, veterinary clinical reasoning must be done, in relation to topics such as the timeline (time of administration of the VMP, start- and end time of the event), evaluation of the available data, other symptoms of underlying diseases and other VMPs that were used in the same timeframe

(EMA/522332/2020). The goal of signal assessment is to evaluate if the balance between de benefits and the risks, still is in favour of the benefits.

During the signal management process incidence must be included, to compare this to any increase in reports of VeDDRA-terms. The incidence is calculated with the following formula: $\frac{number\ of\ animals\ affected \times 100}{estimated\ number\ of\ animals\ treated}$ in a certain timeframe. The estimated number of animals treated is calculated using information about the volume of sales and the factor determining the number of animals that can be treated with one pack of a given pack size (VO 2021/181, art. 14(2)). The volume of sales must be entered into the UPD.

3.4.1 Possible steps after signal assessment

Depending on the conclusion of the signal assessment, the following steps are possible:

- Causality and with that change in the benefit-risk balance or a new risk:
    - In case of an Emerging Safety Issue notify the EMA through IRIS and the BD within 3 business days (see Chapter 3.1 Signal prioritisation)
    - Else, notify the EMA through IRIS and the BD (VO 2019/6, art. 81(2)) within 30 business days with a proposal for regulatory actions (e.g. changing the SPC-texts)
- Available information can neither confirm or rule out a causality between the use of a VMP and an event, however additional information could change this:
    - 'Close monitoring' can be used if the available information cannot rule out the causality. In this case either the BD or the EMA can enforce a higher frequency of reporting. 'Close monitoring' can only be ended after a detailed justification. 'Close monitoring' must also be registered with the EMA through IRIS.
    - Surveillance studies can be started to further investigate the signal (see 'reports based on surveillance studies in Chapter 2.2 Sources of suspected adverse event reports)
- The detected signal appears not to be a signal after analysis:
    - The potential signal is assessed (evaluated), after which it is refuted and the signal management process will continue. The signal could be reopened, in case new information becomes available in the future.
    - The signal must be registered in IRIS before the annual submission (EMA/522332/2021).

3.4.2 Recall

If a detected signal relates to one or more specific batch numbers, or if a quality defect is found which presents a risk for animal or public health, a recall needs to be considered. Recalls could be conducted at the level of the distributor, veterinarian or end-user, depending on the severity of the risk.

Legally, recalls fall under the Implementing Regulation (EU) 2021/1248 article 32. Because this Implementing Regulation applies to good distribution practices of VMPs (GDP), a recall only partly falls under pharmacovigilance. If a problem with a batch is noticed in the context of pharmacovigilance, the Qualified Person responsible for Pharmacovigilance (QPPV) makes the decision to conduct a recall. This decision is made based on the risk for animal health and welfare and public health, the severity of the quality defect, the impact on the industry and the cause of the defect. After the decision for a recall has been made, the QPPV notifies the Qualified Person for GDP (QP), the QP will deploy the recall. All other recalls (e.g. a detected quality defect) will completely go through the QP.

The BD needs to be informed as quickly as reasonable possible about recalls (VO 2021/1248, art. 32(3)), in case of a centrally registered product the EMA must also be notified. In addition, the competent authorities of the countries where the product is distributed as well (inside and outside the EU) need to be informed. If the recall is because of a serious risk regarding animal and public health, the 'rapid alert' system of the EMA can be used.

3.5 Checklist

Signal management	YES	NO
• Is there a procedure which describes based on which properties of a report or a signal it is prioritised?	☐	☐
• Is there a procedure which describes based on which properties signal detection is being conducted and which system is being used for this process?	☐	☐
• Is there a procedure which describes how signal assessment is being conducted, in a way that ensures every signal will be assessed in the same way?	☐	☐

4 Reporting to the EMA

The MAH has several obligations for reporting to the systems of the EMA. Individual spontaneous reports will be reported in EVVet, assessed signals and the annual submission will be reported in IRIS. This guidebook focuses mainly on executing the legislation in practice, and does not look into the way EVVet and IRIS work. More information about how the systems of the EMA work, can be found on the EMA website in the documents about 'user guidance'.

4.1 Reporting signals

If a signal is detected and assessed, and it is not a Safety Emerging Issue, the outcome of the assessment should be registered in IRIS within 30 days using the appropriate form. The following information should at least be added:

- Administrative information: name of the VMP, name of the MAH, active substance.
- Signal-specific information: species and VeDDRA-terms of the type of adverse event, number of cumulative reports and number of reports supporting the signal (including Unique AERID number of every report), report of the signal assessment with the results of the signal management process, including the conclusion on the potential causality and proposition of actions (including actions for minimising risks).

4.2 Annual submission regarding the signal management process

Every year the MAH must register a conclusion of the benefit-risk balance in IRIS for every VMP it has an authorisation for, together with a statement confirming the signal management process has been executed (VO 2019/6, art. 81(2). VO 2021/1281, art. 19(1)). Even if no signal has been detected in the past year, the annual rapport is still obligated. In this case the annual rapport consists of a standard statement which states that the signal management process has been conducted according to the guidelines of the EMA, together with a statement which states that the benefit-risk balance of the VMP has not changed (EMA/522332/2021). These statements are part of the form which has to be filled out in IRIS.

If a signal has been detected in the past year, the signals do not need to be reported in IRIS again. In this case the MAH must state that all the assessed signals have been reported in IRIS. The following fields should at least be filled in (EMA/522332/2021):

- Administrative information: name of the VMP, name of the MAH, active substance.
- For each signal: species and VeDDRA-terms of the type of adverse event, number of cumulative reports (containing a short summary of the reports and a summary of the assessment) and number of reports supporting the signal (including Unique AERID number of every report).

Refuted signals of earlier annual statements, on which no new relevant information has submerged, do not need to be submitted again.

If the VMP is placed under 'close monitoring' and the previous statement for this has been longer than six month ago, an update should be reported. This update consists of a summary of new and similar cases which have been received since the previous update. If 'close monitoring' has lasted for over two years, the MAH is allowed to end this by submitting a statement which contains a detailed justification regarding the reason 'close monitoring' can be ended.

The annual report regarding the signal management process has to be submitted within two months before the due date (EMA/522332/2020). The EMA sets these due dates and communicates them for every VMP based on the active substance.

4.3 Reporting to third countries

If the VMP is also sold outside the EU, pharmacovigilance must also comply with the legislation of that country. Norway, Iceland and Lichtenstein are not members of the EU, however they are members of the European Economic Area (EEA), in that context these countries decided to conduct pharmacovigilance according to the signal management process of the EU as well.

Since the Brexit the United Kingdom (England, Scotland and Wales) is no longer part of the EU. Because they are also not part of the EER, these countries have different pharmacovigilance requirements. At the moment the UK still works with PSURs, however they will probably also want to transfer to the signal management process. Although it is still unknown when this transfer will happen. The latest information about pharmacovigilance requirements of the MAH for VMPs sold in the UK can be found at the website of the Veterinary Medicines Directorate, at their veterinary pharmacovigilance page.

Switzerland is also not part of the EER, and has different requirements for pharmacovigilance. They have a hybrid form of both the system with PSURs and the signal management process of the EU, in which PSURs need to be submitted during the first few years after authorisation of the VMP. The latest information about pharmacovigilance requirements in Switzerland (Swissmedic) can be found at their VMP page; under the heading 'Documents and forms – Veterinary medicinal product' is a document available titled 'PSUR Signal management'.

MAHs with branches in several continents, conduct pharmacovigilance according to the legislation of that specific region. If an authorisation is cancelled in another region due to an increased risk, this must also be reported to the EU and the benefit-risk balance must be assessed again based on this new information.

4.4 Checklist

Reporting to the EMA	YES	NO
• Is there a procedure which describes the way reporting assessed signals to IRIS should be conducted?	☐	☐
• Is there a procedure which describes the way publication of the due dates for the annual reports will be monitored?	☐	☐
• Is there a procedure which describes the way the annual report in IRIS should be conducted?	☐	☐
• Is it clear in which third countries the VMP is sold, and which legal requirements for pharmacovigilance apply in those countries?	☐	☐

5 Pharmacovigilance system

A MAH is required by law to fulfil several responsibilities regarding pharmacovigilance. The MAH should have a pharmacovigilance system which matches with all the obligations, such as a PSMF and accommodating responsibilities with the right employees with the aim to conduct high-quality pharmacovigilance. (VO 2021/1281, art. 77)

5.1 Employees

Many employees are involved with pharmacovigilance in several ways and levels within the organisation of a MAH. The roles and responsibilities of all the employees involved with pharmacovigilance at the MAH are described in the PSMF (VO 2021/1281, art. 4(7)), including the plan for basic- and continuous training which is also recorded in the PSMF (VO 2021/1281, art. 6(2)).

5.1.1 Qualified Person responsible for Pharmacovigilance (QPPV)

The MAH has one or multiple employees responsible for pharmacovigilance; the Qualified Person responsible for Pharmacovigilance (QPPV). The MAH also has the option to hire a third party as QPPV which will take over the responsibilities regarding pharmacovigilance. The QPPV lives and works in a country of the European Economic Area (EEA) and is constantly available to the MAH, also outside office hours (VO 2019/6, art. 77(8)). The QPPV is a veterinarian, or will be supported by a veterinarian (VO 2021/1281, art. 3(2)). The QPPV also has documented experience in pharmacovigilance (VO 2021/1281, art. 3(1)). Because of the legal obligation of the constant availability of the QPPV and supporting veterinarian, back-up procedures should be available in case either of these persons are absent (VO 2021/1281, art. 2(6)). If a MAH has multiple QPPVs, one will be linked to each PSMF (VO 2019/6, art. 77(8)). The QPPV manages and supervises the tasks regarding the PSMF and database used for reports, applying the signal management process, setting up a plan of action when necessary and making sure that it will be executed, reporting in EVVet and IRIS within set timeframes, making sure that requests of the BD and the EMA are complied with and making sure employees involved with pharmacovigilance receive continuous training (VO 2021/1281, art 78(1)). The QPPV is not required to perform these tasks completely by themselves, but can also delegate these to other employees. Delegation of tasks is documented in the PSMF (VO 2021/1281, art. 22 (3b)).

5.1.2 Local or regional representative

Besides the QPPV a local representative is appointed to whom reports of suspected adverse events can be reported. In case the QPPV does not live in the Netherlands, a representative in the Netherlands or Belgium who speaks Dutch must be appointed to report suspected adverse events with (VO2019/6, art. 77(3)). This person does not need to have pharmacovigilance as their main task, but should be adequately trained to recognise suspected adverse events and record a report of it. It is advised this person has understanding of (patho)physiological and pharmacological processes, to make sure the right information is gathered for a high quality assessment of the report and as little information as possible has to be retrieved afterwards.

5.1.3 Employees involved with gathering suspected adverse event reports

Many employees of the MAH are involved with gathering suspected adverse event reports, because the reports may come from various sources (see Chapter 2.2 Sources of suspected adverse events). Partly for this reason it is important for all employees in any way involved with pharmacovigilance to receive basic- and continuous training for this subject (VO2021/1281, art. 6(1)). This way the MAH ensures that employees who are in direct contact with veterinarians or end users recognise suspected adverse events and know what to do in case of these reports.

5.2 Quality management system

Processes, procedures and responsibilities are set in the quality management system, which describe how quality policies and objectives are realised by directing an organisation in such a way that it improves its effectiveness and efficiency on a continuous basis (VO2021/1281, art. 1(a)). Besides procedures for all pharmacovigilance activities, the quality management system also contains policies and processes for document management, training of employees involved with pharmacovigilance, audits and change management (VO 2021/1281, art. 4(1) and (3)), The quality management system is part of the PSMF (see Appendix III Content and structure of the PSMF).

According to the Implementing Regulation (EU) 2021/1281, article 4(8) the quality management system is set up through the use of:

a) Quality planning: establishing structures, integrated planning and consistent processes (=PSMF);
b) Quality adherence: carrying out tasks and responsibilities in accordance with quality requirements (=day-to-day work);
c) Quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are implemented (=audits and inspections);
d) Quality improvements: correcting and improving the structures and processes where necessary (=change management).

5.2.1 Audits, controls and inspections

By performing audits and inspections the quality of the pharmacovigilance system can be tested. Inspections can be conducted by the competent authority (in the Netherlands the BD) (VO 2021/2081, art. 27(1)). If there are no inspections with the MAH for a certain period, it is advised to inspect the system at least once a year by internal and external audits. These checks are done based on performance indicators, being the data collected at regular intervals to monitor the performance of the system (VO 2021/1281, art. 1(b)). The reason why the performance indicators have been chosen and a description of how to use them shall be included in the PSMF under point iii) of Annex IV (VO 2021/1281, art. 7) (see Appendix III).

5.2.2 Change management

Change management is the process in which corrective and preventive measures are set up and implemented, to solve any discrepancies which have been found during audits, daily operational work and findings from inspections (VO 2021/1281, art. 9(1)). If a measure is applied, the MAH takes care of monitoring and assessing it for its effectiveness (VO 2021/1281, art. 9(3)). Measures taken shall be documented and kept for the last five years in the PSMF (VO 2021/1281, art. 9(1)).

5.3 Pharmacovigilance System Master File (PSMF)

The MAH ensures the reliability of the outcome of the pharmacovigilance process by documentation the procedures. These procedures are bundled in the Pharmacovigilance System Master File (PSMF). In Dutch legislation the PSMF is also called ‘basisdossier’. For different categories of VMPs separate PSMFs can be set up (VO 2021/1281, art. 21(3)), but only one PSMF can be linked to every authorised VMP (VO 2019/6, art. 77(2)).

5.3.1 Content and structure of the PSMF

The Implementing Regulation (EU) 2021/1281, art. 22(2) sets requirements for the content and structure of the PSMF. The PSMF consists of a main part (part A to F) and some annexes (VO 2021/1281, art. 22(1)). The reference number of the PSMF and the information about the QPPV will

be added to IRIS after authorisation of the VMP (VO 2019/6, art. 74(1)). A summary of the PSMF needs to be added to the application for registration of a VMP (VO 2021/1281, art. 23):

a) Reference number of the PSMF;
b) File location of the PSMF;
c) Name, contact details and place of operation of the QPPV;
d) Statement confirming the QPPV has the necessary means to fulfil the tasks and responsibilities of VO 2019/6 (signed by the QPPV and MAH);
e) Type of record management system used for adverse events reports including the name of the database, if applicable.

Table 1 shows briefly which topics are covered in the PSMF, the legal requirements of the content are elaborated and summarised in Appendix III.

Section	Content	Annex	Content
A	General information about the PSMF	I	Logbook containing all changes of the main part of the PSMF
B	Information about the QPPV, (if applicable) the veterinarian and back-up procedures	II	Additional information about the QPPV, (if applicable) the veterinarian and back-up procedures
C	Information about the MAH	III	Additional details about the MAH
D	Description of the document management system		
E	Description of the quality management system	IV	Additional details about the quality management system
F	Contractual arrangements between MAH and third parties	V	Additional details about the contractual arrangements between MAH and third parties

Table 1 – Brief overview PSMF

The changes that are kept in the logbook, are saved for at least five years (VO 2021/1281, art. 24(4)).

A MAH has the option to subcontract tasks or responsibilities regarding pharmacovigilance to third parties. In case of subcontracting, the tasks or responsibilities that are subcontracted must also be described in the PSMF, together with details about the third party (VO 2019/6, art. 77(7), VO 2021/1281, art. 21(2)).

5.3.2 Storing and maintaining the PSMF

The PSMF must be kept at the location where the most important pharmacovigilance tasks will be conducted, or at the location where the QPPV works (VO 2021/1281, art. 25(1)). It can be stored digitally, as long as the media used is searchable and stays readable over time (VO 2021/1281, art. 25(2)). The PSMF must always be accessible for the QPPV, for requests for copies of the BD or EMA and available for immediate inspection (VO 2021/1281, art. 24(2) and (5), art. 25(4)).

The MAH keeps the PSMF up-to-date (VO 2021/1281, art 24(1)), the date of the last update is noted in the PSMF and it is subject to version control (VO 2021/1281, 24(3)). The MAH only has to inform the BD or the EMA about changes in the summary of the PSMF (VO 2021/1281, art. 24(6)). These changes do not require assessment by the BD or EMA and must be reported within 30 days (VO 2019/6, art. 61(1)). All alterations of the main part of the PSMF must be saved in detail in the logbook for at least five years (VO 2021/1281, art. 24(4)) and must be kept available for requests by the BD and EMA for copies (VO 2021/1281, art. 24(5)).

5.4 Checklist

Employees	YES	NO
• Are one or more employees with experience in pharmacovigilance who live in the EU (or the EER) appointed as QPPV for pharmacovigilance tasks?	☐	☐
• Is the QPPV a veterinarian, or is the QPPV supported by a veterinarian?	☐	☐
• Is the QPPV constantly available, during and outside of office hours, and are there back-up procedures in case of absence?	☐	☐
• Are the tasks and responsibilities of all employees involved with pharmacovigilance documented in the PSMF?	☐	☐
• If the QPPV is responsible for the signal management process of several countries, is there a local representative speaking the local language for every country?	☐	☐
• Is there for a plan for basic- and continuous training for every employee involved with pharmacovigilance?	☐	☐
• Are all employees who communicate with veterinarians or end users able to recognise suspected adverse events and do they know the procedure of how to act in such cases?	☐	☐

Quality management system	YES	NO
• Is the quality management system set up according to performance indicators which test the effectiveness and efficiency of the organisation?	☐	☐
• Is an overview of the planned audits available in the PSMF?	☐	☐
• Are procedures available that take care of change management in a structural way and of testing the effectiveness of the measures taken?	☐	☐

PSMF	YES	NO
• Is at least one PSMF available for pharmacovigilance?	☐	☐
• Is every PSMF complete? (See Appendix III)	☐	☐
• Is a summary available of every PSMF and are the necessary details registered in IRIS?	☐	☐
• Is the PSMF stored at the location where the most important pharmacovigilance tasks are conducted, or at the location where the QPPV works?	☐	☐
• Is the PSMF always accessible to the right persons?	☐	☐
• Are the tasks that are subcontracted to third parties documented in the PSMF?	☐	☐

6 Communication

In case of serious concerns about the safety of a VMP, this must be communicated to stakeholders (veterinarians, other medical professionals, clients and animal keepers or -owners) in a timely and effective manner. The necessity for communication must therefore be considered during the entire signal management process. Coordination with the authorities before actual communication is required. Because the subjects for communication can vary widely, there must be an overarching communication plan with which specific communication plans can be set up for every situation (VO 2021/1281, art. 20(1)). The overarching communication plan must be documented in the PSMF as a part of the quality management system (VO 2021/1281, art. 4(5)).

The communication plan describes the way (VO 2021/1281, art. 20(2)):

a) The target audience is identified;
b) Effective means for communication with the intended target audience are identified;
c) The specific objectives of the communication are identified;
d) A timetable for the communication is defined;
e) The relevance and clarity of the information for the intended target audience is ensured;
f) All stakeholders involved in the communication are identified and coordinated;
g) Depending of the situation either the BD or the EMA, preferably in advance, but at least simultaneously are notified of the public announcement (according to VO 2019/6, art. 77(1));
h) The effectiveness of the communication is measured.

The VGVP-guideline 'Veterinary pharmacovigilance communication' (EMA/63454/2021) specifies a communication plan can be divided into three phases: preparation, execution and follow-up. The goal of a communication plan for pharmacovigilance is to transfer relevant, clear, accurate, consistent and timely messages to the correct target audience, so they can take appropriate measures. The following items are of importance (EMA/63454/2021):

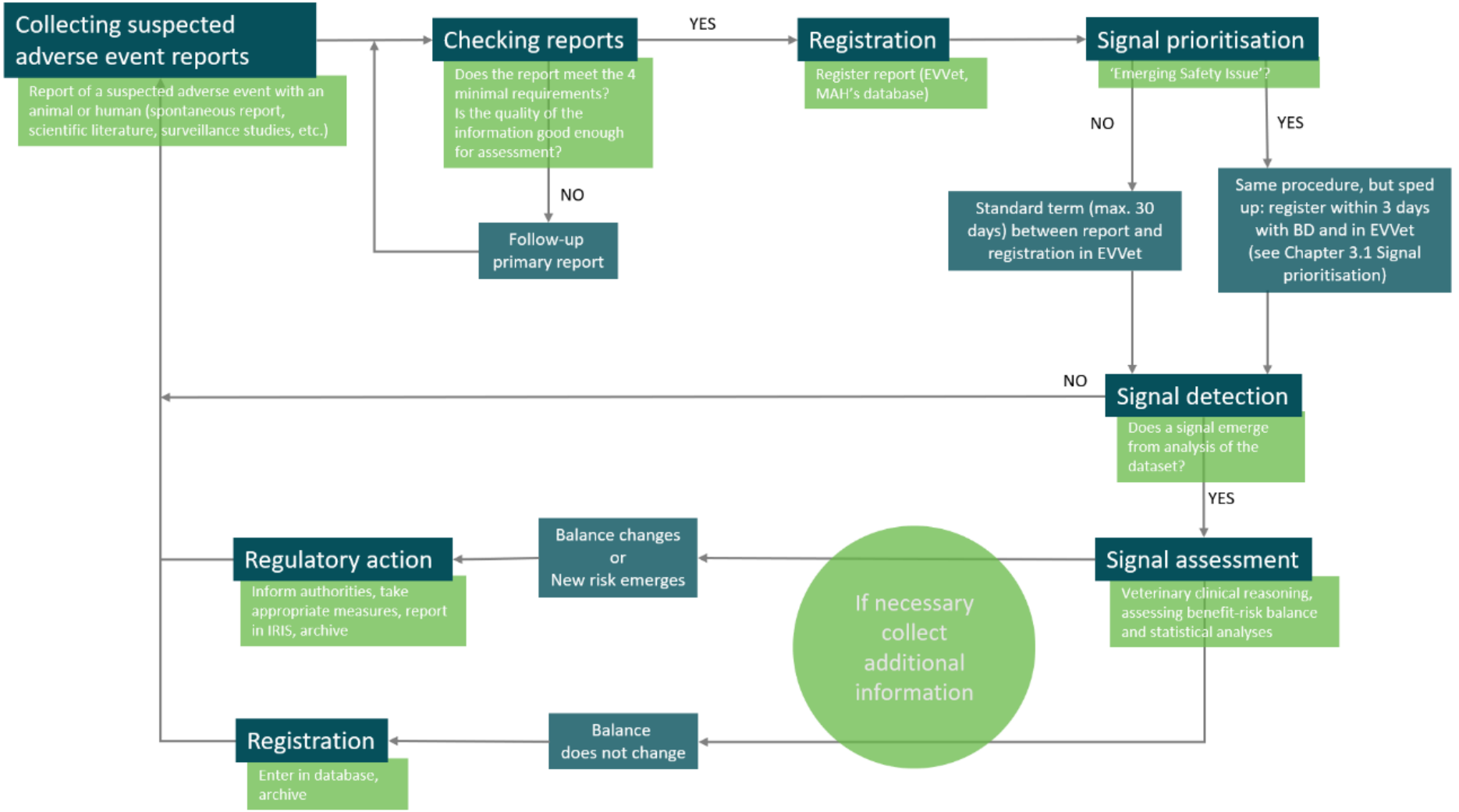
- The content cannot not be promotional or commercial;
- The content should include:
    - The reason for communication;
    - An objective description of the risk;
    - Recommendations for the receiver about how to handle the information;
    - Contact details of a contact person;
    - Any additional information such as scientific literature;
    - If relevant, a reminder to report suspected adverse events.
- The content should be clear, yet concise;
- The content should be in language that is understandable for the recipient.

When following-up on the conducted communication it is important to verify if the message has been received and understood (VO 2021/1281, art. 20(2h)). Following-up and verifying can be difficult, so a reasonable amount of time and effort should be put into this. An evaluation must also be done to check if the procedure for developing a communication plan should be changed to improve it. (EMA/63454/2021)

6.1 Checklist

Communication plan	YES	NO
• Is an overarching communication plan available in case of serious concerns about the safety of a VMP?	☐	☐
• Is the overarching communication plan substantiated based on which considerations a subject specific communication plan is made?	☐	☐
• Is the way it is ensured the message of the communication is received and understood by the target audience documented in the communication plan?	☐	☐

Appendix I Flowchart pharmacovigilance



Appendix II Checklist pharmacovigilance (all chapters)

Collecting of suspected adverse event reports (Chapter 2)	YES	NO
• Is there a procedure which describes the way it is ensured spontaneous reports are collected and reach the correct person or department?	☐	☐
• Is there a procedure which describes the way it is ensured reports from scientific literature are collected and reach the correct person or department?		
• Is there a procedure which describes the way it is ensured reports from non-medical sources are collected and reach the correct person or department?	☐	☐
• Is there a procedure which describes the way it is ensured results relevant to pharmacovigilance from clinical and surveillance studies after authorisation are collected and reach the correct person or department?	☐	☐
• Is there a procedure which describes the way it is ensured reports from third countries are collected and reach the correct person or department?	☐	☐
• Is there a procedure which describes the way incoming reports are processed, checked for the availability of the four minimal requirements and if necessary will be followed up with the reporter?	☐	☐
• Is there a procedure which describes the way it is ensured reports will be reported in EVVet within 30 days, and if applicable will be registered in the database of the MAH?	☐	☐

Signal management (Chapter 3)	YES	NO
• Is there a procedure which describes based on which properties of a report or a signal it is prioritised?	☐	☐
• Is there a procedure which describes based on which properties signal detection is being conducted and which system is being used for this process?	☐	☐
• Is there a procedure which describes how signal assessment is being conducted, in a way that ensures every signal will be assessed in the same way?	☐	☐

Reporting to the EMA (Chapter 4)	YES	NO
• Is there a procedure which describes the way reporting assessed signals to IRIS should be conducted?	☐	☐
• Is there a procedure which describes the way publication of the due dates for the annual reports will be monitored?	☐	☐
• Is there a procedure which describes the way the annual report in IRIS should be conducted?	☐	☐
• Is it clear in which third countries the VMP is sold, and which legal requirements for pharmacovigilance apply in those countries?	☐	☐

Employees (Chapter 5.1)	YES	NO
• Are one or more employees with experience in pharmacovigilance who live in the EU (or the EER) appointed as QPPV for pharmacovigilance tasks?	☐	☐
• Is the QPPV a veterinarian, or is the QPPV supported by a veterinarian?	☐	☐
• Is the QPPV constantly available, during and outside of office hours, and are there back-up procedures in case of absence?	☐	☐
• Are the tasks and responsibilities of all employees involved with pharmacovigilance documented in the PSMF?	☐	☐
• If the QPPV is responsible for the signal management process of several countries, is there a local representative speaking the local language for every country?	☐	☐
• Is there for a plan for basic- and continuous training for every employee involved with pharmacovigilance?	☐	☐

- Are all employees who communicate with veterinarians or end users able to recognise suspected adverse events and do they know the procedure of how to act in such cases? ☐ ☐

Quality management system (Chapter 5.2) YES NO

- Is the quality management system set up according to performance indicators which test the effectiveness and efficiency of the organisation? ☐ ☐
- Is an overview of the planned audits available in the PSMF? ☐ ☐
- Are procedures available that take care of change management in a structural way and of testing the effectiveness of the measures taken? ☐ ☐

PSMF (Chapter 5.3) YES NO

- Is at least one PSMF available for pharmacovigilance? ☐ ☐
- Is every PSMF complete? (See Appendix III) ☐ ☐
- Is a summary available of every PSMF and are the necessary details registered in IRIS? ☐ ☐
- Is the PSMF stored at the location where the most important pharmacovigilance tasks are conducted, or at the location where the QPPV works? ☐ ☐
- Is the PSMF always accessible to the right persons? ☐ ☐
- Are the tasks that are subcontracted to third parties documented in the PSMF? ☐ ☐

Communication plan (Chapter 6) YES NO

- Is an overarching communication plan available in case of serious concerns about the safety of a VMP? ☐ ☐
- Is the overarching communication plan substantiated based on which considerations a subject specific communication plan is made? ☐ ☐
- Is the way it is ensured the message of the communication is received and understood by the target audience documented in the communication plan? ☐ ☐

Other YES NO

- In case of in- or out-licensing, are the responsibilities regarding pharmacovigilance carefully documented? ☐ ☐

Appendix III Content and structure of the PSMF (based on VO 2021/1281, art. 22(2) and (3))

Section A – General information about the PSMF	**Annex I – Logbook containing all changes to the main part of the PSMF**
i) Reference number of the PSMF	Including a description of the part that has been altered, date and nature of the alteration, the person responsible and where appropriate the reason for the alteration (VO 2021/1281, art. 24(4))
ii) File location of the PSMF	
Section B – Information about the QPPV, (if applicable) the veterinarian and back-up procedures	**Annex II – Additional information about the QPPV, (if applicable) the veterinarian and back-up procedures**
i) Information about the QPPV, including name, contact details, and a statement confirming the QPPV has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6 (signed by the QPPV and the MAH)	i) Curriculum vitae (including information on qualifications and training) of the QPPV and if applicable the supporting veterinarian
ii) If applicable, documentation on arrangements concerning the supporting veterinarian, including contact details	ii) Description of the tasks and responsibilities of the QPPV
iii) Back-up arrangements in case of absence of the QPPV or (if applicable) the supporting veterinarian	iii) Proof of registration with EVVet
	iv) List of the pharmacovigilance activities that have been delegated by the QPPV to third parties
Section C – Information about the MAH	**Annex III – Additional details about the MAH**
i) Detailed description of the organisational structure of the MAH, including parent company or group of companies associated	i) List of all VMPs covered by the PSMF, including international non-proprietary name (INN) of the active substances, if applicable, the Member States in which the product is authorised or registered and corresponding authorisation numbers and type of procedure used for authorisation
ii) Position of the QPPV within the organisation	ii) If applicable, a list of reference numbers for other PSMFs held by the same MAH
	iii) List of local or regional representatives for the purpose of receiving reports of suspected adverse events, including their contact details, responsibilities and territories
	iv) List of the sites where pharmacovigilance activities listed in VO 2021/1281, art. 4, paragraphs 3 to 6* are carried out

Section D – Description of the document management system (VO 2021/1281, art. 5), incl. the record management system for adverse event recording (VO 2021/1281, art. 10(2))			
	VO 2021/1281, art. 10(2) = requirements register adverse events:		
a)	Type of record management system used for adverse event reports, if applicable including name of used database		
b)	Location where the record management system is kept		
c)	Description of functionality of the record management system		
d)	Operational responsibility of employees responsible for record management system		
e)	Summary of the assessment of its fitness for purpose		
Section E – Description of the quality management system		**Annex IV – Additional details about the quality management system**	
i)	Description of processes used for pharmacovigilance activities referred to in VO 2021/1281, art. 4, paragraphs 3 to 6*	i)	List of documents, policies, procedures and processes used for the pharmacovigilance activities referred to in VO 2021/1281, art. 4, paragraphs 3 to 6*
ii)	Description of the training management system (as referred to in VO 2021/1281, art. 6(2))	ii)	List of all scheduled and completed audits including outstanding critical and major findings
iii)	Description of the system used for documenting or archiving information (as referred to in VO 2021/1281, art. 5(2)) (including version control of documents)	iii)	List of performance indicators and how to use them (as referred in VO 2021/1281, art. 7)
iv)	Description of the system for monitoring the performance of the pharmacovigilance system (as referred to in VO 2021/1281, art. 7)	iv)	Information on training plans and records (as referred to in VO 2021/1281, art. 6(2))
v)	Description of the responsibilities for quality assurance auditing of the pharmacovigilance system, if applicable including auditing of subcontractors (as referred in VO 2021/1281, art. 8)	v)	Methodology to calculate the incidence factor (as referred to in VO 2021/1281, art. 14(2), see Chapter 3.4 Signal assessment)
vi)	List of audits associated with unresolved critical or major findings	vi)	List of risk management measures and the outcome of risk minimisation measures
vii)	Description of the corrective and preventive action plan management and change management (as referred to in VO 2021/1281, art. 9)		

Section F – Description of contractual arrangements between MAH and third parties	Annex V – Additional details about the contractual arrangements between MAH and third parties
	i) List of pharmacovigilance activities or services subcontracted by the MAH to third parties and information on these third parties, including names and addresses
	ii) List of the tasks of the QPPV that have totally or partially been outsourced, information on who the activities or services are subcontracted to, including names and addresses
	iii) List of existing contracts and agreements with third parties, if applicable including products and territories concerned

Underscored = components of the summary of the PSMF (VO 2021/1281, art. 23)

* VO 2021/1281, art. 4, paragraphs 3 to 6 = The MAH shall ensure that the quality management system includes detailed policies, processes and procedures for pharmacovigilance activities of art. 5 to 20, art. 24 and art. 25. Articles 5 to 20, 24 and 25 discuss: document management system (art. 5), training of staff (art. 6), performance indicators of the pharmacovigilance system (art. 7), audits (art. 8), corrective and preventive measures and change management (art. 9), record management system for adverse events (art. 10), (sources for) suspected adverse events (art. 11), recording of adverse events (art. 12), collection and collation of reports of suspected adverse events and additional data (art. 4(4b) and (4c)), adverse event recording in EVVet (art. 13), monitoring of quality, integrity and completeness of all information registered in EVVet (art.4(4f)), provision of additional data (art. 14), post-marketing surveillance studies (art. 15), archiving of all relevant documents (art. 4(4h)), risk management system (art. 16), signal management process (art. 17), monitoring benefit-risk balance (art. 18), conclusion of the benefit-risk balance (art. 19), communication to all relevant stakeholders (art. 20), maintenance of the PSMF (art. 24) and location and availability of the PSMF (art. 25).

Appendix IV 'Medically Important' (MI) VeDDRA-terms

MI VeDDRA-term	Species
Any event	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 disorders 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	Horse, Ruminant, Camelid
Moribund	All
Multi-organ failure NOS*	All
Myoglobinuria (Horses only)	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

* - NOS: Not otherwise specified

Source: Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Signal Management (EMA/522332/2020). Published on November 18th, 2021. Accessed at May 2nd, 2022.

Appendix V Relevant sources for pharmacovigilance

Regulation (EU) 2019/6

Implementing Regulation (EU) 2021/1281

Regeling diergeneesmiddelen 2022 (Dutch legislation)

Besluit diergeneesmiddelen 2022 (Dutch legislation)

'Guidelines on veterinary good pharmacovigilance practices (VGVP guidelines)' of the EMA, consisting of:

- Module: Collection and recording of suspected adverse events for veterinary medicinal products (EMA/306663/2021)
- Module: Signal Management (EMA/522332/2020)
- Module: Veterinary pharmacovigilance communication (EMA/63454/2021)
- Module: Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files (EMA/595115/2021)
- Module: Controls and pharmacovigilance Inspections (EMA/328998/2021)
- Module: Glossary (EMA/118227/2021)

Website of the EMA where the most recent list of VeDDRA-terms is available

Website of the Bureau Diergeneesmiddelen

Appendix VI Relevant organisations for pharmacovigilance

FIDIN (Branch association of manufacturers and distributors of VMPs)

Postbus 80523, 2508 GM The Hague (NL)

+31 (0) 70 750 31 16

fidin@fidin.nl

www.fidin.nl

BD (Bureau Diergeneesmiddelen)

aCBG – Bureau Diergeneesmiddelen, Department Pharmacovigilance, Postbus 8275, 3503 RG Utrecht (NL)

+31 (0) 88 224 8000

vetpharvig@cbg-meb.nl

https://english.cbg-meb.nl/sections/veterinary-medicines

EMA (European Medicines Agency), veterinary pharmacovigilance

PO Box 71010, 1008 BA Amsterdam (NL)

+31 (0) 88 781 86 24

vet-phv@ema.europa.eu

https://www.ema.europa.eu/en/veterinary-medicines-regulatory-information

Animal Health Europe

168 Avenue de Tervueren box 8, 5th floor, 1150 Brussels (BE)

+32 (0) 2 543 75 60

info@animalhealtheurope.eu

https://animalhealtheurope.eu/

VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products)

c/o HealthforAnimals, Avenue de Tervueren, 168 – Box 8 – 1150 Brussels (BE)

+32 (0) 2 543 75 72

sec@vichsec.org

www.vichsec.org

Appendix VII Abbreviations and definitions

VII.1 Abbreviations

ABON	System for causality assessment which was part of earlier legislation (which is currently no longer in force), but could still be used.
AE	Adverse event
AhE	Animalhealth Europe, association representing the animal medicines industry in Europe.
BD	Bureau Diergeneesmiddelen (EN: Veterinary Medicinal Products Unit), the veterinary branch of the CBG which acts on the behalf of the ministry of LNV in the Netherlands.
CBG / aCBG	College ter Beoordeling van Geneesmiddelen (EN: Medicines Evaluation Board), in the Netherlands (legally) responsible for assessing, monitoring and encouraging the proper use of medications, the Agency of the CBG (aCBG) is part of the CBG.
CVMP	Committee for Veterinary Medicinal Products, committee part of the EMA responsible for veterinary medicines.
EC	European Committee, instigating and implementing of EU-policies.
EEA	European Economic Area, extends the EU's provisions to countries of the European Free Trade Area.
EMA	European Medicines Agency, a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.
EVVet	EudraVigilance Veterinary, centralised European database for pharmacovigilance of the EMA.
FIDIN	Branchevereniging van Fabrikanten en Importeurs van Diergeneesmiddelen (EN: Branche association of manufacturers and distributors of veterinary medicines), association representing the veterinary medicines branche in the Netherlands.
LNV	Ministerie van Landbouw, Natuur en Voedselkwaliteit (EN: Ministry of Agriculture, Nature and Food Quality in the Netherlands).
MAH	Marketing authorisation holder
MI-terms	Medically Important terms, VeDDRA-terms which help with prioritising signals.
MRL	Maximum Residue Limit, maximum amount of (a metabolite of) a pharmacologically active substance which may be permitted in food of animal origin.
PSMF	Pharmacovigilance System Master File, description of the pharmacovigilance system of a MAH which ensures the reliability of the result of pharmacovigilance.
PSUR	Periodic Safety Update Report, periodic report based on which part of pharmacovigilance was conducted under previous legislation.
QPPV	Qualified Person responsible for Pharmacovigilance, the responsible person for (veterinary) pharmacovigilance at a MAH.
SPC	Summary of Product Characteristics, point-by-point summary of the registration file based on which a VMP is authorised.
UPD	Union Product Database, database with VMPs registered in a member state of the EU.
VeDDRA	Veterinary Dictionary for Drug Related Affairs, English terms set up by the EMA which ensure standardisation and harmonisation of the signal management process.
VICH	International Cooperation on Harmonisation of Technical Requirements of Veterinary Medicinal Products, a collaboration between the EU, Japan and the US aimed at harmonising technical requirements for veterinary product registration.
VGVP	Veterinary Good Pharmacovigilance Practices.
VMP	Veterinary medicinal product

VII.2 Definitions

Benefit-risk balance	An evaluation of the positive effects of the veterinary medicinal product in relation to the following risks relating to the use of that product: a) any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health; b) any risk of undesirable effects on the environment; c) any risk relating to the development of resistance. (VO 2019/6, art. 4(19))
Cascade	Use of medicinal products outside the terms of the marketing authorisation, to avoid unacceptable suffering of animals. (VO 2019/6, art. 112 t/m 114)
Third countries	Countries that are not part of the European Union (EU)
Veterinary medicinal product	Any substance or combination of substances which fulfils at least one of the following conditions: a) it is presented as having properties for treating or preventing disease in animals; b) its purpose is to be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; c) its purpose is to be used in animals with a view to making a medical diagnosis; d) its purpose is to be used for euthanasia of animals. (VO 2019/6, art. 4(1))
Pharmacovigilance	Drug monitoring, the science and activities relating to the detection, assessment, understanding and prevention of suspected adverse events or any other problem related to a medicinal product. (VO 2019/6, art. 4(30))
Marketing authorisation holder	A company or legal entity that owns the authorisation to market a veterinary medicinal product.
Report (of a suspected adverse event)	A report of a suspected adverse event after administering a (veterinary) medicinal product in an animal, one or multiple reports may lead to a signal.
Off-label use	Using a veterinary medicinal product in a different way than is recorded in the authorisation (species, indication for use, dose and way of application).
Signal	Information that arises from one or multiple sources, including observations and experiments, which suggests a potentially new causal association, or a new aspect of a known causal association between an intervention and an adverse event or a set of related adverse events, that is judged likely to justify further investigation of possible causality. (VO 2021/1281, art. 1(c))

Signal management process	Process for performing active surveillance of pharmacovigilance data for veterinary medicinal products in order to assess the pharmacovigilance data and determine whether there is any change to the benefit-risk balance of those veterinary medicinal products, with a view to detecting risks to animal or public health or protection of the environment. (VO 2019/6, art. 4(41))
Authorisation	Approval to market a veterinary medicinal product, every authorised veterinary medicinal product has a unique registration number.
Suspected adverse event / Suspected side effect	Every unintended effect with an animal, human or in the environment which occurs after use of a (veterinary) medicinal product.
Suspected adverse event with a human	An unintended effect with a human which occurs after use of a veterinary medicinal product with an animal.

Appendix VIII Form to report suspected adverse events to the BD

Reporting form for suspected adverse events of the Bureau Diergeneesmiddelen (this form is only provided in Dutch)