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Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Signal Management

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Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Signal Management

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Tabulated list of abbreviations

Abbreviation	Term
ABON	Categories of the causality classification system for veterinary pharmacovigilance
AE	Adverse Event
AER(s)	Adverse Event Report(s)
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMR	Antimicrobial Resistance
AR	Assessment report
ATCvet code	Standardised alphanumerical identifier used to classify veterinary medicinal products according to the Anatomical Therapeutic Chemical classification system for veterinary medicinal products
BPG	Best Practice Guide
CAP(s)	Centrally Authorised Product(s)
CI(s)	Confidence Interval(s)
CIR	Commission Implementing Regulation
CVMP	Committee for Veterinary Medicinal Products
DaHPC(s)	Direct Animal Healthcare Professional Communication(s)
DCP	Decentralised Procedure
DLP	Data Lock Point
DWH	Data Warehouse
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EVV	EudraVigilance Veterinary
GABA	Gamma-Aminobutyric Acid
GI	Gastrointestinal
HCP	Healthcare Professional
HLT	High Level Term (VeDDRA hierarchy)
IC025	Information Component (lower bound of the 95% confidence interval)
IgE	Immunoglobulin E
IRIS	EMA's online platform for submitting and managing regulatory and scientific procedures for medicines throughout their lifecycle
IT	Information technology
LEE	Lack of Expected Efficacy
LLT	Low Level Term (VeDDRA hierarchy)
MAH(s)	Marketing Authorisation Holder(s)
MDR1 mutation	Multidrug Resistance Gene Mutation 1 (also known as ABCB1 gene mutation)
MIT(s)	Medically Important Term(s)
MRP	Mutual Recognition Procedure
NAP	National Authorisation Procedure
NCA	National Competent Authority
NOS	Not otherwise specified (suffix to VeDDRA LLTs)
NSAID	Nonsteroidal Anti-Inflammatory Drug
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PhV	Pharmacovigilance
PhVWP-V	Pharmacovigilance Working Party – Veterinary
PI	Product information
PK	Pharmacokinetics
PL	Package leaflet
PMSS	Post-Marketing Surveillance Study
PRR	Proportional Reporting Ratio
PT	Preferred Term (VeDDRA hierarchy)
QPPV	Qualified Person for Pharmacovigilance
ROR	Reporting Odds Ratio
SDR(s)	Signal(s) of Disproportionate Reporting
SOC	System Organ Class (VeDDRA hierarchy)
SPC	Summary of Product Characteristics
SRP	Subsequent Recognition Procedure
TSM	Targeted signal management
TTO	Time-to-Onset

UPD	Union Product Database
UPhV-Database	Union Pharmacovigilance Database
VeDDRA	Veterinary Dictionary for Drug Regulatory Activities
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VGVP	Veterinary Good Pharmacovigilance Practices
VMP	Veterinary Medicinal Product
VSM	Veterinary signal management
WHO–UMC	World Health Organization – Uppsala Monitoring Centre

1. Introduction (background)

This module of the guideline on veterinary good pharmacovigilance practices (VGVP) brings together general guidance for marketing authorisation holders (MAHs), national competent authorities and the European Medicines Agency (the 'Agency') regarding signal management for veterinary medicinal products (VMPs) authorised in the European Union (EU).

The objectives of this module are:

- To provide general guidance on scientific and quality aspects of signal management for VMPs;
- To describe the roles, responsibilities and procedural aspects of the EU signal management process for VMPs.

This module is applicable to VMPs authorised in the EU irrespective of the authorisation procedure (centralised or national procedure, including mutual recognition, decentralised and subsequent recognition procedures) and registered homeopathic VMPs.

This guidance is applicable to both MAHs and competent authorities in the fulfilment of their pharmacovigilance obligations and provides a regulatory framework against which pharmacovigilance inspections are conducted, ensuring consistent implementation, oversight and verification of compliance. This module should be read in conjunction with Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and Commission Implementing Regulation (EU) 2021/1281, laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products (the Implementing Regulation).

The Veterinary Good Pharmacovigilance Practices (VGVP) Module on Signal Management has been revised based on the collective experience gained from all stakeholders involved in the signal management process. It aims to provide a structured and practical framework for the identification, evaluation and management of safety signals related to VMPs. The use of artificial intelligence tools in signal management will be covered in a separate guidance document.

This revision aligns with international standards and the Veterinary Union Pharmacovigilance Database – Best Practice Guide (BPG) and supports a harmonised, transparent and scientifically sound approach to signal management. It also integrates the legal framework established by Regulation (EU) 2019/6, particularly Article 81(2), which outlines the obligation to take appropriate action when new information affects the benefit-risk balance of a VMP.

A key concept in this module is the 'effect on the benefit–risk balance', defined as any new information, data or scientific interpretation that may influence the established understanding of a product's safety or efficacy profile[1]. When such information emerges, MAHs are required to evaluate its potential impact on the benefit–risk balance and determine whether regulatory or other actions are warranted.

This module outlines the key steps in signal management, from detection to decision-making and provides guidance on how to document and communicate findings effectively. This revision reflects current best practices and incorporates insights from real-world pharmacovigilance activities. It supports a proactive, consistent and scientifically sound approach to signal management. The module

[1] See also: Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products (EMA/CVMP/248499/2007 – Rev.1)

emphasises the importance of clinical judgement, qualitative data review and transparent decision-making throughout the signal evaluation process.

The term 'clinical signs' is used in this document in line with general understanding/ common terminology and in the context of this guideline also refers to symptoms reported in humans.

Examples are provided in grey boxes throughout the text to aid understanding. They are used only to illustrate complex concepts and should never be considered an exhaustive list of possible scenarios.

1.1. Definitions

1	**ABON system**	A causality assessment system previously used in European veterinary pharmacovigilance to classify the likelihood of a causal association between a veterinary medicinal product and an adverse event.
2	**Adverse event**	Adverse events are defined in Article 73(2) of Regulation (EU) 2019/6. The term adverse event implies that it is suspected. 'Adverse event' may also be used in veterinary pharmacovigilance to describe events included in the product information.
3	**Amendment of the product information**	A type of regulatory action to the authorised product information to reflect updated knowledge, including additions, modifications or removal of existing information as authorised by the competent authorities.
4	**Annual Statement**	A submission made in IRIS at least annually. It is the practical solution for MAHs to comply with the requirement set out in Regulation (EU) 2019/6 Art. 81(2) to 'record, at least annually, all results and outcomes of the signal management process, including a conclusion on the benefit-risk balance'.
5	**Case series**	A group of individual case reports related to the same or similar event and product, analysed collectively.
6	**Causal association**	The likelihood that a veterinary medicinal product caused an adverse event or contributed significantly to the occurrence of it.
7	**Causality assessment**	A structured evaluation of the likelihood that a veterinary medicinal product caused or contributed to an adverse event.
8	**Close monitoring**	Enhanced pharmacovigilance activities applied to a signal for which the available evidence remains insufficient to warrant implementation of risk minimisation measures at this point in time, but which is subject to continued assessment to determine the need for future action and where new information is expected within a reasonable time frame. Deliberate effort is made to seek additional information in order to reach a conclusion. Submission of updates to a signal under close monitoring is expected at least annually. See section 2.5.2.
9	**Concurrent products**	Medicinal products that are administered or used at the same time or in close temporal proximity and that may contribute to or influence the occurrence of an adverse event. See also co-reported product.
10	**Confounding factor**	A variable that may influence the observed association between a product and an adverse event.
11	**Co-reported products**	Medicinal products that are reported in the same adverse event report, regardless of their temporal relationship or suspected involvement. See also concurrent products.

12	**Data lock point**	The point in time up to which data is included in a signal assessment or the last date covered by an annual statement.
13	**Dechallenge**	The withdrawal of a veterinary medicinal product, or in some cases a reduction in dose, following the occurrence of the adverse event of interest.
14	**Disproportionality in adverse event reporting**	A method used to identify whether an adverse event is reported more frequently for a specific product or substance than would be expected, typically based on comparison with other products in a database. Many different methods are available to determine disproportionality in AE reporting.
15	**Dose–response relationship**	When a higher dose or prolonged treatment leads to an increased occurrence of the event, or to increased severity of the event.
16	**Educational material**	Targeted materials designed to inform and guide users or animal healthcare professionals to reduce risks and ensure the safe and appropriate use of a veterinary medicinal product.
17	**Follow-up assessment of a signal**	A subsequent assessment of a signal under close monitoring, where newly available information is assessed in context of the cumulative data.
18	**Inflated disproportionality**	When a bias falsely increase disproportionality, inflating it above the true level of disproportionality.
19	**Lack of expected efficacy (LEE)**	A situation in which a veterinary medicinal product does not achieve the intended therapeutic effect under the approved conditions of use, as reflected by treatment failure or insufficient clinical response.
20	**Masking of disproportionality**	When a bias falsely lowers disproportionality, masking the true level of disproportionality.
21	**Medically Important Terms (MIT)**	The MIT list comprises VeDDRA PTs that correspond to medical conditions which are commonly involved in suspected adverse events across different pharmacological or therapeutic classes, or which are considered medically important independently of any established causal association with a veterinary medicinal product, due to their seriousness or potential impact on animal health or welfare, public health, user safety or the environment.
22	**Medically linked VeDDRA term**	VeDDRA terms that are conceptually or clinically linked to the same adverse event or underlying condition, representing different manifestations, stages, complications or descriptors of a shared pathophysiological process.
23	**New aspect of a known risk**	Information relating to a known adverse event, such as changes in frequency, severity, outcome, affected population or conditions of occurrence, which is not described in the currently approved product information.
24	**New risk**	An adverse event or risk associated with a veterinary medicinal product which is not described in the currently approved product information.
25	**Non-validated signal**	A signal for which the signal validation process could not verify that the available data was of sufficient quality and substance and/or justify further investigation of the possibility of a causal association between the product(s)/substance(s) and the suspected adverse event(s) or where the events are considered adequately described in the product information.

26	**Pharmacovigilance Alert**	Any suspected unexpected serious risk which may require urgent regulatory action and communication by the MAH, or the competent authorities as referred to in Article 129, Article 130 and Article 134 of Regulation (EU) 2019/6.
27	**Rechallenge**	The reintroduction or dose increase of a veterinary medicinal product after a dechallenge to assess whether the adverse event reoccurs or worsens.
28	**Refuted signal**	A validated signal for which, following further assessment, a causal association is not supported by the available evidence at the time of assessment.
29	**Regulatory action**	An intervention or decision arising from signal assessment and the evaluation of the benefit–risk balance, intended to address identified or potential risks associated with a veterinary medicinal product and to ensure its safe and effective use. A regulatory action can be initiated by the MAH or the responsible competent authority.
30	**Reporting incidence**	An estimate of the frequency of an adverse event, based on number of reports in relation to estimated exposure (in accordance with the guideline on calculation of dose factor).
31	**Reporting odds ratio (ROR)**	A quantitative measure used in pharmacovigilance to detect disproportionate reporting, comparing the odds of reporting a specific adverse event for a given product with the corresponding odds for all other products in the database.
32	**Risk based approach**	An approach in which the methodology, extent and frequency of pharmacovigilance activities are determined based on factors such as product characteristics, time on the market, safety profile and identified and potential risks and the need for additional information.
33	**Risk characterisation**	The process of describing the nature, severity, frequency and conditions of occurrence of a risk based on the totality of available evidence.
34	**Risk minimisation measures**	Interventions intended to reduce the occurrence, severity or impact of adverse events associated with a veterinary medicinal product through risk communication or other actions.
35	**Routine pharmacovigilance monitoring**	The ongoing and systematic surveillance of safety information for a veterinary medicinal product as part of standard pharmacovigilance activities, aimed at detecting, evaluating and managing potential risks.
36	**Severity**	The intensity of an adverse event, reflecting the degree of deviation from normal clinical status (e.g. mild, moderate or severe), without implying its medical significance or outcome.
37	**Signal**	Information that arises from one or multiple sources, including observations and studies 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 (Art. 1(c) of CIR (EU) 2021/1281). 'New' should be understood as compared to the currently approved product information.
38	**Signal assessment**	The process of evaluating a validated signal through a comprehensive and structured review of all available data in order to assess the likelihood of a causal association and to support decision-making on appropriate action, if necessary.
39	**Signal detection**	The process aimed at identifying new potential signals through monitoring of post-authorisation safety data to identify patterns which could suggest a new potential risk or a new aspect to a known risk.

40	**Signal of disproportionate reporting (SDR)**	Signals of disproportionate reporting (SDRs) refer to statistical associations between veterinary medicinal products and suspected adverse events. It is important to separate the concepts of 'disproportionate reporting' in general from the specific concept of an SDR. The difference is that the latter reaches a pre-defined 'level of disproportionality'. The criteria used to define an SDR are often specific to the database used for signal detection and the method used to calculate disproportionality.
41	**Signal outcome**	The final conclusion of signal assessment reflecting the outcome and the subsequent proposed actions or follow-up, if necessary.
42	**Signal prioritisation**	A continuous process aiming to evaluate the potential impact of a signal in comparison to other signals in order to identify relevance, determine urgency and perform efficient signal management through a risk-based approach.
43	**Signal requiring risk minimisation measures**	A validated signal for which signal assessment supports a likely causal association between the veterinary medicinal product and the adverse event. The signal is considered to warrant risk minimisation measures.
44	**Signal trigger**	The source from which a potential signal originates, initiating further evaluation through the signal management process.
45	**Signal validation**	An initial screening of the data that triggered the potential signal, with the aim of determining whether the signal is supported by information of sufficient quality and substance to justify further assessment. Therefore, signal validation is not intended to determine causality.
46	**Supportive case**	A case report that, based on assessment of relevant clinical and temporal factors, provides evidence supporting a causal association between an adverse event and a veterinary medicinal product.
47	**Temporal association**	When the reported event(s) occurred after the time of exposure to the veterinary medicinal product(s).
48	**Time-to-onset (TTO)**	The time interval between exposure to a veterinary medicinal product and the onset of an adverse event.
49	**Validated signal**	A signal is considered validated when the signal validation process has verified that the data triggering the signal is of sufficient quality and substance to justify a need for further analysis and the event(s) of the signal are not already adequately described in the product information.

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2. Signal Management process

A 'signal' is defined as information that arises from one or multiple sources, including observations and studies 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[2].

The 'signal management process' is defined in Article 4(41) of Regulation (EU) 2019/6; in practice, this is the collective term used to describe the steps of signal detection, signal prioritisation, signal validation, signal assessment and recommendation for action (risk mitigation) as a whole and the outcome should be documented[3]. It is a structured process that should enable continuous monitoring of the benefit-risk balance of a product[4] and therefore should be conducted with a sufficient frequency to ensure timely identification, assessment and management of potential risks related to the use of VMPs.

A risk-based approach shall be applied to determine the methodology, extent and frequency of the signal management process[5]. The frequency of monitoring should be proportionate to the identified risk[4]. Use of a risk-based approach means that the following key factors should be taken into account: type of product, length of time on the market, stability of the pharmacovigilance profile, identified and potential risks and the need for additional information[5]. The rationale for the chosen approach shall be documented[3] (see also section 5).

Application of a risk-based approach is not only fundamental but also dynamic throughout the signal management process. Rather than applying a fixed set of criteria, a risk-based approach involves continuously evaluating the context and evolving nature of the signal. By integrating the above-mentioned key factors, the process ensures that clinical relevance and potential impact on public health guide prioritisation and decision-making. This flexible strategy allows for more efficient use of resources, focusing efforts on signals that pose the greatest potential risk or require urgent attention.

[2] Article 1(c) of the Commission Implementing Regulation (CIR) EU 2021/1281
[3] Article 17(1) of CIR (EU) 2021/1281
[4] Article 77(4) of Regulation (EU) 2019/6
[5] Article 17(3) of CIR (EU) 2021/1281

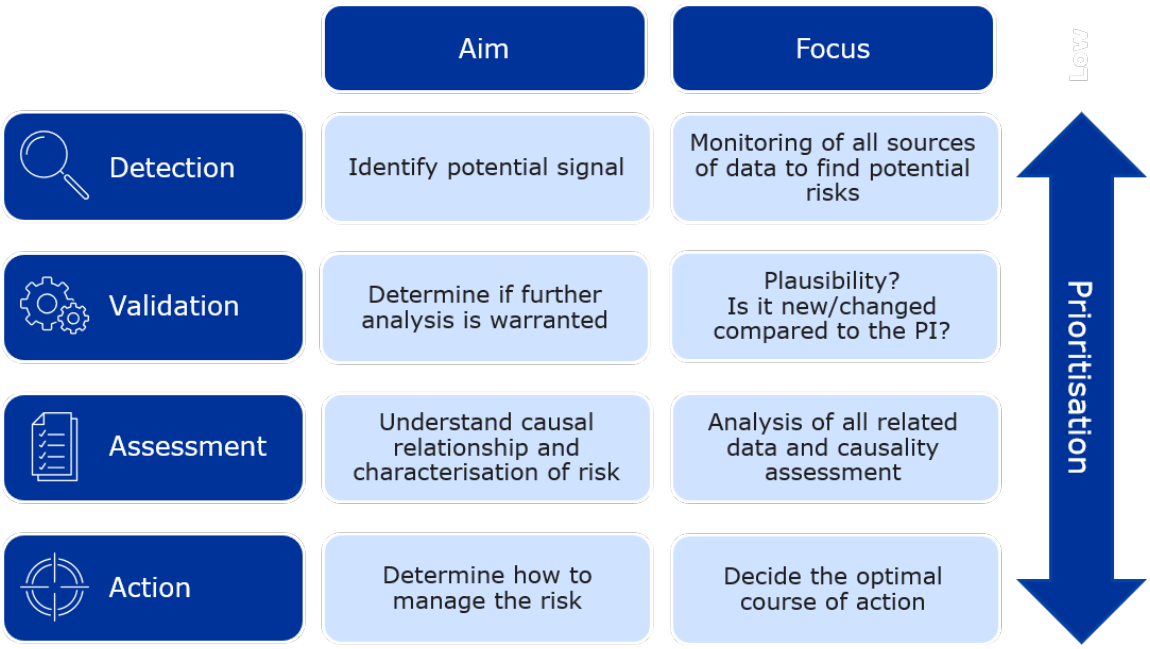

Figure 1: Signal management process

Throughout all phases of signal management, clinical judgement plays a critical role. It is essential not only in interpreting data but also in selecting what data may support a potential signal. The ability to discern meaningful patterns and assess clinical relevance is key to ensuring that signals are neither overlooked nor overestimated.

Signal Detection:

The detection phase aims to identify new potential signals. It focuses on identifying new or changed risks through detection of abnormal patterns or monitoring of new information. Signal detection should be objective and non-biased and based on previous knowledge of the product and the pharmacological and biological characteristics of the active substance. It should ideally be based on a combination of quantitative (e.g. disproportionality, number of cases, number of reacting animals) and qualitative (e.g. review of case narratives, literature reviews) methods.

Signal Prioritisation:

Signal prioritisation is an integral part of the signal management process and may be performed continuously throughout the entire process. Prioritisation aims to evaluate the potential impact of a signal in comparison to other signals in order to identify the most relevant signals, determine their urgency and perform efficient signal management through a risk-based approach.

Signal Validation:

Signal validation aims to determine if additional analysis of a potential signal is warranted. It focuses on determining whether the potential signal is supported by data of sufficient quality and substance to justify further assessment.

Signal Assessment:

Signal assessment aims to decide whether any action is necessary. Through a broader and deeper analysis of all available data pertaining to the signal, focus is placed on understanding the causal relationship between the potential risk and the VMP and further characterisation of the risk.

Outcomes and Risk minimisation measures:

This stage focuses on determining how to manage the potential risk and deciding on the optimal course of action. It involves analysing the potential risk in relation to the benefits of the product, recommending appropriate risk minimisation measures, if necessary, as well as documenting the outcome of the signal management process.

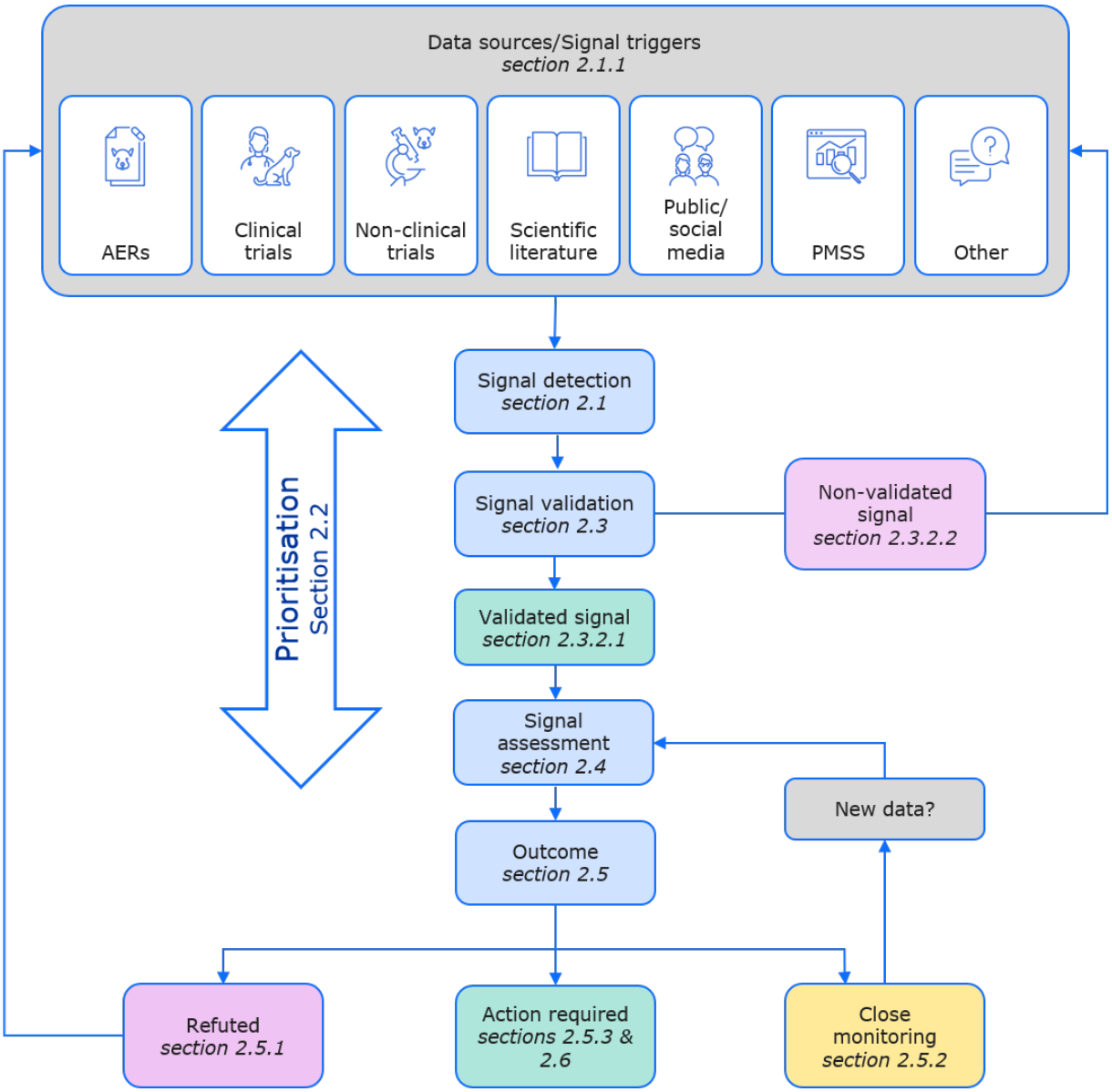

Figure 2: Flow diagram of signal management process

2.1. Signal detection

Signal detection is the process of monitoring post-authorisation safety data for information that could suggest a new potential risk or a new aspect to a known risk. Potential risks may be related to animal or public health or to protection of the environment[6]. The detection phase is focused on the

[6] Article 4(41) of Regulation (EU) 2019/6

observation of new potential risks or new aspects and/or change in reporting patterns. The detection phase generally does not require deep analysis of data.

Irrespective of the frequency of monitoring according to the chosen risk-based approach for a product, MAHs are obliged to conduct a signal detection analysis for each of their active substances or products in the Union pharmacovigilance database (UPhV-database) at least once a year[7]. In practical terms, the reference to UPhV-database means the EudraVigilance Veterinary Data Warehouse (EVV-DWH) in this context. This analysis should be performed within 2 months of the annual due date (see also section 3.1.1.2).

Signals may be detected from any source, using a variety of methods. This section will summarise the most important considerations relevant for signal detection.

2.1.1. Signal triggers

The source of a detected signal is also called 'the signal trigger'. Signals can arise from any source, including e.g. from case reports, clinical trials, scientific literature or public/social media. Potential signals should not be dismissed or validated based solely on their source. Regardless of the original source of a potential signal, other data sources may be investigated for relevant evidence during further assessment (see also section 2.4). Depending on the source of a potential signal, different methods may be used to determine whether it should be treated as a signal (see also section 2.1.2).

Signal triggers for any signal progressing on to the validation stage should be recorded in a traceable manner.

Below are examples of the more common signal triggers. The list should not be considered exhaustive.

2.1.1.1. Adverse event reports:

The most common signal trigger is adverse event (AE) reports. AE reports are the basis of adverse event databases such as the UPhV-database (EVV-DWH) or the MAHs' own safety databases. Many MAHs maintain their own pharmacovigilance databases, which may be used for signal detection in addition to the UPhV-database (EVV-DWH). AE reports in databases may be spontaneous or solicited (e.g. from clinical trials) and may concern one or more suspected adverse events, lack of expected efficacy, medication errors or a combination of these. The threshold for when AE reports trigger a signal may vary and different methods can be applied to detect signals in databases (see section 2.1.2.1).

2.1.1.2. Scientific literature:

Monitoring of scientific literature can be used to detect potential signals arising from e.g. clinical trials, non-interventional studies, literature reviews or meta-reviews, published case studies or case series or potential signals pertaining to the active substance or to a class of substances (e.g. NSAIDs, beta-lactam antibiotics etc.). Some of these types of literature may also be found as case reports in adverse event databases.

2.1.1.3. Public/Social Media:

Monitoring of public and social media is usually part of the collection and recording of adverse events as AERs in the UPhV-database (see also VGVP module on collection and recording of suspected adverse

[7] Article 17(7) of CIR (EU) 2021/1281

events for VMPs[8]). In such cases, information from these sources is included in the signal management process as AERs.

However, there may be situations where the information detected is not suitable for creation of AERs for submission into the UPhV-database but may still constitute a signal trigger (i.e. justify further investigation). It may be relevant to progress a signal from such a source through the signal management process, to either be able to ease public concern or to ensure proper risk mitigation measures are in place. Swift and thorough management of signals from media sources may also contribute to maintain trust from the public. However, such signals should, like all other signals, be further supported by other evidence in order to progress through the different steps of the signal management process.

2.1.1.4. Other sources

Potential signals may be triggered from other sources than the ones mentioned above. Such sources include, but are not limited to:

- Requests for signal submissions from the CVMP or a national competent authority in the EEA.
- Alerts, communications or reports from other regulatory authorities (non-EEA).
- Communication from manufacturers or distributors (potential impact on quality).
- Veterinary toxicology centres or human poison control centres.
- Academic poster presentations, conferences or collaborations.
- Environmental monitoring (e.g. for antiparasitics with wildlife impact).
- Slaughterhouses (residues).
- Signals arising from other signals; when patterns or associations noted during assessment of one signal leads to other signals. This occurs most often with signals that are new aspects of known risks but may also occur in more complex situations for new risks (see example 1). Similarly, signals of interactions between two drugs may also arise from noticing patterns of co-reported drugs during assessment of broader signals.
- Direct communication from the public (e.g. a veterinarian, pet owner or farmer) providing information of a nature not suited for a regular case report (e.g. questions, observation of unspecific trends, complaints, etc.).
- Ongoing post-marketing clinical trials.

Example

1: A signal of an event, e.g. seizure, is suspected to be more serious in a subpopulation of the target animal species which also have impaired renal function. This is suspected due to a pattern of co-reporting of the event with kidney-related VeDDRA terms. The signal assessment should therefore include an assessment of both the overall drug-event-combination (all reports of any type of seizure in the entire population) and a specific assessment of the drug-event-combination in the specific subpopulation (i.e. reports in animals who also have renal impairment).

[8] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-collection-recording-suspected-adverse-events-veterinary-medicinal-products_en.pdf

2.1.2. Methods for signal detection

Signals can arise from many different sources and may concern an array of different topics; hence different methods may be needed to ensure that all relevant signals are detected. Signal detection benefits from the use of a combination of quantitative and qualitative methods.

- Quantitative methods are mostly used to detect signals in adverse event databases and examples include; use of disproportionality measures, counting of reports, trend analyses and other forms of mathematics/statistics applied to data. In some circumstances, quantitative methods may also be applied in a limited manner to other signal sources. For example, trend analyses of (social) media reports, scientific publications or other external information sources may help identify potential emerging safety concerns requiring further evaluation.
- Qualitative methods are based on review and interpretation of non-numerical information, e.g. screening of case narratives or abstracts of scientific literature. They are often applied during detection of signals arising from other sources than adverse event databases. However, qualitative methods may be applied during signal detection in databases as well, although caution should be taken to not cross over to signal validation (see section 2.3). During signal detection, qualitative review should focus on identifying potential signals and more detailed evaluation should be left for the validation and assessment steps.

Following detection, it is important to prioritise signals before moving on to validation (see section 2.2).

Before initiating signal detection, prior knowledge about the following aspects is expected: product information, the mechanism of action of the product/substance in question, the outcome of previous signal management activities and any other safety-related activities or procedures and any other relevant pharmacovigilance data of which the MAH can reasonably be expected to be aware.

2.1.2.1. Signal detection in adverse event databases

Signal detection in adverse event databases should generally be performed at the VeDDRA level of preferred terms (PTs).

However, it may occasionally be appropriate to perform signal detection at a higher level (HLT or SOC) (see example 2). Conversely, there are situations where it may be relevant to stratify into LLT level because certain LLTs belonging to a PT are already listed in the product information (see example 3) (see also sections 2.2.1.6 and 2.2.1.8 on signal prioritisation and section 2.3.1.2 on signal validation). The VeDDRA system is structured around organ classes, but sometimes signals may concern 'syndromes' or collections of clinical signs from different organ systems, or there may be more than one way to code the same event, leading to a need for combination of several terms to catch all relevant reports. In such situations, it may be necessary to combine several similar PTs or LLTs from different SOCs into one signal to allow for detection of broader signals or account for differences in coding of reports (see example 4).

Whether there is a need to broaden or narrow a particular search at the signal detection stage will need to be determined based on the clinical picture on a case-by-case basis.

It is generally not advised to combine different species in the same signal. However, there may be situations where this can be relevant (e.g. product use errors, prescription errors, etc.).

Examples

2: Since similar events may be coded differently, it may be relevant to consider a high level group of VeDDRA PTs together, e.g. an event where the animal experienced local swelling redness and pain at the injection site, may be coded with any combination of 'injection site erythema', 'injection site inflammation', 'injection site lesion', 'injection site mass NOS', injection site pain' and/or several other PT's, leading to a need for analysis of all 'Injection site reactions' (HLT) together.

3: In a situation where the PI includes the LLT 'enteritis', it may be relevant to monitor other LLTs belonging to the PT 'enteritis', either because they are more specific than what is currently in the PI, e.g. 'lymphoplasmacytic enteritis', or more serious, e.g. 'haemorrhagic enteritis'.
Or, it may be relevant to monitor only specific LLTs out of the 102 LLTs belonging to the PT 'Lack of efficacy' due to properties of the product. For example, it may only be necessary to monitor 'Lack of efficacy – Parvovirus' and the unspecified LLTs 'Lack of efficacy NOS' and 'Partial lack of efficacy' in case of a vaccine against parvovirus.

4: 'Pancreatitis' (digestive tract disorders SOC) may be combined with 'Elevated pancreatic enzymes' (investigations SOC), or
'Reluctant to move' (systemic disorders SOC) may be combined with 'Lameness' and 'Joint pain' (musculoskeletal disorders), or
PT's from the SOC 'Application site disorders' may be relevant to combine with PTs from the SOC 'Ear and Labyrinth disorders' for an ear product, or
PT's 'Anaemia', 'Haemolytic anaemia', 'Immune mediated haemolytic anaemia' and 'Aplastic anaemia' for a signal on anaemia to capture all relevant cases.

Number of cases or reacting animals

During signal detection in databases the first parameter to consider would be number of cases reporting the different VeDDRA terms, both cumulatively from the date of authorisation and/or in a specified time period (e.g. since the data lock point of the last annual statement). Special attention should be paid to what is most commonly reported for the product and any observed changes in such patterns over time. The number of reacting animals should also be taken into account. For reports in species usually kept in herds, the number of reacting animals should be interpreted together with the number of cases (representing independent herds), as a large number of reacting animals from a single herd may provide different information from similar events reported across multiple independent herds.

VeDDRA terms with a high cumulative number of reported cases or a large number of reacting animals should be considered as potential signals. Such VeDDRA terms may not necessarily present with disproportionate reporting due to masking effects (see next sub-section), yet their volume of reports can still be clinically relevant and warrant further assessment.

Disproportionality in reporting

The concept of disproportionality in reporting is mostly used when analysing case reports in adverse event databases such as the UPhV-database (EVV-DWH) or the MAHs' own safety databases. When an adverse event is described as having 'disproportionate reporting', or as being 'disproportionately reported' in general, it means that the drug/product event combination is reported more often than

expected; i.e. the adverse event in question is reported more often in combination with the product/drug in question compared to the average for all other products in the database.

The difference between the concept of 'disproportionate reporting' in general and the specific concept of a 'Signal of Disproportionate Reporting' (SDR) is that the latter reaches a pre-defined 'level of disproportionality'. The criteria used to define an SDR are often specific to the database used for signal detection and the method used to calculate disproportionality, which is why it is important to document which database an SDR was detected in and the specific criteria/threshold values and method for calculation of disproportionality it uses.

It should be noted that disproportionate reporting does not automatically imply causality. It is a mathematical tool flagging up product-event pairs and disproportionate reporting can be seen for a product-event pair with no causal association, while it may be absent for a product-event pair with a well-established causal association (see also section about factors influencing the ROR below). Detection of disproportionate reporting should therefore always be combined with qualitative review of data during further assessment.

Methods of calculating disproportionality

When performing signal detection, disproportionality measures should generally be evaluated based on cumulative data, but comparison of disproportionality between different time periods may be relevant to identify trends and changes in disproportionality.

Disproportionality can be calculated using different methods such as Proportionate Reporting Rate (PRR), Information Component (IC025) or Reporting Odds Ratio (ROR). The three mentioned methods are all based on a 2x2 contingency table:

	Reports of adverse event of interest	Reports of other adverse events
Reports with drug/product of interest	a	b
Reports with other drugs/products	c	d

Table 1: 2x2 contingency table

Note that the contingency table only states the number of reports and therefore does not take into account that reports may have multiple reacting animals. Therefore, in species with herd level reports, it may be necessary to apply other quantitative measures during signal detection such as number of reacting animals or use more qualitative methods such as case review.

The UPhV-database (EVV DWH) uses ROR for calculation of disproportionality. ROR can be calculated from the contingency table using a simple formula:

$$ROR = \frac{a/c}{b/d}$$

If ROR is precisely 1, the adverse event of interest is reported with the drug/product at a rate identical to the average for all products in the database. Consequently, if ROR is greater than 1, there is disproportionality in the reporting. However, the ROR alone is not sufficient to judge whether an association between a product and an adverse event is statistically robust. This is why 95% confidence intervals (CIs) are calculated and displayed as ROR(–) and ROR(+). A useful rule of thumb is based on the lower bound:

If ROR(–) > 1, the association is considered *statistically significant*, meaning the reported event occurs more frequently than expected.

Other measures of disproportionality may be used by MAHs during signal detection. MAHs should justify and document their choice of method(s) and include a description of those methods, including the underlying principles and any criteria and thresholds applied.

Criteria for SDRs in the UPhV-database (EVV DWH)

In EVV-DWH, an SDR is defined as a signal fulfilling all the following criteria:

- ROR ≥ 2
- ROR(-) ≥ 1
- Cumulative number of reports ≥3 for Medically Important Terms (MI terms, see section 2.2.1.3) or ≥5 for all other VeDDRA terms.

SDRs can be a useful tool to detect signals, but not all VeDDRA terms highlighted as SDRs are necessarily signals; for example, terms highlighted as SDRs may already be listed in the product information (see sections 2.2.1.6 and 2.2.1.8 on signal prioritisation and section 2.3.1.2 on how to determine coverage by the PI during signal validation). In addition, there are factors potentially affecting disproportionality which should be considered, as described below. Further signal validation may also end in non-validation of an SDR (see section 2.3 on signal validation). See also 'Veterinary Union Pharmacovigilance Database – Best Practice Guide'[9] and 'Veterinary Pharmacovigilance EVVET - Data Warehouse user manual'[10].

Factors affecting disproportionality

Certain factors beyond true disproportionate reporting may affect disproportionality. When such factors lead to an increase in the ROR, this is referred to as 'artificial inflation of disproportionality'. Conversely, when such factors lead to a decrease in the ROR, it is referred to as 'masking of disproportionality'. Many of these factors can affect the ROR in both directions depending on the situation. It is therefore important to consider these factors on a case-by-case basis during signal detection.

Such factors include, but are not limited to:

- Stimulated reporting: This may occur e.g. in cases of media attention on a certain product or adverse event or immediately following publication of new warnings. Stimulated reporting may artificially inflate the ROR.
- Increase in exposure (sales): Increased exposure may lead to increased disproportionality (i.e. artificial inflation), although the reporting incidence remains stable.
- Duplicate reports: A high number of duplicate reports in a database may both artificially inflate or deflate disproportionality. If there is a high number of duplicates only on the specific term of interest that would lead to an artificial inflation of the ROR, while the reverse situation (high number of duplicates for other adverse events or other products) could lead to masking. In the UPhV-database (EVV DWH) duplicates are considered to most often lead to inflation of the ROR.
- Co-prescription (bystander products): Drugs/products that are often prescribed with other drugs with a more high-risk safety profile or to animals with many co-morbidities may experience artificially inflated disproportionality measures.

[9] https://www.ema.europa.eu/en/documents/other/veterinary-union-pharmacovigilance-database-best-practice-guide_en.pdf
[10] https://www.ema.europa.eu/en/documents/other/evvet-data-warehouse-user-manual_en.pdf

- Confounding by indication: When there is disproportionality of clinical signs which may be related to the indication of the product/drug the ROR may be either artificially inflated or masked. Artificial inflation occurs in a situation where signs of the underlying disease are mistakenly reported as AEs, while masking occur in a situation where AEs are not reported as they are falsely assumed to present signs of the underlying disease.
- Rarity and common/general clinical signs:
    - Rarity may artificially inflate ROR in certain situations; for example, for rare product types, disproportionality may be artificially inflated for certain VeDDRA terms which, by nature, are linked only to a small subset of products e.g. implant site reactions occur only with products that are implants. In such situations, it may make sense to also determine disproportionality in relation to a smaller subset of similar products rather than all products in the database. However, the robustness of calculations is compromised when based on very small datasets.
    - Conversely, clinical signs (VeDDRA terms) that are non-specific and may have many causes, or signs often related to drugs or specific classes of drugs may be so widely reported on all products/drugs in the database, that differences become difficult to detect (masking). Hence, the ROR for an event which is commonly occurring for many other products but only occurs very rarely for the product of interest, may be masked by the large amounts of reports present for other products.
- Composition of the database: If a database includes only a limited number of products, or mostly a few specific types of products (e.g. mostly antiparasitics, mostly vaccines etc.) this may lead to both artificial inflation and masking of events, depending on the situation. This is very important to consider when MAHs perform disproportionality analyses in their own safety databases.

These and any other potential factors which may affect disproportionality should be considered when appropriate during interpretation of disproportionality in signal detection.

Screening of case narratives

Screening of case narratives (qualitative review) may be necessary in some cases, to determine if there is a signal or not. For example, for signals concerning large flocks/herds of poultry or schools of fish or other production animals, there may be few cases concerning very large number of animals, leading to a need for review of the case to determine if a signal is present. Another example may be in cases of more complex signals involving new aspects of known risks or concerning more specific subpopulations or other special circumstances of the signal that cannot readily be identified through quantitative methods alone. Sometimes, such complex signals are triggered from screening or reviewing of case narratives during validation or assessment of other signals (see example 5).

Example

5: When reports of similar events are coded under different VeDDRA terms they may not generate a clear quantitative signal, e.g. situations of syndromes or newly arising disorders, where no precise VeDDRA terms exist yet, where there is no consensus on nomenclature in the veterinary field, or where general knowledge of the condition may be low, can lead to reports of varied clinical signs related to the syndrome/disorder rather than the diagnosis itself. Review of the case narratives reveals that the events are described similarly, despite differences in coding. Identification of such a recurring pattern may trigger further investigation of a potential signal.

Identification of potential quality and batch-related issues through signal detection

Signals related to one or more specific batches of a VMP are often detected from adverse event databases by recognition of certain patterns of reporting. Examples of important patterns to monitor for in adverse event databases are included below:

- Temporal or geographical clustering: A cluster of adverse event reports linked to the same batch number within a short period or localised area is a key indicator of a potential batch-related issue (see examples 6-7).
- Increased frequency of a specific adverse event associated with a single batch: An unusual increase or clustering of reports of a particular adverse event associated with an individual batch, compared to other batches or historic data, indicates a batch related issue (see examples 8-9).
- Signs of contamination or sterility failure: An unusual pattern or clustering of adverse events suggestive of contamination or loss of sterility in the suspected VMP may indicate a quality defect or batch-related issue (see examples 8 and 10-11).

The above list should not be considered exhaustive and other methods may be applied in addition to these for detection of quality and batch-related issues.

Examples

6: Multiple reports within 24–72 hours following administration of a specific batch.

7: Reports originating from the same region or distributor, all citing the same batch.

8: Higher frequency of anaphylactic reactions linked to a specific batch.

9: Sudden increase in 'lack of efficacy' reports linked to a specific vaccine batch.

10: Several reports, associated with the same batch, describe injection-site abscesses, swelling and local infections occurring shortly after administration. Although the individual events differ, the clustering of reports concerning a single batch may suggest contamination or loss of sterility and warrant further investigation.

11: Injection-site infections emerging across multiple animals after use (of the same batch).

2.1.2.2. Monitoring of scientific literature:

Monitoring scientific literature is part of the signal management process[11]. Its purpose extends beyond searching for adverse event reports and it should be considered a tool to keep up with current scientific knowledge.

Monitoring of scientific literature usually involves performing searches for literature in databases and specific journals if applicable and/or setting up automatic notifications on such platforms. The MAH should establish the most relevant source(s) of published literature for each product. In order to narrow down the search, relevant filters should be applied.

Monitoring of scientific literature is ideally performed on active substance level[12]. Active substances may have several different names and/or spellings, which should be taken into account when performing literature searches; it is recommended to leave out names of salts (e.g. 'hydrochloride'). In certain cases, it may make sense to also monitor closely related active substances (e.g. prednisone, prednisolone and methylprednisolone), while for vaccines, it may be necessary to broaden the search strategy to include terms related to the vaccine's disease indication and relevant immunopathological mechanisms, rather than relying exclusively on specific antigen names. Further filters may be applied, but care should be taken to avoid narrowing the search too much.

Consideration should be given to scientific literature concerning potential environmental concerns related to the active substance of the VMP or its metabolites as well as concerns regarding resistance for antimicrobials and antiparasitic agents as these issues are difficult to detect through adverse event reporting alone.

Once search results have been retrieved, an initial screening of abstracts and/or the whole article should be performed in order to determine if the article in question is relevant to the product or the active substance(s) of the product and contains information on safety or (lack of) efficacy which is either new or may represent a new aspect of a known risk (e.g. frequency, outcome, further characterisation etc). Thorough assessment of methods and validity of the articles is not necessary during signal detection but may be applied during validation (see section 2.3.1.3).

2.1.2.3. Monitoring of other sources

Although pre-emptive monitoring is not possible for all potential alternative sources of signals (e.g. spontaneous communication directly to the MAH), others (e.g. social media) are often monitored to some extent as part of the collection and recording of adverse events. There may be situations, where the information detected from other sources (see also sections 2.1.1.2 - 2.1.1.4) is not suitable for creation of AERs to be entered into the UPhV-database, but may in itself constitute a signal trigger (i.e. justify further investigation). Examples of additional sources which may be monitored are:

- Non-peer-reviewed literature sources; e.g. public media targeting veterinarians or other animal professionals in the countries of authorisation, national media in the countries of authorisation, etc.
- Social media; particularly the MAH's own social media platforms.
- Relevant websites or online forums, e.g. websites of EMA, NCAs or the MAHs own website.
- Relevant veterinary or other scientific conferences.

[11] Article 81(1) of Regulation (EU) 2019/6
[12] Article 13(3) of CIR (EU) 2021/1281

Pharmacovigilance staff should be sensitised to treat such information, when becoming aware of it, as a potential signal trigger. It is recommended to include this in internal process documents for e.g. monitoring of social media. The reasoning for it to be treated as a signal trigger should be recorded as well as the date it was decided that the known information should be looked into further (and hence classified as a trigger).

2.2. Signal prioritisation

Signal management should utilise a risk-based approach proportionate to the identified risk[5]. It is therefore important to have an established and documented process of signal prioritisation throughout the process[2].

Signal prioritisation should be a continuous process throughout all steps of the signal management process and is often carried out in parallel with each step. In many cases, signals may move directly from detection through the validation phase and sometimes even through the assessment phase. However, where multiple potential signals are identified simultaneously, prioritisation may be necessary to ensure that the signals with the greatest potential impact on safety are progressed to the next stage. If a potential signal is not prioritised at this point in time, the potential impact on safety should be carefully considered. Pharmacovigilance alerts should always be prioritised.

Signal prioritisation during and following signal detection is essential to decide:

1. Which signals to start a validation on first,
2. Their urgency, both in general and in relation to other signals,
3. The extent of continued monitoring of the issue in the future.

Rationale behind prioritisation of signals should be documented.

2.2.1. Factors to consider during prioritisation

The factors listed in this section can help determine impact on overall safety, as well as urgency of the signal and should be considered during prioritisation. Not all factors listed in this section may be relevant for all signals during all steps of the signal management process, e.g. due to lack of knowledge, or because another factor already determined the conclusion on the prioritisation.

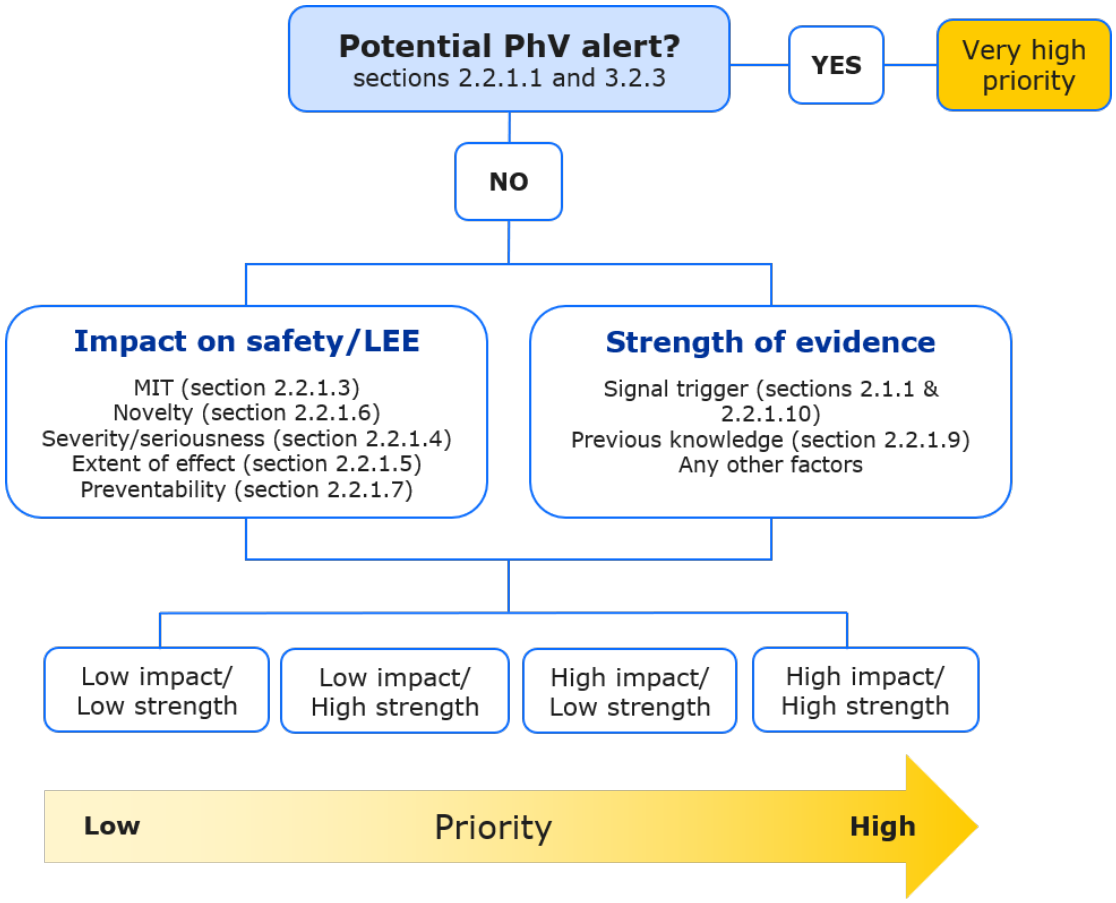

Figure 3: Decision tree for prioritisation during signal detection
Priority is determined by weighing impact on safety against the strength of evidence. All three exist on a continuum. Safety should always be weighed highest.

2.2.1.1. Pharmacovigilance Alerts (PhV Alerts)

First and foremost, it is important to determine whether a potential signal could be a PhV Alert. A Pharmacovigilance alert is defined as any suspected unexpected serious risk which may require urgent regulatory action and communication by the MAH or the competent authorities as referred to in Article 129, Article 130 and Article 134 of Regulation (EU) 2019/6.

When a MAH becomes aware of a PhV Alert from any source, they should notify the competent authority(ies) of the Member State(s) where the VMP is authorised or the Agency in case of centrally authorised products. This should be done as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source constitutes a PhV Alert. See also section 3.1.3.

In some cases, PhV Alerts may concern or involve a quality issue, or recalls of specific batches may be necessary. However, a batch recall in itself, i.e. without evidence of a safety risk, is not considered a PhV Alert.

See examples 12-16 of what may be considered PhV Alerts and examples 17-18 of what is not a PhV Alert.

Examples of potential Pharmacovigilance Alerts

12: Major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpected increase in rate of fatal or life-threatening adverse events. Where applicable, separate (national) regulatory reporting requirements for studies should also be considered.

13: Major safety issues identified from any source, which may lead to considering a contraindication, a restriction of use of the VMP or its withdrawal from the market.

14: Major safety-related regulatory measures outside the EU, e.g. a restriction of the use of the VMP or its suspension.

15: Major negative impact on the environment possibly caused by the use of a VMP.

16: Increased level of residues in food-producing animals that may represent a safety concern for humans. For example, detection of residues exceeding the MRL in cases where the approved withdrawal period has been respected.

Examples that should not be considered a Pharmacovigilance Alert

17: Events that are associated with the use of a veterinary medicinal product in humans as part of a suicidal attempt are not considered Pharmacovigilance Alerts. However, repeated reports of suicidal attempts or emerging patterns indicating an unusual association between a specific VMP and the adverse event may constitute a potential signal and should be evaluated through the signal management process.

18: New safety information related to quality defects or suspected falsified medicinal products which might influence the evaluation of the benefits and risks of the VMP. These should be notified in accordance with quality defect processes.

2.2.1.2. Safety (for the animal, user or environment):

For all remaining potential signals, the main focus during prioritisation should always be placed on the risk to safety (for the animal, user or the environment). Some signals are likely to affect the benefit-risk balance of a product more than others, if a causal association is considered possible in the end. This is most often correlated with the seriousness and severity (see section 2.2.1.4) of the clinical sign/disorder, but other factors may also come into play, such as size of the affected population and properties of the signal itself; e.g. number of cases and affected animals already reported, number of fatal cases etc. (see example 19).

The Medically Important Terms list (MIT-list, see section 2.2.1.3) is a useful tool when assessing seriousness and severity of a signal during the signal management process. However, the specifics of the signals should always be considered (see example 20).

The expected extent of future risk minimisation measure(s) arising from the signal may be considered for guidance, as this is usually related directly to patient safety (see example 21).

The remaining aspects in this section (2.2) can also be considered but should always be secondary to overall safety in the decision-making when prioritising potential signals for validation and further assessment.

Examples

19: A validated signal of acute renal failure which appears to occur in the entire target population (i.e. not only in a subset of the population), that already has many reported cases and a high number of fatal cases, would appear more urgent to assess for causality compared to a validated signal of mild injection site inflammation occurring in a specific breed, with no fatal cases. Both signals will need to be assessed, but the first is likely to affect patient safety the most, if causality with the product is found to be confirmed.

20: The MI-term 'Anorexia' may cover signals of great severity and/or seriousness, but could also concern less severe/serious cases of mildly lowered appetite and further assessment of a validated signal of severe 'Anorexia' in a species that is sensitive to sequela from anorexia should be prioritised higher than assessment of a validated signal of mildly lowered appetite in a less sensitive species.

21: The following questions may be considered regarding potential future risk minimisation measure(s):
If the events of the signal are concluded to be causally associated to the product, what actions would that necessitate?
Would the product information need amendment and to what extent? Addition of adverse reactions? Warnings or precautions? Additional monitoring advice? Relative or absolute contraindications?
Could there be a need to disseminate immediate information through Direct Animal Healthcare Professional Communication (DaHPC or 'Dear Doctor'-letter)?
Or is it serious enough that a suspension or revocation of the marketing authorisation may be considered?

2.2.1.3. VeDDRA Medically Important Terms (MIT)

The MIT list comprises VeDDRA PTs that correspond to medical conditions which are commonly involved in suspected adverse events across different pharmacological or therapeutic classes, or which are considered medically important independently of any established causal association with a veterinary medicinal product, due to their seriousness or potential impact on animal health or welfare, public health, user safety or the environment.

How to interpret and apply the MIT list in signal management:

Medically Important Terms (MITs) in veterinary pharmacovigilance are intended to function as a prioritisation tool within signal detection and signal management activities. These events represent medical concepts that require enhanced attention, prioritised assessment and timely regulatory follow-up, in line with a proportionate pharmacovigilance approach.

In food-producing animals, MITs additionally include VeDDRA PTs that may be associated with significant herd- or flock-level consequences (e.g. substantial productivity losses, reproductive impairment or increased mortality). Where such effects reflect or accompany medically important safety concerns, they justify prioritisation within signal detection, validation and assessment activities.

For events occurring in humans, all reports are regarded as medically important and should therefore be handled as MITs for the purposes of prioritisation and signal management, irrespective of the reported clinical term, seriousness classification or outcome.

All events that are reported as 'parent-offspring' events should be considered medically important and particularly any congenital conditions reported in this setting.

Malignant neoplastic conditions and neoplastic conditions which otherwise have a serious impact on animal health and welfare should be considered medically important on a case-by-case basis.

Detected signals involving MITs should generally be prioritised particularly in the following situations:

- Where they fulfil the criteria of a signal of disproportionate reporting (SDR) in DWH.
- Where an unusual or unexpected increase in reporting frequency or number of affected animals is observed.
- Where there is evidence of increased severity or a change in outcome (compared to the product information), such as an increase in fatal cases.

2.2.1.4. Severity and/or seriousness

Severity and seriousness are usually defined at case level. Here, severity refers to the intensity of an adverse event, e.g. mild, moderate or severe, but severity does not express anything about the medical significance of the event itself. Seriousness of an event is linked to outcome e.g. whether an event was fatal, led to hospitalisation and/or long-term harm to the patient (see example 22).

While general criteria for seriousness can be found in the VICH GL24 (Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs)), it is not possible to establish general criteria for severity, as that is affected by the sign or disorder considered.

Both seriousness and severity may be used to prioritise signals. Seriousness can be evaluated by screening for fatal cases, number of cases leading to full recovery and in some cases by clinical judgement of the VeDDRA term itself (see example 23). The MI terms described in section 2.2.1.3 above may provide guidance in the evaluation of seriousness and severity.
Severity can sometimes be estimated by looking at reported LLTs (i.e. if it is the more or less severe LLTs belonging to the PT that are mostly reported), or duration of the event, but many times a screening of narratives is necessary to evaluate whether e.g. the PT 'Anorexia' covers a transient partial loss of appetite or a more severe case of complete anorexia for a prolonged period of time.

Signals where the majority of the reported events are considered serious should be prioritised over signals concerning less serious events, although rarity of the event should also be considered here (see section 2.2.1.5).

Similarly, signals reporting more severe events should be prioritised higher compared to signals reporting mild versions of the same event. Severity will, however, always need to be weighed against seriousness and number of reports/reacting animals and potentially other factors, when comparing different signals.

Examples

22: For example, pruritus may be mild, moderate or severe, but a severe case of pruritus may still not always be a serious case – if the animal recovered on its own with no long-term sequelae. Conversely, severe heart failure is usually linked to serious outcome and even 'mild' heart failure may be considered serious as it is likely to have a long-term negative effect on the patient. Furthermore, a severe hypersensitivity reaction is usually serious, while a mild hypersensitivity reaction is usually not. Hence severity and seriousness are sometimes linked and sometimes not.

23: For example, 'heart failure' can be assumed to be more serious in general, compared to e.g. 'injection site pain'.

2.2.1.5. Number of reported events and effect on special populations

Signals with higher numbers of reports and/or reacting animals or signals with increasing numbers should have a higher priority. However, this should, as a minimum, be weighed against seriousness and severity and other factors may come into consideration as well.

Signals affecting certain special populations e.g. pregnant animals, very young animals, or animals of food-producing species that are close to slaughter may generally be prioritised, albeit with consideration to potential off-label use (see section 2.2.1.11). Conversely, signals affecting a very small subpopulation of animals, e.g. animals with a specific uncommon co-morbidity, may be prioritised lower if there are other, more urgent signals to perform validation on.

2.2.1.6. Novelty

Novelty of the information may also be considered in the sense that it will often be more important to progress with potential signals which may represent completely new information (e.g. a new adverse event for the product) rather than signals concerning further characterisation of an already known adverse event (new aspect of a known adverse event). The evaluation of novelty should, however, be secondary to the evaluation of patient safety e.g. a potential signal that changes an already known event from 'mild and transient' to 'potentially life-threatening and/or chronic' may affect patient safety more than a new adverse event that in and of itself is mild and non-serious.

2.2.1.7. Preventability

One of the main aims of the entire signal management process is to mitigate the risks of treatment with VMPs as much as possible. Any knowledge on preventability of the clinical signs/disorders or the most severe outcomes can be taken into consideration during prioritisation. If a serious adverse effect or outcome is known to be easily preventable, the information is of high value, as the benefit of treatment will remain, while the risk is mitigated. However, preventability should not be regarded as a decisive criterion for prioritisation and should be considered alongside other factors relevant to the potential impact of the signal.

2.2.1.8. Potential signals concerning VeDDRA terms listed in the SPC

Known adverse events of a product are generally listed in section 3.6 of the SPC, while additional information contributing to the description of adverse events as well as advice regarding risk mitigation may also be found in sections 3.3 and 3.5. Information relating to efficacy and lack thereof is usually included in section 3.4. It should be noted that adverse events are included in the SPC at VeDDRA LLT

level, while signals are usually detected at PT level. Therefore, when a signal is detected at PT level, it may be necessary to review the reported LLTs of cases to determine whether the reported events are already adequately covered by the SPC or whether they represent a new or insufficiently characterised aspect of the risk.

1. Monitoring of adverse events that are already listed with the exact wording in SPC section 3.6 should generally not be prioritised, with the exception of certain specific situations and factors, where potential signals on listed events should undergo further prioritisation as normal:

    a) Signals concerning increased frequency, both sudden and gradual.

    b) Signals for VeDDRA PTs that include an LLT listed in the SPC, but also include LLTs considered more severe/serious in nature, or more specific, compared to the listed LLT. In these cases, monitoring of such LLTs should still be part of routine monitoring (see section 2.1.2.1 and 2.3.1.2 for further guidance).

    c) Signals concerning a change in outcome towards more a severe outcome compared to what is described in the SPC, e.g. a rise in fatal cases.

    d) Signals further characterising the already known risk where the additional information may impact the understanding, management or communication of that risk.

2. Even if certain VeDDRA terms are not explicitly included in section 3.6 of the SPC it may be the case that the suspected adverse event is already adequately covered by the text included in the product information. If so, they should be handled as described in point 1 above.

Further guidance on how to determine whether a potential signal is adequately covered by the SPC is provided in section 2.3.1.2.

2.2.1.9. Other previous knowledge on subject

Previous knowledge on the subject of the signal includes knowledge from previous signal validations (irrespective of outcome), previous signal assessments, knowledge from previously assessed clinical trials or any other procedure on the product in question including the initial authorisation procedure. For example, a signal validation performed recently, which led to non-validation of the signal, may lead to not prioritising the signal when detected again if the number of new cases received since then is low. Conversely, in a situation where new data has been received and a causal association was highly suspected in a recent signal assessment, but the evidence was not sufficient at the time of the assessment, such previous knowledge may lead to prioritisation of the signal.

Knowledge from other products with the same active substance or with an active substance in the same drug class may also be considered. For example, if the event is listed in the PI of another product with the same substance, it may lead to increased suspicion of a potential causal association and prioritisation of the signal.

2.2.1.10. The signal trigger

The signal trigger may in certain circumstances influence prioritisation. For example, in cases of intense media interest, it may be of interest to the public and the MAH themselves to prioritise such a signal, despite other factors. In other cases, a signal triggered from social media discussions with no corroborating evidence from other sources, e.g. adverse event reports, product complaints or literature, may not be prioritised. For example, discussion about lack of efficacy circulating on social media, while there are no actual adverse event reports on lack of efficacy received in the period of concern.

In other cases, the strength of evidence of a source may factor into the decision e.g. a signal triggered from a newly published double-blinded clinical trial indicating a new risk may be prioritised higher than if the same signal was identified in an adverse event database.

2.2.1.11. Special situations

Batch-related issues

If a batch-related issue is detected from the signal management process (i.e. is a potential cause of reported adverse events or lack of efficacy), it should be considered a potential/validated signal. Batch-related issues which are not related to a detected signal (e.g. if the faulty batches never reached end users or there were no reports related to the affected batches), do not need to be considered as signals and should follow the process related to quality defects[13]. If there is suspicion of a batch-related issue involved in a signal, it should be considered whether the issue could be a PhV Alert (see sections 2.2.1.1 and 3.1.3).

Batch-related issues, such as those arising from manufacturing deviations, quality defects, stability failures or supply chain problems, are generally considered high-priority due to their potential to affect large numbers of animals within a short timeframe and their preventable nature. The criteria explained in section 2.2.1.4 regarding seriousness and severity of the events should be taken into consideration during prioritisation of batch-related issues.

Signals involving off-label use, overdose or medication errors

The obligation to perform pharmacovigilance extends to include use outside the terms of the marketing authorisation (i.e. off-label use, overdose or medication errors)[14].

The following signals in non-target species should always be prioritised:

1. Signals concerning user safety, i.e. occurring in humans, should always be prioritised and all VeDDRA terms are considered MI-terms in humans.
2. Signals concerning serious consequences of accidental exposure (a medication error) in non-target species.
3. Signals concerning serious and severe adverse events in non-target species, where the expected risk minimisation measures following a conclusion of a possible causal association would involve a need to at least inform the public (see examples 24-25).

Signals involving some extent of use outside the terms of the marketing authorisation should generally be prioritised in a similar way to all other signals and the evaluation of the role of non-authorised use will usually be performed at a later stage.

In situations where there is knowledge of widespread use outside the terms of the marketing authorisation for specific purposes, e.g. in a specific non-target species or for a specific off-label indication in the target species, safety signals occurring in these circumstances should give rise to further analyses of the signal(s) and considerations of whether it may be relevant to implement risk minimisation measures in an attempt to reduce the off-label use to reduce the risk. For example, safety signals where the majority of cases report use against a contraindication listed in section 3.3 may often not require prioritisation immediately. However, continued reporting of adverse events in

[13] https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/compliance-post-authorisation/quality-defects-recalls
[14] Article 11 of CIR (EU) 2021/1281

such cases should lead to concern that risk mitigation through a contraindication is not sufficiently effective and thus may require further action from the MAH (see section 2.6 and example 26).

Signals specifically concerning previously unknown risks connected to overdose in the target species can usually be prioritised below signals concerning use within the terms of the marketing authorisation. However, as the MAH also has an obligation to keep the section of the PI concerning overdose up to date with newest scientific knowledge, such signals cannot be dismissed with the argument of overdose alone.

Signals concerning medication errors should be prioritised according to the risk the errors pose, as well as preventability of the errors observed.

Signals receiving media attention

In some circumstances, signals that could cause/are causing media attention and/or public concerns may deserve special attention. Prioritising further analysis of such signals may ensure a faster conclusion (no matter the final outcome of the signal) and increase trust from the public.

Antimicrobial or antiparasitic resistance

Signals which may be a sign of antimicrobial/antiparasitic resistance should generally be prioritised.

Environmental risks

Signals may directly concern a risk to the environment. However, even for signals which do not primarily concern the environment, it may be relevant to consider whether there could be consequences for the environment. This is especially true for signals involving adverse events in an animal or species other than the treated one, e.g. accidental exposure. Please also refer to section 2.3.1.3 on validation of environmental signals.

Signals with the primary topic of an environmental risk may arise from adverse event reporting, scientific literature or other sources and should generally be prioritised. An additional environmental aspect to a signal primarily focused on an adverse event would similarly increase priority.

Examples

24: A signal suggests that a serious adverse event may occur in a non-target species following exposure to a veterinary medicinal product. Early recognition and discontinuation of treatment appear to improve the clinical outcome. If confirmed, communication to veterinarians and animal owners may be necessary to ensure prompt recognition and intervention.

25: Several reports describe severe neurological adverse events in a non-target companion animal species following accidental exposure to a product intended for another species. If a causal association is confirmed, a precaution may be added to SPC section 3.5 and the corresponding section of the PL under the sub-heading 'other precautions' in accordance with the QRD template for VMPs.

26: A product contraindicates use in animals below a certain age, but serious adverse events continue to be reported predominantly in that age group. This may indicate that the existing risk minimisation measure (the contraindication) is insufficient and additional measures are therefore implemented, e.g. strengthened wording of the contraindication, additional warning added to the package or other measures as described in section 2.6.

2.2.2. Impact on future prioritisation during 'routine monitoring'

If a potential signal is not prioritised for immediate progression to validation, it will usually return to 'routine monitoring' and should be considered again during subsequent signal detection activities. Such signals may be re-detected and prioritised at a later time.

If a validated signal is not prioritised for immediate assessment, it should be subject to enhanced monitoring until the signal assessment has been completed. Any new information received during this time should lead to a new assessment of urgency.

Non-validated and refuted signals (see sections 2.3.2.2 and 2.5.1 respectively) usually return to 'routine monitoring'.

However, factors determined during prioritisation, prior signal validations or assessments may influence future prioritisation during routine monitoring for both potential signals for which progression to validation were previously deferred, previously non-validated signals and previously refuted signals (see also sections 2.3.2.2 and 2.5.1, see examples 27 and 28 and figure 4):

Examples

27: A specific VeDDRA term has been determined to be biologically implausible during signal detection and/or prioritisation. Future (routine) monitoring may have lower priority.

28: A potential signal of low seriousness and severity was not prioritised for immediate progression to validation due to presence of other signals determined to have a greater impact on overall safety. However, a causal association could be possible based on mechanism of action. The issue should then be given higher priority if re-detected during routine monitoring.

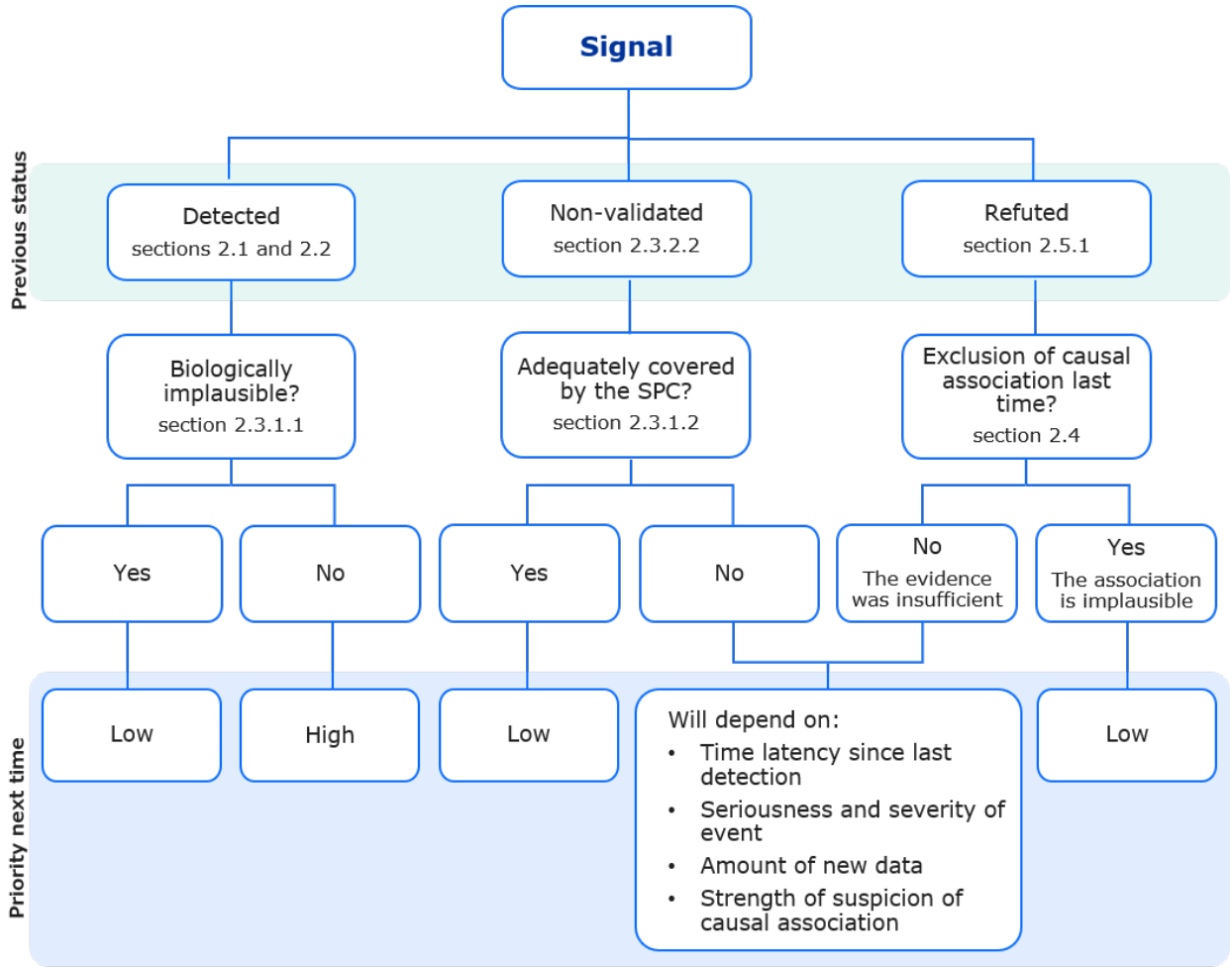

Figure 4: Impact on future prioritisation of previously detected signals
Previous status: Refers to the outcome of previous prioritisation validation or assessment of the same signal, depending on how far the signal came in the signal management process.
Previously detected signals, which led to risk minimisation measures, are not covered by this figure.

2.3. Signal validation

Once a signal has been identified through the signal detection process and has been prioritised for validation, the next step in signal management is to conduct the signal validation. Signal validation is an initial screening of the data that triggered the potential signal, with the aim of determining whether the signal is supported by information of sufficient quality and substance to justify further assessment. Therefore, signal validation is not intended to determine causality. At this stage of the signal management process a causal association is only suspected and further assessment is needed to conclude on causality.

When to perform a signal validation on a detected signal is determined through signal prioritisation (see section 2.2).

The outcome of signal validation is either to 'validate' the signal, or 'non-validate' the signal. All validated signals should be further assessed (see section 2.4) and entered into IRIS[15] Veterinary Signal Management (VSM), irrespective of the eventual conclusion (see sections 2.5 and 3.1).

[15] https://iris.ema.europa.eu/ - EMA's online platform for submitting and managing regulatory and scientific procedures for medicines throughout their lifecycle

It is important to have an established protocol for signal validation. However, different steps might be required for different signals depending on their origin. As a minimum, a documented process for validation of signals originating from adverse event databases should be established and made available for inspection.

All signal validations performed should be documented and recorded in a traceable manner and the documentation should be sufficient to demonstrate the rationale and outcome of the validation during inspections as well as what data the validation process was based on. See also section 5.

2.3.1. Methods for signal validation

The methods used to validate a signal may differ depending on the origin and other properties of the signal. Signal validation is usually performed on the initial data present when the signal was detected (the signal trigger). The process of validation is thus not meant to include searching for additional data from other sources, except for in specific circumstances (see sections 2.3.1.1 and 2.3.1.3).

2.3.1.1. Initial considerations

During signal validation, clinical judgement should always be applied and signals which are biologically implausible should be non-validated. Hence, the product should be able to reasonably cause the event (see examples 29 and 30).

However, caution should be exercised as to not dismiss signals due to confirmation bias; i.e. signals should not be non-validated simply because they are not considered to fit the known safety profile. Not everything is discovered in clinical trials and it is important to stay open-minded and unbiased to possible associations.

Additionally, a critical assessment of whether the reported events are similar enough to constitute a signal may be necessary in some situations, while in others it may be relevant to consider whether the initial signal needs to be expanded to e.g. cover several similar or medically linked VeDDRA terms in the validation. Certain VeDDRA terms are very broad or non-specific and may encompass a variety of disorders, while others overlap and may be used interchangeably by reporters leading to a need for a combined validation (see examples 31 and 32).

Examples

29: A topical product with a well-established pharmacokinetic profile, known to have no or very limited systemic uptake, is unlikely to be causally associated with a signal of 'fracture'.

30: A product not used in the ears would be unlikely to directly cause 'tympanic rupture'.

31: In case of a detected signal on a VeDDRA PT such as 'carcinoma NOS' the cases may all be reporting the same or at least similar types of carcinomas, or they may be reporting completely different carcinoma types, which would affect the decision on whether to validate the signal.

32: In case of a detected SDR on 'gastrointestinal ulceration' it may be relevant to also include any additional cases reporting 'intestinal perforation' and 'gastric perforation'.

2.3.1.2. Data screening

An initial verification of the data (most often case reports) should be performed. The verification should, as a minimum, ensure that:

- There is a temporal association,
- The adverse event is not already adequately described in the current product information,
- The signal is not based on duplicate reports (which would artificially inflate the apparent number of reports and any potential disproportionality).

Temporal association:

Temporal association is usually discussed using the term 'time-to-onset' (TTO). TTO is usually expressed as the time period (in minutes/hours/days/weeks etc.) from initiation of treatment with the product and until the first clinical signs of the event occur.

Presence of a temporal association means that the reported event(s) occurred after the time of the first exposure to the VMP(s). Cases where the events occurred prior to the time of exposure do not have a temporal association (also sometimes expressed as having a 'negative TTO'). Such cases would never be considered supportive of the signal, regardless of any other factor considered in future causality assessment (see also section 2.4.2).

In addition to determining whether there is a temporal association, exclusion of cases with a very unreasonable TTO can be considered, even when a temporal association exists. It should be emphasised that the goal of the validation stage is not to evaluate causality and therefore also not to evaluate the finer details of TTO in each case. However, there may be certain situations where TTO is unrealistically long (e.g. anaphylactic shock occurs many months following a single administration of an inhalant anaesthetic) or unrealistically short (e.g. cancer is diagnosed the day after the first administration). The pharmacokinetic profile of the product needs to be taken into account when evaluating these situations - some products are known to have a very short half-life and are usually given as single administration only, while other products are used for longer periods of time or are specifically designed to elicit a long-term effect or have special delivery systems prolonging the effect.

Description in the product information:

Known adverse events of a product are generally listed in section 3.6 of the SPC and section 7 of the PL, while additional information contributing to the description of adverse events as well as advice regarding risk mitigation may be found in sections 3.3 and 3.5 of the SPC and the corresponding sections of the PL. Information relating to efficacy and lack thereof is usually included in section 3.4 of the SPC and the corresponding section of the PL.

Even if certain VeDDRA terms are not explicitly included in the PI it may be the case that the suspected adverse event is already covered by the text included in the product information.

It should be noted that adverse events are included in the PI at VeDDRA LLT level, while signals are usually detected at PT level, therefore it may sometimes be necessary to check the reported LLTs of the cases belonging to a given PT (see also section 2.2.1.8).

Furthermore, the product information for a generic or hybrid product should be kept in accordance with the PI of the reference product[16]. Therefore, potential signals which are already included in the PI of the reference product should be non-validated. Instead, the generic MAH should submit a variation to the terms of the marketing authorisation without undue delay, in order to rectify any inconsistencies.

In cases of doubt as to whether the suspected adverse event(s) is covered by the PI, focus should be on the following:

[16] Article 18(6) of Regulation (EU) 2019/6

- *Are the events of the potential signal more serious or severe in nature compared to the terms already included in the PI? (see also section 2.2.1.4)*

If the events of the signal are considered more serious compared to the terms included in the PI, the events of the signal should not be considered covered by the current PI (see example 33).

Since one PT may include both more and less serious LLTs, situations may arise where a signal is detected on a PT where one LLT is already listed. In such cases it would be necessary to check the reported LLTs of the cases (see example 34).

- *Are the events of the potential signal more specific compared to the terms already included in the PI?*

If the events of the signal are more specific compared to the currently approved PI, this may be a signal that would further characterise a known risk (i.e. a new aspect) or the signal may represent a separate subgroup and should therefore not be considered covered by the PI in most cases (see examples 35-36).

In these situations, the listed events should not be considered a reason to non-validate the signal on their own. However, the clinical relevance of the signal should be evaluated and the relation to already listed events may play a role in the prioritisation of signals (see section 2.2.1.6).

Since one PT may include both more and less specific LLTs, situations may arise where a signal is detected on a PT where one LLT is already listed. In such cases it would be necessary to check the reported LLTs of the cases (see examples 37-38).

There may be certain exceptions to this rule, e.g. if the PI already includes adverse events that encompass other events in a way where additional specification may not provide useful information (see example 39).

- *Does the potential signal constitute a new aspect of the already included term?*

For example, is it a signal of potentially increased frequency or severity? Or potentially increased frequency or severity in a subset of the target population (e.g. animals with certain comorbidities, certain breeds, certain age groups, pregnant females etc.)? Would it constitute a change in duration or outcome compared to what is currently described in the PI? To answer questions regarding frequency, it would be relevant to check the rate of reporting against the estimated exposure of the VMP (incidence of reported adverse events).

- *Are the events of the potential signal always linked to the terms included in the PI?*

Some terms may be linked in some cases and not in others. For such situations, it may be needed to review how many of the cases concern events related to the already listed event (see example 40).

Examples

33: In a case where 'Elevated creatinine' is included in the PI, but the validation is performed on a signal of 'Acute kidney injury', the signal would not be considered covered by the current PI.

34: In a situation where LLT 'Elevated temperature' is included in the PI and a signal has been detected on the PT 'Hyperthermia', which the listed event belongs to. However, the cases mostly report the LLT 'Fever'. Since 'Elevated temperature' may include temperature increases below the threshold of fever, a signal where the LLT reported is 'Fever' would be considered more serious and more specific.

35: If the currently approved PI lists 'Injection site reaction' and the signal undergoing validation concerns 'injection site necrosis' this could be further specification of the risk.

36: If the PI lists 'Neoplasia' and the signal concerns 'injection site neoplasm' that would further specify the risk.

37: In a situation where the LLT 'Colitis' is already listed in the PI and the cases turn out to mostly report the specific illness of 'Ulcerative colitis' this would be considered to either further characterise the risk, or it may represent a new risk.

38: Similarly, if the PI lists 'cardiac enlargement' however the reported cases of the signal mostly code 'hypertrophic dilated cardiomyopathy' this would be considered further characterisation (specification) of the risk, as hypertrophic dilated cardiomyopathy is a specific type of cardiac enlargement.

39: If the signal undergoing validation concerns 'injection site oedema', but the PI already lists 'injection site inflammation' in section 3.6, the added information of including 'injection site oedema' may be considered negligible, since oedema is a well-known cardinal sign of inflammation, despite oedema being more specific.
However, in the reverse situation, where 'injection site oedema' was the listed term, 'injection site inflammation' should not be considered automatically covered by the PI, as more clinical signs than oedema are usually connected to inflammation (e.g. warmth and erythema).

40: If 'Hepatic failure' is listed in section 3.6 of the PI, validation of a signal of 'Jaundice' may focus solely on cases where non-hepatic causes of jaundice are suspected.

Duplicate reports:

In cases of doubt as to whether reports are in fact duplicates of each other or not, it is better to consider the reports as unique.

It may also be relevant to consider the source of the reports; in situations where all reports originate from the same reporter, it should be assessed whether there may be factors related to the reporter which are more or at least equally likely to have caused the events (e.g. geographical, concurrent treatments, prior disease history, handling of the products or animals, etc.). Signals concerning medication errors, where all reports originate from the same reporter, can usually be non-validated.

2.3.1.3. Special types of signals

Certain types of signals may need to be assessed differently and therefore other criteria may be relevant during validation as well.

As mentioned in section 2.1.1, signals may arise from other sources than analysis of adverse event databases. Often, such signals are detected using qualitative methods and, in some cases, they may be considered validated based on the initial screening during signal detection.

If a signal has arisen from more than one source e.g. both a new published article and data from an adverse event database, both sources should be verified using appropriate methods and considered in the final decision on whether to validate the signal or not.

Signals arising from monitoring of scientific literature:

Validation of a signal arising from scientific literature may encompass an evaluation of the strength of the article(s) or study/studies that triggered the signal but does not necessarily need to encompass searching for additional data. Furthermore, presence of AE reports in adverse event databases concerning the same term may be used to validate the signal where relevant.

Signals arising from media (including social media):

Signals arising from media attention or social media comprise a challenge during the validation process, as the triggering information may not always be verifiable in nature. In such cases the validation step may include considerations mentioned in the above sections 2.3.1.1 and 2.3.1.2, combined with targeted signal detection in adverse event databases and scientific literature to see if the signal can be verified through other sources.

Medication errors:

For signals (in animals) involving medication errors it is particularly important to consider whether the reports originate from different (unrelated) sources. Signals of medication errors which can all be traced back to the same source may be non-validated, if they are considered related to the specific source rather than representing a general problem with the product. Furthermore, for reports of medication errors it is particularly relevant to check whether the reported medication or product use error is related to the investigated product, or to another product. Additionally, whether the medication error has led to safety concerns and the severity and seriousness of any such concerns should be taken into consideration, as well as the number of reports and reacting animals. Co-reported safety issues may be checked against the PI.

Considering that many of the VeDDRA terms related to medication errors are rather broad, it may also be important to identify patterns in the reported events; are they reporting similar types of errors or completely different errors? In situations where no trend or pattern can be identified, the signal can be non-validated.

Signals involving overdose:

When referring to overdose in pharmacovigilance, it is usually in reference to use of greater dosages than what is approved (e.g. 20 mg/kg rather than the approved 10 mg/kg). However, depending on the pharmacodynamic and pharmacokinetic properties of a drug (e.g. if accumulation is expected), it may also be relevant to consider prolonged use as overdose in some situations.

It is necessary to evaluate at what level overdose becomes relevant to the assessment of the reported events. For some products, a minor overdose may be irrelevant and should thus be evaluated on the same 'terms' as non-overdose cases, while for others the therapeutic index is narrower and even a

minor overdose is considered significant for the risk profile. Patterns of reported events may also differ between different levels of overdose.

The MAH should also keep the product information up to date regarding clinical signs of overdose and systematic exclusion of overdose cases at the signal detection stage is therefore not recommended.

Suspicion of batch-related risks:

For signals suspected to be tied to batch-related issues, case reports can be checked for presence of batch-numbers as well as which precise batch-numbers apply. However, the basic principles of signal validation should still be considered. In cases where batch-related risks are coupled to safety signals, it is necessary to evaluate whether it could be a PhV alert.

Lack of expected efficacy (LEE):

When validating a potential signal of lack of efficacy, the data screening will need to be modified for the purpose. If the signal originates from an adverse event database (i.e. is based on AE reports), the cases may be screened for a temporal association in a similar manner as described above, but it will be highly important to know the expected time-to-onset of expected effect as well as duration of the expected effect to determine if there is a temporal association with potential lack of efficacy. In addition to screening for temporal association, duplicate reports and whether lack of efficacy is already described in the PI, it is usually important to assess which expected effect is reported as lacking and whether this is actually an indication of the product. Furthermore, it may be assessed whether the product was handled and used in accordance with the product information and whether the deviations are likely to affect efficacy. In cases where LEE is already described in the product information, it may be of relevance to check whether frequency has increased or whether there are new aspects to the already described lack of efficacy.

Signals concerning a risk to the environment:

When validating a signal where the primary focus is a risk to the environment, it is important to consider whether the signal can be traced back to use of the product or active substance in animals, either in a specific or unspecific way. If a potential environmental risk cannot be led back to use of the product in animals, it is not considered a signal (see examples 41-43).

Environmental signals should otherwise be validated using the same methods as described in sections 2.3.1.1 and 2.3.1.2.

Examples

41: Published scientific literature describing a toxic effect on the environment after experimental exposure (e.g. pouring out the active substance with the purpose of studying the effect) would not be considered a signal.

42: Adverse event reports describing death of fish and plant life in a local pond after treated dogs bathed in the water would be considered a signal.

43: Detection of the active substance of a product in natural water sources; This is considered a signal if the active substance is only commercially available as product(s) for use in animals, since there would not be other reasonable sources than the product. However, if the substance is also available from other sources, e.g. human medicinal use, pesticides, feed additives etc., it would not be considered a signal as the presence in the environment may be from these sources.

2.3.2. Outcome of signal validation

When finalising signal validation, the signal should be concluded as either validated or non-validated.

2.3.2.1. Validated signal

A signal is considered validated when the signal validation process has verified that the data triggering the signal is of sufficient quality and substance to justify a need for further analysis and the event(s) of the signal are not already adequately described in the product information.

Validation of a signal does not imply that a causal association with the VMP has been established, only that the observations meet the criteria for a plausible hypothesis, with sufficient data to justify its progression to further analysis/assessment.

Validated signals will need to be investigated further to assess causality with the product/substance (see section 2.4). All validated signals should be submitted to authorities through IRIS-VSM following assessment. The timeline of signal submission in IRIS depends on the outcome of the assessment (see section 3.1.2.2).

2.3.2.2. Non-Validated signal

A non-validated signal is a signal for which the signal validation process could not verify that the available data was of sufficient quality and substance to justify further investigation of the possibility of a causal association between the product(s)/substance(s) and the suspected adverse event(s) or where the events are considered adequately described in the product information (see section 2.3.1.2).

Just as validation of a signal does not imply establishment of a causal association, nor does non-validation of a signal mean that a causal association has been ruled out.

Furthermore, a non-validated signal should not be confused with a refuted signal (see also section 2.5.1). A non-validated signal has not been assessed fully and the question of causality has not been considered, while a refuted signal is a validated signal, where further assessment found the evidence insufficient to support a causal association.

Outcome and rationale behind non-validation of signals should also be documented in a sufficient manner to allow for inspection[17] i.e. the decision to non-validate a signal and why this conclusion was reached should be documented by the MAH and this documentation should be made available to inspectors.

It should be emphasised that a previous non-validation of a signal does not imply that the signal should never be investigated again. Following non-validation, monitoring of the issue should usually return to routine pharmacovigilance practices although there may be situations where future monitoring can be prioritised lower e.g. if a causal association was determined to be biologically implausible. Thresholds for when the signal is considered detected again may be established on a case-by-case basis and would need to consider both latency until redetection, seriousness and severity of the event as well as the amount of new data available and trends in reporting.
Future validation processes may or may not lead to validation of a previously non-validated signal and previous non-validation of a signal should not automatically determine the outcome of any future validation. However, prior knowledge from validations may be taken into account when prioritising signals for validation (see also sections 2.2.1.9 and 2.2.2).

[17] Article 17(6) of CIR (EU) 2021/1281

2.3.3. Signal prioritisation after signal validation

All validated signals will need to go through a full assessment and subsequently be submitted to IRIS-VSM. In most cases, it will likely make sense to move directly from the validation phase to the assessment phase. However, where multiple validated signals exist for the same product, it may be necessary to prioritise which signals to assess first. The general principles, factors to consider and impact on future monitoring explained in section 2.2. may be applied after validation as needed. If assessment of a validated signal is deprioritised, the potential impact on safety should be carefully considered and documented with the validation together with the rationale for deprioritisation.

2.4. Signal Assessment

Signal assessment is the comprehensive process of examining all relevant sources of information with the aim of determining whether there is a need for action. In order to achieve this, signal assessment should focus on assessing the causal relationship between a VMP and the AEs of interest for a validated signal. Therefore, signal assessment focuses on establishing whether the validated signal is likely to reflect a new causal association or a new aspect of a known causal association with the VMP, as well as further characterising the risk in order to implement appropriate action, if necessary. This assessment is based on a cumulative review of all available information, including, but not limited to, case reports, scientific literature, pharmacological data, clinical information and epidemiological findings.

Clinical judgement is central to signal assessment and requires expert evaluation of the potential biological mechanism, the clinical and environmental context of the signal and the consistency of reported events. Within this framework, review of individual case narratives in the context of a case series is essential, as narratives provide additional critical information that cannot be captured through coded data or quantitative analyses alone.

The outcome of a signal assessment may ultimately lead to a recommendation for actions, such as enhanced monitoring, a need for further investigation or implementation of risk minimisation measures, including updates to the product information (see also sections 2.5 and 2.6).

Signal evaluation should therefore be conducted using a structured and scientifically sound set of methods applied in a proportionate manner and adapted to the characteristics of the specific signal under assessment and the available data. These methods aim to support a consistent and transparent assessment of whether the validated signal represents a new risk or new aspect of a known causal association of the VMP.

The key elements to consider during signal assessment are outlined below. The list is not exhaustive and additional methods may be applied where considered relevant.

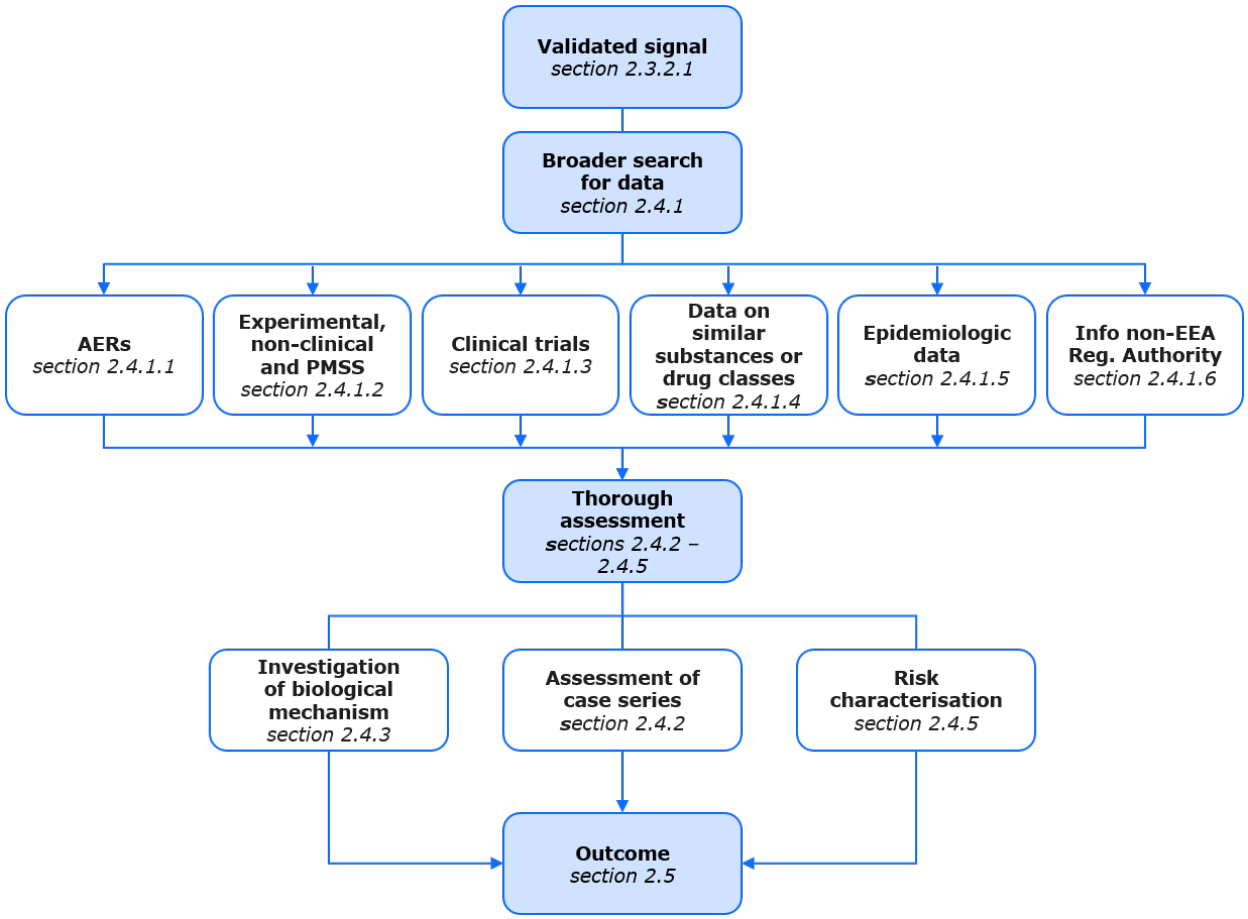

Figure 5: Signal assessment

2.4.1. Broader search for data

One of the cornerstones of the signal evaluation phase is the conduct of a comprehensive and systematic search for evidence from all relevant sources, with the objective of ensuring that the safety topic under assessment is thoroughly explored and that all available evidence is taken into consideration and put into the correct context. Beyond the analysis of spontaneous reports and quantitative signal detection outputs, a broad search for additional data is essential to conclude on the outcome of the signal.

The following section therefore outlines the key data sources that should be considered during signal assessment. Searching for further information through these sources helps ensure that conclusions are based on all the available evidence.

2.4.1.1. Adverse event reports

If the signal was not initially triggered by adverse event reports, a cumulative search for cases should be performed in relevant databases. These cases should be included for assessment of causality (see also section 2.4.2).

However, even if the signal was triggered from AERs, it may be relevant to perform additional broader searches for data to ensure all relevant evidence is captured (see also section 2.1.2.1).

It should be assessed whether conceptually related VeDDRA terms are reported, which may represent clinical sequelae, complications or different stages/descriptors of the same event. A predefined

grouping of VeDDRA terms can be applied to capture the full clinical spectrum and avoid double-counting and display both grouped and individual-term analyses (see examples 44-45).

Examples

44: Related terms reflecting organ-specific toxicity:
For a suspected hepatic adverse reaction, reports may include VeDDRA terms such as elevated liver enzymes, jaundice, hepatic failure, hepatic necrosis or hepatic encephalopathy. These terms may represent different clinical stages, severity levels or sequelae of the same underlying hepatic injury and should therefore be considered together using a predefined grouping, while still allowing presentation of individual term analyses.

45: Related terms reflecting a recognised clinical syndrome:
For known syndromes, conceptually linked clinical signs should be assessed collectively. For example, in a Limping-syndrome, reports of limping, pyrexia, lethargy and joint swelling may be recorded under separate VeDDRA terms but represent manifestations of a single clinical entity. Grouping such associated terms helps capture the full syndrome presentation and avoids underestimation of the signal due to fragmented reporting.

2.4.1.2. Experimental, non-clinical data and post-marketing surveillance studies

Toxicology, pharmacokinetic (PK), pharmacodynamic (PD) and target organ data can provide evidence of a potential biological mechanism or identify susceptible organ systems or biochemical pathways. Data sources may be from the pre-authorisation phase of the product itself or new pre-clinical studies, or from scientific literature concerning the product, active substance(s) or similar substances published before or after authorisation of the product in the same or a different species (including humans).

In addition, post-authorisation data generated under field conditions, including post-marketing surveillance studies (PMSS), may provide relevant complementary evidence. The definition of PMSS can be found in the VGVP module: Glossary[18].

2.4.1.3. Clinical trial findings

When pre- or post-authorisation clinical trial data exist, they can help characterise the adverse event regarding frequency, time-to-onset, dose administered and controlled-use conditions. Although veterinary clinical trials often have limited sample sizes, they may corroborate patterns seen in post-marketing pharmacovigilance.

However, attention should be given to the fact that sample size of clinical trials affects the ability of the trial to detect very rare, rare and sometimes also uncommon events. Therefore, absence of an adverse event during clinical trials is not in itself sufficient reason to refute a signal but may point to the event occurring less commonly. Again, data sources may be from the pre-authorisation phase of the product itself or may be from scientific literature concerning the product, active substance(s) or similar substances published before or after authorisation of the product in the same or a different species (including humans).

[18] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-glossary_en.pdf

2.4.1.4. Other published literature (including data on similar substances or within the same product class)

Scientific literature should be reviewed to identify evidence of the same or similar adverse events in the same species, in other species or in products that share the same active substance(s), excipients (if an excipient is suspected in the mechanism of the signal), mechanisms of action or pharmacological class. Exploring related VeDDRA terms can help capture different clinical manifestations or stages of the same pathophysiological process.

2.4.1.5. Epidemiological data

Information on the background prevalence of the reaction or disorder might provide contextual information to assess whether observed reporting incidences may exceed those expected. Background incidence may be available for the overall reference population or for relevant subpopulations (e.g. breed, underlying conditions, management practices).

This factor may be particularly relevant for events with a long time-to-onset (e.g. neoplasia) or multifactorial aetiology (e.g. atopy, inflammatory bowel disease).

However, important limitations must be considered. Comparisons between background incidence estimates and reporting incidences derived from spontaneous reports are inherently challenging due to underreporting, reporting biases and differences in study design and population definitions. Spontaneous reporting systems are not designed to estimate true incidence.

Consequently, background incidence data should not be used in isolation to support or refute a causal association. Epidemiological information should be interpreted cautiously and qualitatively, in conjunction with other lines of evidence, including case-level data, biological plausibility and clinical pattern analysis (see examples 46-48).

Examples

46: Long latency events with high background incidence

For adverse events that develop slowly and have a relatively high background incidence in the target population, epidemiological context is essential to interpret a potential signal. For example, a signal concerning mast cell tumours in dogs requires careful consideration of background incidence, as mast cell tumours are among the most common cutaneous neoplasms in this species and neoplastic processes typically have a long TTO. Knowledge of the expected incidence in the general dog population is therefore important to assess whether the number and pattern of reported cases following exposure to the product exceed what would be anticipated by chance alone and to avoid false attribution of causality.

47: Multifactorial diseases with fluctuating clinical course

Background incidence data are particularly informative for adverse events or conditions with multifactorial aetiology and variable clinical expression, such as atopy, inflammatory bowel disease or chronic renal disease. In these cases, episodic worsening may coincide temporally with treatment initiation without being causally related. Population-level data on expected prevalence and incidence help contextualise observed reporting patterns and support differentiation between disease progression and a treatment-related effect.

48: Situations where background incidence alone is insufficient

Abortions in sheep have a known background incidence and are commonly associated with infectious, nutritional or management-related causes. The background incidence may vary considerably depending on region, flock management practices and breed. When evaluating a signal of abortion potentially associated with a VMP, the overall abortion rate observed in exposed flocks may not exceed the expected background level. However, epidemiological evaluation should consider whether exposure is associated with:

- Abortions occurring shortly after treatment (plausible and shortened TTO) and/or
- Temporal clustering of abortion cases following product administration.

In such situations, the product may not increase the overall incidence of abortion but may act as a trigger, shifting the timing of events. Therefore, background incidence alone may be insufficient to assess the clinical relevance of the signal.

2.4.1.6. Information from other regulatory authorities worldwide

Information originating from non-EU regulatory authorities may provide valuable complementary evidence during signal assessment. Signals detected, risk communications issued, or regulatory measures taken by authorities outside the EU can serve as indicators of potential risks or provide important contextual information, particularly when EU case data are limited or still emerging.

Such information may include relevant pharmacovigilance data as well as regulatory measures adopted by competent authorities in third countries (e.g. restrictions of use, updates to product information, suspensions or withdrawals), particularly where these are not yet reflected in the EU product information and may have an impact on the benefit-risk balance.

The information from these sources should be evaluated critically, taking into account differences in authorised indications, formulations, target species, patterns of use, reporting systems and regulatory frameworks. While actions taken by non-EU authorities do not automatically imply a causal association

under EU conditions of use, they may be supportive of the signal, or they may highlight potential class effects, or help identify subpopulations or conditions of use which may lead to increased risk.

This information may be particularly relevant for serious, unexpected, or rare adverse events, for products or active substances used globally, or where similar safety concerns emerge independently across regions (see examples 49-50).

Examples

49: A safety communication issued by a non-EU authority warning of rare but serious neurological adverse events associated with a specific pharmacological class may include information in support of a similar signal detected in EU pharmacovigilance data.

50: Regulatory restrictions or label changes implemented in another region following reports of environmental harm linked to an antiparasitic product (e.g. effects on non-target invertebrates) usually indicates that an analysis in that country has found a correlation. Available information may be valuable for assessment of a similar signal in the EU. It may also provide relevant context when assessing an environmental signal under EU conditions, particularly where exposure patterns or use scenarios are comparable.

2.4.2. Assessment of case series

The completeness, clarity, internal consistency and reliability of each case are important determinants of the ability to assess causality. High quality, well-documented cases provide a more robust and reliable evidence base and are critical for drawing scientifically sound conclusions and determining the appropriate signal outcome.

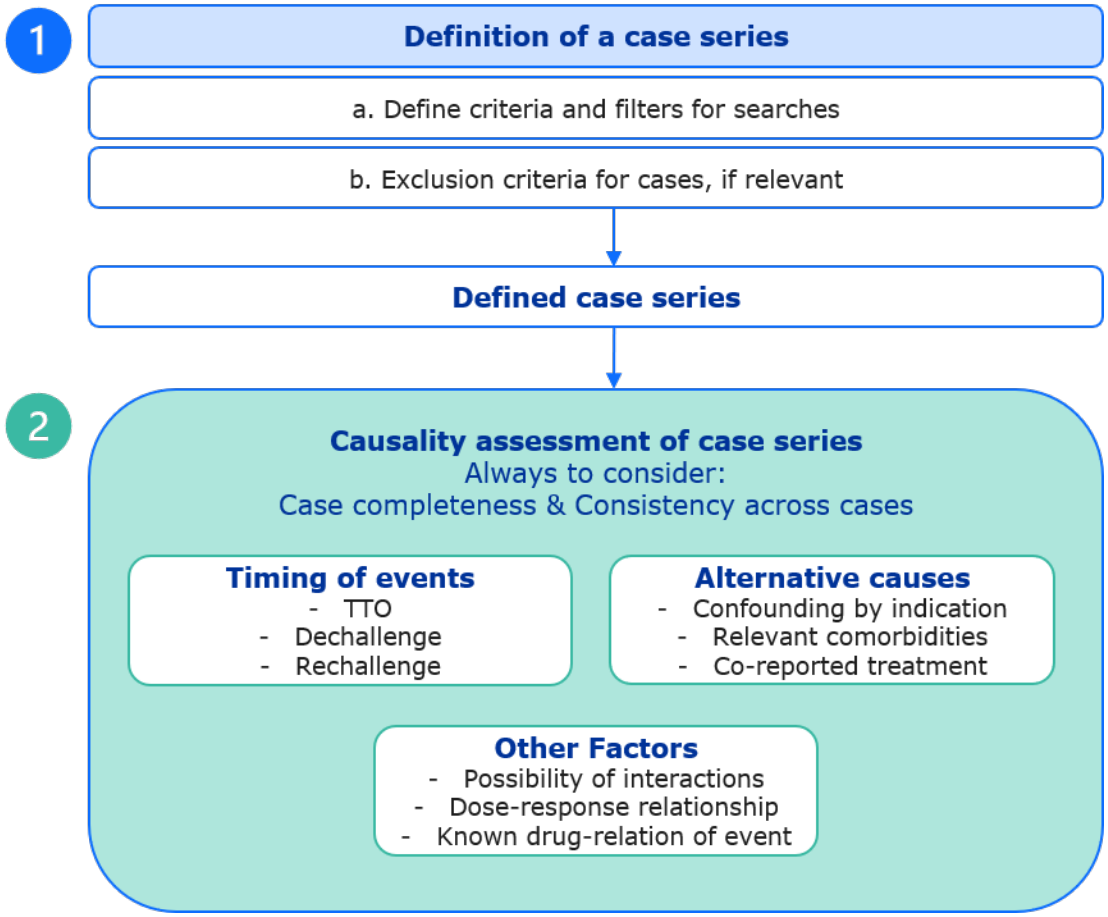

Figure 6: Assessment of case series

2.4.2.1. Case selection and search methodology

For any analysis of case series conducted in the context of signal assessment, the methods used for case identification and selection should be clearly defined and transparently reported. This includes the databases searched, search strategies (e.g. terms or groupings applied), inclusion and exclusion criteria and any applied filters (e.g. seriousness, species, time period or level of documentation).

Where focused analyses are conducted as part of the signal assessment (e.g. for a specific adverse event or signal of interest), it is essential that the approach to case selection is reproducible and sufficiently detailed to allow independent evaluation. Lack of clarity in case selection or search methodology may limit interpretability and introduce bias into the assessment.

In situations where a complete review of all individual reports may not be feasible, selection criteria maybe useful to reduce the number of cases to be reviewed. The use of percentages may support interpretation, and the criteria should always be clearly stated.

2.4.2.2. Key components of causality assessment at signal level

The detailed review and assessment of adverse event reports (AERs), including case narratives, is a key component of signal assessment. This step aims to evaluate the potential causal association between exposure to a VMP and the AEs of interest, thereby contributing to the identification and characterisation of potential safety risks and supporting timely, proportionate regulatory decision-making.

The assessment of individual cases in the context of signal assessment should not be interpreted as a requirement to assign a formal causality category to all reported adverse event reports. A distinction should be made between assigning a formal overall causality assessment of an AER (which may involve multiple events and/or multiple products) and the targeted assessment of a defined case series addressing a specific event (or group of related events) included in the signal and its potential causal association with a specific product/substance. The purpose of the latter is to determine the extent to which the available cases support or weaken the product-event association under investigation.

As most AERs are based on clinical suspicion, certainty regarding causality is rarely achievable and not required for decision making. The structured evaluation of individual cases should provide a transparent and reproducible framework to assess causal plausibility, distinguishing potentially product-related events from coincidental or background occurrences.

This assessment also supports the prioritisation of signals for further benefit–risk evaluation and the consideration of appropriate risk minimisation measures, including potential updates to product information. Relevant contextual factors, such as co-reporting of lack of expected efficacy and use outside the terms of the marketing authorisation (off-label use), may also be considered.

All relevant cases should be assessed using a consistent approach and, where appropriate, categorised according to the strength of evidence supporting a causal association. The total number of supportive cases should be determined and their strength as evidence of an overall causal association should be clearly evaluated.

When assessing whether cases support a causal association, the following elements should be considered:

Quality and completeness of case data

Adverse event reports, including case narratives and structured data fields, should include sufficient detail to support evaluation of causality and clinical plausibility. In addition to the minimum criteria, ideally cases should include: a description/diagnosis of the AE, the temporal relationship to VMP exposure (which may be captured in structured fields such as time-to-onset), relevant animal characteristics and clinical background, co-reported treatments, outcomes and available follow-up. The information should also enable identification of potential confounders and alternative aetiologies.

Review of case narratives remains essential to provide clinical context, risk characterisation and interpretative detail that may not be captured in coded or structured data. However, ideal cases are not the norm, and flexibility should be applied even when all desired information is not present.

Cases with incomplete, unclear or inconsistent information limit interpretability and may introduce uncertainty or bias into the assessment. Such poorly documented cases should therefore be interpreted with caution and weighed accordingly in the overall evaluation, in conjunction with other lines of evidence.

Where the overall information available from the entire case series is insufficient to assess causality or clinical plausibility, additional data or clarification should be sought whenever feasible, applying a risk-based and proportionate approach. Where relevant, this may include the identification of specific information needed (e.g. additional diagnostic investigations or clinical details) to support improved assessment in future cases.

Time-to-onset (TTO)

It should be assessed whether the interval between exposure to the VMP and the onset of the adverse event is compatible with a biologically plausible mechanism of action. The expected TTO depends on the pharmacological properties of the product and the nature of the adverse event. Both very short

and delayed onsets may be plausible, provided they are consistent with the pharmacokinetics and pharmacodynamics of the product and/or known or hypothesised mechanisms, if available.

A TTO that is poorly compatible with the expected pharmacology or pathophysiology may weaken the causal relationship for the case in question, whereas a consistent and reproducible TTO across cases can strengthen the signal. Characterising typical TTO over the entire case-series is also relevant for characterisation of the risk (see examples 51-53).

Examples

51: Compatible TTO (acute pharmacodynamic effect):
In horses treated with an α2-agonist, profound sedation and bradycardia occurring within 5 minutes of administration is highly compatible with the known mechanism of action and supports a signal of bradycardia.

51: Compatible TTO (delayed toxicity):
In cats, elevations of Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP) occurring 3–4 weeks after initiation of an azole antifungal are compatible with subacute or idiosyncratic hepatotoxicity.

53: Non-compatible TTO:
The occurrence of an adverse event on the same day as first administration for an event known to require prolonged exposure (e.g. cataract formation, malignant neoplasia or chronic organ damage), represents a time-to-onset that is not biologically plausible and argues against a causal relationship.

Dechallenge

A dechallenge refers to the withdrawal of a VMP, or in some cases a reduction in dose, following the occurrence of the adverse event of interest. Dechallenge may be undertaken intentionally to observe the effect of treatment withdrawal or may occur incidentally as part of routine clinical management.

A dechallenge is considered positive when the adverse event or clinical signs improve after discontinuation or dose reduction. When assessing a dechallenge, it is important to consider potential confounding factors that may influence recovery, such as concurrent treatments, supportive care or the expected natural course and duration of the event. The time to improvement following withdrawal should also be evaluated to determine whether it is consistent with the elimination time of the product and expected end of clinical effect.

A positive dechallenge is generally considered to significantly strengthen the causal association for any individual case and the presence of one or more cases with positive dechallenge(s) is considered supportive evidence in favour of the signal (see example 54).

Example

54: A signal is identified in dogs presenting with intense pruritus during treatment with an ectoparasiticide administered via a collar. Across several cases, a consistent pattern is observed: pruritus develops shortly after collar application, in the absence of concurrent medications or other identifiable triggers (e.g. no evidence of flea or other ectoparasite infestation, allergic disease or environmental factors).
Following removal of the collar, clinical signs improve markedly within a few days without additional therapeutic intervention. This clear temporal relationship between exposure (collar application) and resolution of clinical signs upon withdrawal (collar removal) constitutes a positive dechallenge. Considering the known pharmacological activity of the ectoparasiticide, this observation supports a causal association between collar use and pruritus.

Rechallenge

A rechallenge occurs when a product or active substance is reintroduced, or the dose is increased, after a previous dechallenge. A rechallenge is considered positive if the adverse event reoccurs or worsens following re-exposure.

Reintroduction of treatment suspected to cause adverse events may be unethical or present unacceptable risk to the animal, particularly when the suspected adverse events are serious. When a rechallenge is available, the assessment should consider the same factors as for dechallenge, including timing of recurrence, consistency of clinical signs and potential alternative explanations.

Cases with positive rechallenge are considered very strong evidence in favour of a causal association (see example 55).

Example

55: (Same dogs with pruritus from an ectoparasiticide from example 54): In a few of the cases described in example 54, following complete resolution of pruritus after removal of the ectoparasiticide collar (positive dechallenge), the same product is re-applied at a later time. Intense pruritus reappears shortly after re-exposure, consistent with the previous clinical presentation and in the absence of alternative explanations.
This recurrence of clinical signs upon re-administration constitutes a positive rechallenge and provides very strong support for a causal relationship between the ectoparasiticide collar and the observed adverse reaction.

Alternative causes

When assessing a signal, it is essential to systematically evaluate whether the reported adverse event may be more likely explained by causes other than exposure to the VMP. Consideration of alternative explanations helps avoid false attribution of causality and supports a balanced, scientifically robust assessment.

Potential alternative causes may include underlying or concurrent disease, infectious agents, management or husbandry factors, diagnostic or therapeutic procedures, environmental exposures or the natural course of the condition being treated.

The assessment of alternative causes should take into account:

- Clinical context: e.g. presence of pre-existing conditions, comorbidities, age-related susceptibility or disease progression that could reasonably explain the event fully or partially.
- Temporal relationships: Whether the timing of onset is more consistent with an alternative cause than with exposure to the product.
- Population patterns: e.g. occurrence of similar clinical signs in animals not exposed to the product, suggesting a background, management-related or infectious origin.
- Procedures and environment: e.g. recent interventions (e.g. surgery, injection, transport), housing conditions, feed changes, environmental stressors or toxins.

Alternative causes should be evaluated in the context of all available information and weighed against evidence supporting a product-related effect (see examples 56-57).

Examples

56: Diarrhoea is reported in calves following administration of an antibiotic. However, PCR testing confirms rotavirus infection and similar diarrhoeal clinical signs are observed in multiple untreated calves on the same farm. The temporal and epidemiological pattern is therefore more consistent with an infectious background cause than with a drug-related adverse event, making a causal association with the product unlikely.

57: An acute anaphylactic reaction is reported shortly after administration of multiple vaccines during the same visit. The presence of more than one concurrently administered product represents a relevant alternative explanation and prevents attribution of causality to a single vaccine. Nevertheless, anaphylaxis is a well-defined, highly specific clinical syndrome with a strong association with medicinal product exposure and few plausible non-drug causes. In this context, the causal association with vaccination remains possible, even though attribution to an individual product is not feasible.

Co-reported treatments and potential drug–drug interactions

The presence of co-reported treatments and their potential to contribute to, modify or fully explain the reported adverse event should be assessed. This assessment should include consideration of possible drug–drug interactions, including pharmacokinetic and pharmacodynamic interactions, additive or synergistic effects, as well as confounding by indication or by underlying disease requiring co-treatment.

Particular attention should be paid to whether a co-reported medicinal product has a known association with the reported event, as documented in its product information or in the published literature and whether the time-to-onset is plausible and consistent with the reported event. In such situations, attribution of the event to the product under investigation may be weakened, especially when the alternative explanation offers a more plausible or well-established causal relationship (see examples 58-60).

Examples

58: Drug–drug interaction (additive or synergistic effects)

Bradycardia is observed during sedation in a dog receiving an α2-adrenergic agonist in combination with acepromazine and an opioid. All administered products are known to exert cardiovascular depressant effects, and the timing and clinical presentation are consistent with an additive or synergistic pharmacodynamic interaction. Unless overdose of a specific product is identified, the event is more plausibly explained by combined drug effects rather than by a single causal agent.

59: Concurrent treatment as the more likely culprit

A signal of gastrointestinal ulceration is reported in dogs receiving long-term phenobarbital therapy. However, review of case narratives identifies recent concurrent administration of a non-steroidal anti-inflammatory drug (NSAID) in the period immediately preceding onset of clinical signs. NSAIDs are well recognised to be associated with gastrointestinal ulceration and bleeding, with a plausible TTO, whereas phenobarbital is not commonly linked to this adverse event. In this context, the concurrent NSAID represents a more plausible causal explanation, weakening attribution to phenobarbital.

60: Equal plausibility of concurrent treatments

A dog receives an NSAID and an antibiotic concurrently and subsequently develops diarrhoea and anorexia. Both medicinal products are known to be associated with gastrointestinal adverse events and the TTO is compatible with exposure to either treatment. In the absence of dechallenge or other distinguishing clinical features, both products represent plausible contributors and attribution of causality to a single product is not possible. The causal association with each product should therefore be considered possible.

Adverse events specifically known to be drug-related

Assess whether the reported adverse event represents a highly specific clinical syndrome or a well-defined medical condition that is known to be strongly associated with drug exposure and has a limited number of alternative causes. Adverse events with a characteristic and recognisable clinical presentation may have a high predictive value for a drug-related effect and can therefore strongly support causality, even in the absence of multiple cases.

This criterion focuses on the nature and specificity of the event itself, rather than on its frequency or TTO. Events that are considered medically significant conditions often fall into this category due to their seriousness and strong association with medicinal products.

Examples of specific syndromes known to be drug-related include immediate anaphylaxis, toxic epidermal necrolysis, agranulocytosis or acute hepatic failure, where alternative explanations are limited and a drug-related mechanism is well recognised (see also example 61).

Example

61: A cat develops a progressive, locally invasive fibrosarcoma at a previous injection site. Injection-site sarcoma in cats is a well-recognised, specific pathological entity strongly associated with prior parenteral administration of VMPs, particularly vaccines or other injectable substances. Although TTO may be prolonged, the characteristic tumour type, anatomical localisation and clinical progression form a highly specific clinical picture with limited alternative explanations. The specificity of this malignancy therefore provides strong support for a causal association with previous injection exposure, even in the absence of clustering in time or multiple comparable cases.

Consistency across cases

Assess whether similar patterns are observed across multiple cases, including consistency in TTO, clinical presentation, severity, outcome or affected subpopulations. Reproducible patterns strengthen the signal and support a causal association, particularly when they are observed independently and are not readily explained by alternative causes.

Use of predefined VeDDRA groupings is recommended to capture the full clinical spectrum of an event, including related clinical signs, stages or manifestations and to avoid fragmentation or double counting of conceptually linked terms (see example 62).

Example

62: A series of reports describes dogs developing urticaria followed by facial oedema within 30 minutes of injection. Similar time-to-onset and clinical progression are observed across cases, with small breeds disproportionately represented. The consistency of clinical features, timing and affected subpopulation supports a coherent hypersensitivity signal.

Dose-response relationship (if applicable)

Assess whether there appears to be a relationship between dose, duration of exposure, or cumulative exposure and the occurrence, severity or duration of the adverse event. The key question to address is whether higher doses, longer treatment duration or use outside the authorised conditions are associated with an increased likelihood, earlier onset or greater severity of the event. Identification of such patterns may support pharmacological plausibility and strengthen the causal assessment.

However, it is important to recognise that not all adverse events are dose dependent. Idiosyncratic reactions, immunologically mediated events or hypersensitivity reactions may occur independently of dose or exposure duration. Therefore, absence of a clear dose–response relationship does not exclude a causal association and should be interpreted in the context of the known pharmacology of the product and the nature of the event (see examples 63-65).

Examples

63: A cat develops polyuria/polydipsia and elevated liver enzymes following administration of a high dose of a corticosteroid over a prolonged period. The severity and persistence of clinical signs increase with continued exposure, consistent with a dose and duration dependent adverse event and supporting a causal relationship.

64: A cat tolerates long-term treatment with low-dose corticosteroids without adverse events. Following an increase in dose due to disease flare-up, the cat develops clinical signs consistent with iatrogenic Cushing's syndrome. Across several cases, more severe clinical signs are observed in animals receiving higher doses compared with those treated at lower doses, supporting a dose-dependent relationship.

65: Several dogs develop acute hypersensitivity reactions following administration of an ectoparasiticide. The reactions are reported after standard authorised doses and there is no evidence that higher doses increase either the frequency or severity of the reactions. As hypersensitivity reactions are typically immune-mediated and not dose-dependent, the absence of a dose–response relationship does not argue against a causal association.

2.4.2.3. Standardised systems for causality assessment

All case reports included in signal evaluation should be categorised for causality using consistent and predefined categories and supported by a clear and explicit rationale. The assessment should document the applied criteria as well as the key elements supporting or arguing against a causal association, such as temporal relationship, dechallenge/rechallenge, biological plausibility and the presence of alternative causes.

Use of standardised causality assessment systems ensures transparent, reproducible and harmonised evaluations, facilitates prioritisation of signals for further follow-up and supports proportionate and consistent benefit–risk decision-making at both MAH and regulatory authority level.

Although standardised systems can support these objectives, there is no longer a regulatory requirement in the EU to assign a formal overall causality category to each adverse event report. Nevertheless, a structured and transparent evaluation of causal plausibility remains essential for the identification and selection of cases supporting a signal, as well as for the overall signal assessment.

This approach reflects the distinction between assigning an overall causality classification to a single case and evaluating the causal plausibility of a specific medicinal product–event association across a series of cases within the context of signal management.

Several causality assessment systems and criteria have been described in pharmacovigilance, however, the only system specifically adapted for veterinary pharmacovigilance is the ABON system, which is widely used and accepted within the EU veterinary regulatory framework (see examples 66-69).

Examples

66: ABON System

The ABON system provides a structured approach to classify the likelihood of a causal association between a VMP and a reported adverse event. It is specifically adapted for use in veterinary pharmacovigilance and supports consistent and transparent assessment of individual cases.

The ABON causality categories are defined as follows:

A – Probable: A reasonable temporal relationship to product administration is present; the event is consistent with known pharmacological or biological properties of the product; alternative causes are unlikely; and, where available, dechallenge information is supportive.

B – Possible: A temporal relationship exists; however, alternative explanations such as underlying disease or concurrent treatments cannot be excluded.

O1 – Insufficiently documented (assessment pending): A causal association cannot be assessed because key information is missing or still under investigation. Additional data may reasonably be expected to allow further evaluation.

O – Unclassifiable / insufficient data: Available information is inadequate, contradictory or incomplete, preventing meaningful assessment and no further data are expected to become available.

N – Unlikely: The event shows no reasonable temporal relationship to product administration or is more plausibly explained by alternative causes.

The ABON system is based on evaluation of six core factors:

1. Temporal relationship between exposure and event
2. Pharmacological or biological plausibility
3. Clinical and/or pathological findings
4. Prior knowledge, including published literature and product information
5. Consideration of alternative causes
6. Quality and reliability of the available data

By systematically applying these criteria, the ABON system supports harmonised interpretation of individual cases and provides a common framework and terminology for causality assessment in veterinary pharmacovigilance.

Several systems, optimised for use in human pharmacovigilance also exist, for example:

67: WHO–UMC Causality Assessment System

The WHO–UMC system classifies the likelihood of a causal association using standardised categories (Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified, Unassessable).

68: Naranjo Algorithm

The Naranjo algorithm is a questionnaire-based scoring system designed to provide a structured estimate of causality (Definite, Probable, Possible, Doubtful) based on factors such as temporal relationship, dechallenge/rechallenge, alternative causes and prior knowledge.

69: Bradford Hill Criteria

The Bradford Hill criteria describe a set of general epidemiological considerations (e.g. strength and consistency of association, temporality, biological gradient, plausibility and coherence) to support inference of causality between an exposure and an outcome.

References:

https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf

Naranjo CA et al. *A method for estimating the probability of adverse drug reactions*. Clin Pharmacol Ther. Clin Pharmacol Ther. 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154.

Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965 May;58(5):295–300. doi: 10.1177/003591576505800503

2.4.3. Investigation of biological mechanism

The investigation of a biological mechanism is a critical component in the assessment of a pharmacovigilance signal. It aims to determine whether there is a scientifically plausible explanation for the potential causal relationship between the suspected adverse event and the VMP. Establishing such a mechanism strengthens the case for a causal association and supports regulatory decision-making.

A structured assessment of biological plausibility typically begins with the key question:

- *Is there a reasonable biological mechanism that could explain the adverse event?*

If the answer is yes, this biological rationale reinforces the signal, increases its credibility and may guide further actions (e.g. targeted data collection, risk minimisation measures).

If no plausible mechanism is identified, it is crucial to distinguish between a genuine absence of biological plausibility, suggesting that a causal association is unlikely, or insufficient data or incomplete scientific understanding, meaning that the lack of a mechanism should not be interpreted as disproving the association.

Elements to consider when investigating whether there is a potential biological mechanism are summarised in this section. The list should not be considered exhaustive.

2.4.3.1. Pharmacodynamics (PD)

It should be evaluated whether the intended mode of action or secondary pharmacological effects of the product could logically lead to the observed event (see example 70).

Example

70: A prostaglandin analogue used for oestrus synchronisation is known to also cause smooth muscle contraction. Contraction of smooth muscle in airways would be a plausible mechanism for an adverse event such as broncho-constriction in susceptible animals.

2.4.3.2. Pharmacokinetics (PK)

The following aspects should be considered: systemic exposure, absorption, distribution, metabolism and excretion of the product, including the formation of active or toxic metabolites, potential accumulation with repeated dosing and pharmacokinetic interactions with concurrent treatments (see examples 71-73).

Examples

71: A product that is predominantly excreted via the kidneys, either unchanged or as metabolites, may be more plausibly associated with renal adverse events than a product primarily cleared through hepatic metabolism and biliary excretion. Such considerations are particularly relevant when evaluating signals related to renal toxicity, changes in renal function parameters or exacerbation of pre-existing renal disease.

72: A signal of hepatic encephalopathy is identified for a VMP that is extensively metabolised in the liver and cases appear to occur primarily in treated animals with pre-existing hepatic disease. Impaired hepatic metabolism and clearance may result in accumulation of the parent compound or active metabolites, leading to increased systemic exposure and neurological signs. Therefore, the pharmacokinetic reliance on hepatic function supports a plausible mechanism for the observed adverse events.

73: A drug known to cross the blood-brain barrier (in all or certain individuals) is more likely to cause seizures or other neurological AEs.

2.4.3.3. Toxicology and Non-Clinical Findings

Prior or newly identified knowledge from non-clinical studies, including toxicology, safety pharmacology and target-organ findings, should be considered when investigating the potential biological mechanism behind a signal. Such data may originate from the product itself, related substances, or experience in other animal species or in humans and can provide important insight into relevant biochemical pathways or susceptible organs (see example 74).

Example

74: Mild liver enzyme elevations observed in repeat-dose toxicology studies in dogs, or evidence of hepatotoxicity reported in another species or in humans, can support the plausibility of hepatobiliary adverse events reported post-authorisation in the target species.

2.4.3.4. Specific susceptibility of subpopulations

Certain subpopulations may present specific physiological, genetic or pathological characteristics that increase their vulnerability to adverse events. Such susceptibilities may be related to species-specific or breed-specific traits, explicit genetic factors (e.g. polymorphisms affecting metabolism or target

receptors), age, reproductive status, or the presence of underlying diseases or concurrent conditions. Identification of these factors can support biological plausibility and help refine the risk characterisation of a signal. Where a susceptible subpopulation is identified and considered clinically relevant, this information may contribute to subsequent risk minimisation measures or amendments to the product information (see examples 75-78).

Examples

75: Genetic or breed-related susceptibility:
Dogs of collie-type breeds carrying the MDR1 gene mutation have increased susceptibility to ivermectin-induced neurotoxicity due to impaired P-glycoprotein function at the blood–brain barrier.

76: Comorbidity-related susceptibility:
Epileptic dogs may be more susceptible to seizures when exposed to medicinal products with the potential to lower the seizure threshold, such as certain ectoparasiticides.

77: Age-related susceptibility:
Very young puppies, with immature hepatic metabolic capacity, may be at increased risk of adverse effects when treated with non-steroidal anti-inflammatory drugs (NSAIDs).

78: Species-specific sensitivity:
Cattle exhibit markedly higher sensitivity to alpha-2 adrenergic agonists compared to dogs, resulting in a greater risk of overdose and pronounced pharmacodynamic effects at relatively low doses.

2.4.3.5. Literature and Post-Marketing Experience

Published scientific literature and accumulated post-marketing experience should be considered specifically to support the assessment of biological plausibility of a signal. This includes relevant evidence from case reports, mechanistic or pharmacological studies and clinical or field observations that help interpret the observed association.

Particular attention should be given to evidence of known class effects, experience with the same active substance or information reflected in the product information of currently authorised products. Such data can provide important mechanistic context or indicate consistent patterns of adverse events, even when the precise underlying mechanism is not fully established (see example 79).

Example

79: If adverse gastrointestinal events are well recognised for other VMPs containing the same active substance, or for products belonging to the same pharmacological class, this supports the plausibility of a substance or class-related mechanism.

2.4.4. Special types of signals

Some signals require specific consideration during assessment of causality due to their nature or inherent characteristic. These include signals related to lack of efficacy, medication errors, user safety, residues and public health and environmental risks. While the general principles of signal management apply, the assessment approach may need to be tailored to adequately address the specific risks involved and their broader implications.

2.4.4.1. Signals concerning lack of efficacy and antimicrobial resistance

Signals of lack of expected efficacy (LEE) may arise from individual reports of treatment failure or from emerging patterns across multiple cases. Assessment should distinguish between issues related to conditions of use (e.g. incorrect dosing, non-compliance, inappropriate indication, management factors) and those potentially reflecting reduced effectiveness of the product.

Causality assessment should focus on whether the reported lack of effect is reasonable in light of the authorised indication(s). For products with multiple indications (e.g. treatment of different conditions or both clinical and microbiological claims), consistency across reports regarding the disputed indication should be examined.

In the context of antimicrobials and antiparasitics, LEE signals may be indicative of emerging resistance, including antimicrobial resistance (AMR). Evaluation should consider evidence of reduced susceptibility of target organisms, regional or species-specific patterns and consistency with known or plausible resistance mechanisms.

For vaccines, LEE signals may also reflect the emergence or spread of new or variant strains against which the currently authorised vaccine provides insufficient cross-protection. In such cases, the assessment should consider the antigenic match, epidemiological trends and available evidence on circulating strains, as well as the precise indication of the VMP and statements in the PI regarding demonstrated cross-protection against other or specific strains.

Such signals may warrant closer monitoring, further investigation and coordination with resistance surveillance systems, antimicrobial stewardship activities and, where relevant, epidemiological and vaccine strain monitoring programmes.

2.4.4.2. Signals concerning medication errors

Signals related to medication errors may involve incorrect dosing, wrong route or species, misuse, accidental exposure of target or non-target species, or issues related to product presentation, labelling or administration devices.

Assessment should focus on identifying:

- The type and frequency of the error;
- Whether a pattern or recurrent cause can be identified;
- Whether the error is reasonably foreseeable and preventable;
- The potential consequences for animal health, user safety, public health or the environment.

Medication errors may be considered preventable when they are reasonably foreseeable and linked to product design, labelling, instructions for use or real-world use conditions.

In cases of intentional misuse, the assessment should focus on the extent of occurrence, preventability and, where identifiable, the underlying reasons for the misuse (see also Guidance notes on the use of VeDDRA terminology for reporting suspected adverse events in humans and animals).

2.4.4.3. Signals concerning user safety

Signals affecting the people who are handling and administering the VMP, i.e. users (e.g. veterinarians, farmers, animal owners) require particular attention. All VeDDRA terms are considered medically important for humans.

The focus of the assessment is often similar to an assessment of medication errors, where focus is placed on identifying patterns leading up to the risk and the potential preventability of the risk and available treatment options.

For example, needlestick injuries associated with mineral oil adjuvanted vaccines can result in severe human tissue injury and long-term morbidity. Such signals may warrant strong warnings in product information, enhanced training, changes in handling recommendations or implementation of safer administration practices.

2.4.4.4. Signals concerning Residues/Public health

Signals related to residues in food producing animals may indicate potential issues with withdrawal periods, compliance with authorised use conditions or residue depletion assumptions. Evaluation should consider whether reported findings suggest that existing withdrawal periods may be insufficient under certain conditions of use, animal categories or management practices.

Such signals are of particular importance due to their potential implications for consumer safety and may require targeted investigations, review of residue data or regulatory action to protect public health.

2.4.4.5. Signals concerning environmental risks

Environmental signals relate to unintended adverse effects on non-target organisms or ecosystems following use of VMPs (see also sections 2.2.1.11 and 2.3.1.3). These may include, for example, adverse effects on dung fauna or water-environments associated with certain antiparasitic products.

Assessment should focus on analysis of plausible routes of environmental exposure, assessment of preventability and consistency with known ecotoxicological properties of the active substance and potential real-world consequences for the environment. Where appropriate, the need for risk-mitigation measures or restrictions of use should be considered.

2.4.5. Risk characterisation

Risk characterisation aims to describe the risk clearly and comprehensively, based on the totality of available evidence, in order to support benefit–risk evaluation and regulatory decision-making. It focuses on defining the nature, seriousness, severity and frequency of the event(s).

The outcome of the risk characterisation should clearly describe:

- What the risk is, including its clinical definition, seriousness and medical importance, as well as the observed range of severity and associated uncertainty;
- Who is at risk, taking into account species, breed, genotype, age, physiological status and relevant comorbidities;
- When and under which conditions it occurs, including time-to-onset, on-label or off-label use, route of administration, dose and conditions of use;
- How often the event occurs, where feasible.

2.4.5.1. Defining the risk precisely

In order to define the risk more precisely, the collective experience of the event(s) from all available sources should be summarised. The summary should clearly describe what occurred and in which animals, humans or environmental compartments.

Where available, the summary should include:

- Average time-to-onset, preferably together with the observed range (from–to) and/or distribution of time-to-onset should be reported where available, to capture variability and support a more precise characterisation of the temporal pattern of the event;
- Clinical course;
- Reversibility of the event(s), including the outcome of any dechallenge;
- Overall final outcome (recovered, recovered with sequelae, not recovered/outcome unknown, fatal);
- Any reported long-term sequelae.

Based on this summary, consideration should be given to identifying the VeDDRA term(s) that most precisely describe the event(s).

An assessment of overall seriousness, severity and medical importance should then be performed. This includes classification of whether the event(s) meet seriousness criteria (e.g. death, life-threatening, significant disability, congenital anomaly or other medically important events), in accordance with internationally harmonised definitions (VICH GL24) (see also section 2.2.1.4). The range of severity, from mild to severe and where possible the proportion of severe cases among all assessed cases should also be characterised. The list of medically important terms may also be used at the step of signal assessment to assist the assessment of medical importance.

Following causality assessment, the number and/or percentage of supportive cases should be known. A reporting incidence may be provided, calculated from the cumulative number of spontaneous reports and the estimated cumulative exposure. Reporting incidence is subject to limitations, including under-reporting, case ascertainment bias, stimulated reporting and uncertainty in exposure denominators. Therefore, other data sources, such as clinical trials or post-marketing surveillance studies, should be considered where available. Reporting incidence may contribute to signal characterisation but is neither supportive nor dismissive of a signal in itself.

See examples 80-82 on how to summarise information.

Examples

80: Based on EVVet data, the MAH safety database and literature, 18 cases of acute reactions were identified in adult cattle following administration of an inactivated vaccine. Clinical signs typically occurred within 5–30 minutes and included dyspnoea, collapse and convulsions. Most affected animals improved following appropriate symptomatic treatment and recovered completely. The final outcome was recovery in 13 animals and death in 5; no long-term sequelae were reported. The most appropriate VeDDRA terms were Anaphylactic reaction and Acute hypersensitivity. The events met VICH GL24 seriousness criteria (life-threatening and fatal), with approximately 30% of cases classified as severe. Following causality assessment, 14 cases were considered supportive. A reporting incidence was estimated and interpreted with caution.

81: A total of 245 spontaneous reports described vomiting and diarrhoea in dogs treated with an NSAID at authorised doses. The average time-to-onset was 2–5 days after treatment initiation. Clinical signs were generally mild and reversible, resolving shortly after treatment discontinuation. Most animals recovered fully and no long-term sequelae were reported. The VeDDRA terms Vomiting and Diarrhoea were considered most appropriate. The events did not meet seriousness criteria and severity was predominantly mild to moderate, with a low proportion of severe cases. Following causality assessment, 180 cases were considered supportive. A reporting incidence was calculated as a descriptive element of signal characterisation.

82: Thirty-two reports described injection-site reactions in cats following administration of a long-acting injectable product. The average time-to-onset was 7–21 days. The clinical course included local swelling and, in some cases, abscess formation. Reversibility was variable and surgical intervention was required in several cases. Most animals recovered, although persistent local masses were reported as long-term sequelae. The most relevant VeDDRA terms were Injection site reaction and Injection site mass. While most events were non-serious, some were considered medically important. Following causality assessment, 20 cases were considered supportive and a reporting incidence was provided with the usual limitations.

Frequency estimates

Following causality assessment, the number and/or percentage of supportive cases should be known. Where feasible, an estimate of event frequency may be provided to support signal characterisation. Frequency may be estimated either from the number of supportive cases identified through causality assessment or as a reporting incidence calculated from the cumulative number of spontaneous reports in relation to the estimated cumulative exposure (see Guideline on the calculation of dose factor to be submitted to the Union Product Database (UPD)[41]).

Reporting incidence and other frequency estimates are subject to important limitations inherent to spontaneous reporting systems, including under-reporting, reporting bias (including stimulated reporting following communications or media attention), case ascertainment bias and uncertainty in exposure denominators. Frequency estimates should therefore be interpreted with caution and considered hypothesis-generating only. Where available, additional data sources, such as clinical trials, post-authorisation surveillance or epidemiological studies, should be taken into account to support interpretation. Estimates should be reviewed as more robust data become available.

Irrespective of the method used, frequency estimates cannot be used to conclude on the likelihood of a causal association. They represent one element of risk characterisation and may become relevant where the outcome of the signal assessment is an update of the product information (see example 83).

Example

83: There were forty cases reported cumulatively. Twenty-five of these were considered supportive following causality assessment. Frequency may be estimated from the 25 supportive cases alone, or a reporting incidence may be calculated from the total number of 40 reported cases.
Based on estimated cumulative exposure, the reporting incidence suggests that the frequency is rare while the frequency estimate from supportive cases alone suggests that the event is very rare. However, given the likelihood of under-reporting and uncertainty in exposure estimates, estimates should be interpreted cautiously and used primarily to support signal characterisation rather than to quantify true incidence. If one of the two frequencies are to be used for a future product information update, the worst-case-scenario is generally preferable.

2.4.5.2. Identifying special circumstances of the risk

The risk characterisation should identify and describe any special circumstances under which the risk is more likely to occur or may be exacerbated. These circumstances may relate to specific subpopulations, conditions of use, or product-related factors and are critical for refining risk awareness and informing appropriate risk minimisation measures. Additionally, any circumstances identified which reduce the risk of the event(s) either with respect to occurrence or outcome, should also be described.

Restriction to specific subpopulations

Certain risks may be confined to, or more pronounced in, particular subgroups due to physiological, genetic or pathological characteristics. These may include:

- Species, breeds or genotypes: For example, dogs of herding breeds carrying the *MDR1 (ABCB1)* gene mutation are predisposed to neurotoxicity when exposed to certain macrocyclic lactones or loperamide, necessitating tailored warnings, dose restrictions or avoidance at higher doses.
- Age or physiological status: Increased susceptibility may be observed in neonates, geriatric animals, pregnant or lactating animals, or specific production classes (e.g. high-yield dairy cattle).
- Comorbidities and concurrent medication: Underlying renal or hepatic impairment, dehydration, or the use of interacting medicinal products (e.g. concurrent NSAIDs and corticosteroids) may increase the likelihood or severity of adverse outcomes.

Conditions of use

The circumstances under which a product is used may significantly influence the risk profile and should therefore be carefully evaluated. Relevant factors may include:

- Use outside authorised conditions: Off-label use, overdose, incorrect route or frequency of administration, misuse, medication errors, or issues related to product quality or specific batches.

- Environmental or management factors: external conditions such as temperature extremes, transport or handling stress, housing conditions or, in aquaculture, water quality parameters, which may contribute to or exacerbate adverse effects.

Product and formulation-related factors

Specific characteristics of the product or its formulation may influence the occurrence or nature of the risk, including:

- Formulation and excipients: Certain excipients, solvents or adjuvants may contribute to hypersensitivity reactions or exacerbate toxicity.
- Presentation and delivery devices: Issues related to applicators, syringes or other delivery systems may facilitate incorrect dosing, misuse or accidental exposure.

See examples 84-86.

Examples

84: Genotype-restricted neurotoxicity (macrocyclic lactones/loperamide in MDR1-mutant dogs): Use of certain macrocyclic lactones or loperamide is associated with acute neurological adverse events (e.g. ataxia, tremors, seizures) in dogs carrying the MDR1 (ABCB1) gene mutation, predominantly affecting herding breeds. Events may be severe but are uncommon and mainly reported following off-label or high-dose use or in the presence of interacting co-medications. When products are used according to authorised conditions and breed-specific precautions are followed, the likelihood of occurrence is low. Risk minimisation includes strengthened SPC/PL warnings, avoidance or dose adjustment in susceptible breeds and targeted monitoring.

85: Several reports described increased incidence and severity of adverse cardiovascular and respiratory events in pigs treated with a sedative during periods of high ambient temperature. Most cases occurred during summer months and were associated with treatment administered shortly before transport under conditions of heat and handling stress. Clinical signs included hyperthermia, respiratory distress and collapse, with rapid onset after administration. When the same product was used under comparable conditions but at moderate temperatures and without transport-related stress, adverse events were infrequently reported and generally non-serious. This suggests that high environmental temperature combined with handling stress may exacerbate the risk and severity of adverse outcomes.

86: Several reports described increased acute gill irritation and respiratory distress in salmon following bath treatment with an antiparasitic medicinal product formulated as a concentrated aqueous solution. Clinical signs occurred during or shortly after exposure and included increased opercular movement, surfacing behaviour and, in some cases, mortality. The events were more frequently reported when the product was used at the upper end of the authorised concentration range and in sea water with elevated salinity. Comparable adverse events were rarely reported for alternative formulations of the same active substance administered via in-feed treatment. This pattern suggests that formulation-related characteristics affecting local exposure at the gill level, in combination with water parameters, may exacerbate the risk.

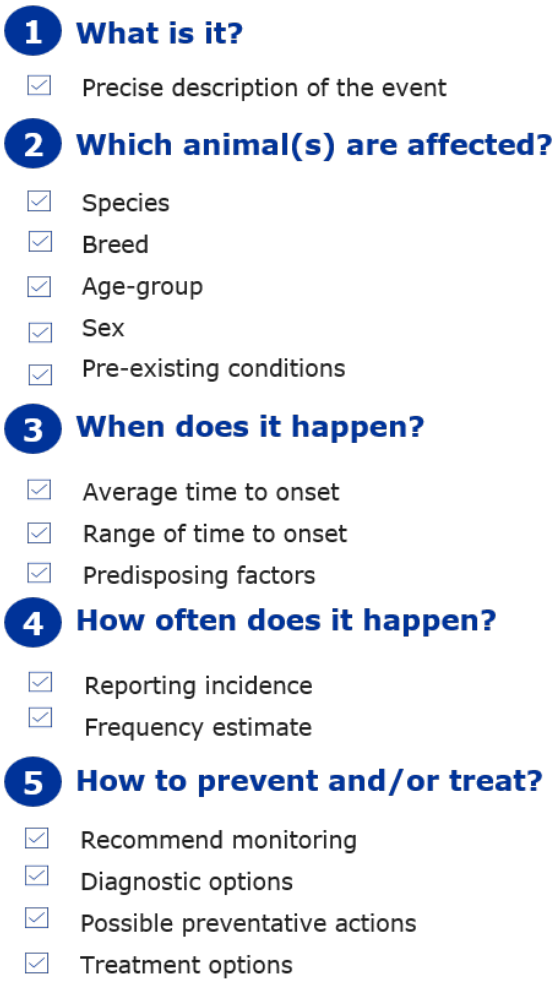

Figure 7: Risk characterisation checklist

2.4.6. Overall conclusion

The overall conclusion of a signal assessment should be comprised of both a risk statement and an overall evaluation of the causal association.

Risk statement

The outcome of risk characterisation should be summarised in a clear and concise risk statement that captures the key elements necessary to support regulatory decision-making and risk communication. The risk statement should explicitly address:

- Nature of the risk: A precise clinical description of the adverse event, including seriousness and medical importance and an assessment of how frequently it occurs and how severe it appears to be acknowledging any uncertainty associated with the available data.
- Population at risk: Identification of the animal, user or environmental subpopulations at increased risk, including relevant species, breeds, genotypes, age groups, physiological states or comorbidities.
- Circumstances of occurrence: Description of when and under which conditions the risk occurs, including authorised versus off-label use, route of administration, dose or duration of treatment and relevant environmental or management factors.

- Broader implications: Consideration of potential implications for user safety, public health or the environment, where applicable.
- Likelihood under normal conditions of use: An overall assessment of the likelihood of the risk occurring when the product is used in accordance with the authorised conditions.
- Consequences and preventability of the risk: Outcome and consequences of the risk, including any identified circumstances which may reduce the risk (occurrence or severity), or ways to treat the consequences.

Causality statement

The overall conclusion on causality should be derived from a structured and balanced assessment of the likelihood of a causal association between the VMP and the reported adverse event(s), integrating the key findings from signal assessment and characterisation and reflecting the weight of the available evidence.

The conclusion should summarise the strength of evidence supporting or refuting the signal, including biological and pharmacological plausibility and the principal causality elements considered (e.g. temporal relationship, dechallenge and rechallenge where available, evaluation of alternative explanations and consistency across cases).

Key uncertainties and limitations should be explicitly acknowledged, including small numbers of cases, incomplete documentation, reporting bias, confounding by underlying disease or concurrent medication and uncertainty in exposure and frequency estimates, together with their impact on interpretation of frequency and severity. Limitations of studies and other literature may also be summarised.

Overall, the conclusion should set out a reasoned, evidence-based assessment of the likelihood of a causal association, providing a transparent and proportionate basis for choosing the correct outcome of the signal assessment.

2.5. Outcomes

The outcome of the signal assessment and the justification thereof, shall be recorded internally and the rationale shall be kept ready for inspection[17]. The justification should explain the reasoning behind the outcome, not simply confirm that data were reviewed.

All validated and assessed signals, including refuted signals and signals under close monitoring, should be submitted to IRIS-VSM in accordance with the Best Practice Guide[9].

Where the regulatory outcome of the signal assessment differs from the MAH's initial proposal, it is expected that the MAH takes due account of the position (e.g. when conducting follow-up activities), in line with its pharmacovigilance obligations under Regulation (EU) 2019/6.

A signal assessment should culminate in one of the following outcomes: the signal is refuted, the signal is placed under close monitoring, or the signal is determined to require risk minimisation measures.

2.5.1. Signal refuted

A refuted signal is a validated signal for which, following further assessment, a causal association is not supported by the available evidence at the time of assessment. The subject of the signal should return to routine pharmacovigilance activities. However, a refuted signal may be considered again as a potential signal, and it may be re-detected and re-submitted if new relevant information becomes available (see section 2.2.2).

Refuted signals should not be confused with non-validated signals (see section 2.3.2.2). Non-validated signals have not undergone full signal assessment and therefore the question of causality has not been considered.

Where signal assessment has been completed and the available evidence was not sufficient to support a causal association, the rationale should be clearly documented. See also section 2.4 regarding factors to consider.

2.5.2. Signal under close monitoring

Where signal assessment indicates a potential causal association between the VMP and the adverse event, but the available evidence is currently insufficient to confirm or refute this association, the signal is not closed and the VMP is placed under close monitoring. At the time of assessment, the signal does not justify immediate risk minimisation measures.

Signals under close monitoring require increased pharmacovigilance activities, which may include increased monitoring frequency, a focus on specific searches, targeted follow-up of incoming adverse event reports, initiation of a PMSS or survey etc. The scope and nature of monitoring should be determined by the data required to conclude the signal assessment, including focused review of relevant incoming information and consideration of cumulative as well as period-specific data. The signal should be re-assessed as additional evidence becomes available.

MAHs are required to submit follow-up assessments of their findings to IRIS-VSM at the latest at the next annual statement submission date. Shorter reporting intervals may be set by the MAH or in certain circumstances by regulators. If shorter reporting intervals are set by the MAH, they are encouraged to notify the relevant regulators by including this information in the signal assessment report. The signal assessment report should clearly state the additional data which has been considered since the last submission as well as a reasoning for the proposed outcome.

Signals under close monitoring would normally be expected to progress to a conclusion (signal refuted or signal requiring risk minimisation measures) within two years. Where close monitoring needs to extend beyond this period, the continued need for close monitoring should be justified, taking into account whether the data required to conclude the signal assessment can reasonably be expected to become available. Cessation of close monitoring may be proposed by submitting a new signal (e.g. with the proposed outcome of 'refuted' or 'amendment of the product information'), supported by a detailed justification. The justification provided within the signal submission will be assessed by regulators and the MAH will be informed of the recommended outcome (see also section 3.1.2.3).

For signals related to outcomes with long latency or slow accumulation of evidence (e.g. neoplasia or rare adverse events in specific sub-populations), longer periods of close monitoring may be appropriate, provided that this is supported by a clear scientific rationale and an active monitoring strategy. If uncertainty remains despite close monitoring, further data generation (e.g. post-marketing surveillance studies) should be considered.

2.5.2.1. Post marketing surveillance studies

In accordance with Article 15(1) of Commission Implementing Regulation (EU) 2021/1281 post-marketing surveillance studies may be conducted by MAHs on their own initiative or shall be conducted by MAHs on request of a competent authority or the Agency in accordance with Article 76(3) and (4) of Regulation (EU) 2019/6.

2.5.3. Signal requiring risk minimisation measures

A signal requiring risk minimisation measures is a validated signal for which signal assessment supports a likely causal association between the VMP and the adverse event. The signal is considered to warrant risk minimisation measures.

Where a signal requires risk minimisation measures, appropriate measures should be identified and implemented in a timely manner. The choice of risk minimisation measures should be proportionate (see also section 2.6).

Outcome of assessment	At the time of assessment	Next step
Signal refuted	Causality not supported	Routine pharmacovigilance activities
Signal under close monitoring	Potential causal association; evidence inconclusive	Additional activities (in addition to routine monitoring), Periodic update with signal re-assessment
Signal requiring risk minimisation measures	Causality supported	Implementing risk minimisation measures, monitor effectiveness, Routine pharmacovigilance

Table 2: Summary of signal assessment outcomes and subsequent actions

2.6. Risk minimisation measures

Risk minimisation measures are interventions intended to reduce the occurrence, severity and / or impact of adverse events associated with veterinary medicines. Their aim is to support veterinary healthcare professionals and animal owners in addressing the risks associated with veterinary medicines.

The key routine risk minimisation tools available for authorised veterinary medicines are the summary of product characteristics (SPC) and the package leaflet (PL). These documents include a description of the risk of use of the veterinary medicine and intended actions for risk minimisation (e.g. contraindications for use). Following signal assessment it may be concluded that risk minimisation measures are required to help manage a specific risk that has been identified.

If it is concluded that a causal association with a new or changed risk is considered likely (see also sections 2.4 and 2.5) then the need for any of the risk minimisation measures described in this section and/or any other measures should be considered, including a variation to the terms of the marketing authorisation. It is recommended to follow up on the effect of risk minimisation measures on the identified risk. Additionally, MAHs may be requested to specifically evaluate the impact.

2.6.1. Amendment of the product information

Following signal assessment changes to the product information may be required by either the addition, amendment or removal of currently authorised text e.g. in the SPC:

- Section 3.2 e.g. removal or restriction of an indication.

- Section 3.3 e.g. a new contraindication.
- Section 3.5 e.g. a new special precaution for use in the target species, user safety or environmental risks.
- Section 3.6 e.g. a new adverse event or change of frequency.
- Section 3.7 e.g. addition of a warning that the product cannot be used during pregnancy or lactation.
- Section 3.8 e.g. limitations on concurrent use with other medicinal products.
- Section 3.9 e.g. a change to instructions for use.
- Section 3.10 e.g. addition of clinical signs of overdose.
- Section 3.11 e.g. special restrictions for use.
- Section 10 e.g. a change to the prescription classification.

The Regulatory outcome of the signal in IRIS will be published as 'Amendment of the product information' and, in accordance with Article 77(10) of Regulation (EU) 2019/6, the applicant should submit either a G.I.19 or G.I.4 variation requiring assessment. This variation will be assessed by the relevant authorities as per the established variation procedures.

When submitting the variation, the MAH should refer to all relevant guidance on variations requiring assessment. Depending on the update, it may be necessary for MAHs to publish communication to end users informing of the change to the product information. EMA/the NCAs may also publish communication regarding changes to product information if considered necessary.

As stated in section 2.3.1.2 if the product information update is related to harmonisation with the reference product, then this is not considered part of the signal management process and should be addressed via the relevant variation procedure.

2.6.2. Additional risk communication

Following signal assessment, if there is a need for immediate or targeted risk communication, a Direct Animal Healthcare Professional Communication (DaHPC) can be circulated to veterinarians and other animal healthcare professionals to inform them of important new safety information about a veterinary medicine and any actions they should take. This could be to advise that:

- A new serious adverse event has been discovered which requires direct communication with animal healthcare professionals.
- Another important change has occurred e.g. a restriction of an indication, a new contraindication, suspension, withdrawal or revocation of a product for safety reasons.
- The product isn't being used as intended e.g. where post-marketing surveillance has highlighted a need for increased awareness regarding specific characteristics of the product.

DaHPCs should contain specific advice, recommendations or information regarding a veterinary pharmacovigilance concern, in particular which may require certain action to be taken or changes in relation to the administration of a VMP.

For more detailed information on the preparation, content, approval and dissemination of DaHPCs please refer to the VGVP module on veterinary pharmacovigilance communication[19].

Other communication initiatives could include short information videos on EMA/NCA/MAH websites, publication of articles raising awareness of an identified risk in veterinary journals or information on the correct use of a product to minimise risk for the animal or the user.

2.6.3. Batch recall, suspension, withdrawal or revocation of the marketing authorisation

On occasion, the risk identified during signal assessment may require the recall of particular batches of product(s). This recall can be to wholesale, veterinary or other end user level (e.g. farmers, companion animal owners, etc). On rare occasions, in accordance with Article 129 of Regulation (EU) 2019/6, the suspension of the sale of any of the product may be required for a certain period of time until the identified risk has been mitigated.

On very rare occasions, if the newly identified or changed risk(s) is deemed to outweigh the benefit of the product then the marketing authorisation may be revoked, meaning the VMP is withdrawn from the market and cannot be marketed anymore without submission of a new marketing authorisation application[20].

2.6.4. Other risk minimisation measures

In addition to the risk minimisation measures listed above other less frequently used measures are also available if required.

2.6.4.1. Educational material

Another option for minimising an identified risk and assisting with measures for prevention could be to provide educational material.

Examples may include:

- Printed leaflets for distribution in veterinary practices or other animal healthcare settings.
- In-person training for veterinarians/other animal healthcare professionals by representatives of the MAH.
- MAH/NCA social media content.
- Internal training of sales representatives/product managers or other relevant staff.
- Creation of a user manual or update of an existing user manual.

See examples 87-89.

[19] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-veterinary-pharmacovigilance-communication_en.pdf
[20] Article 130 of Regulation (EU) 2019/6

Examples

87: A signal of a medication error concerning product use leading to increased risk to users: An educational video or pamphlet is made to support the correct use and administration of the product to avoid accidents.

88: A signal concerning user safety with a very toxic substance (e.g. products used for chemotherapy): A video or pamphlet is made explaining the importance and showing the correct use of personal protective equipment.

89: A signal where adequate monitoring may prevent the AE: A pamphlet is created for the vet and a 'monitoring' schedule/diary for the owner to help them keep track of veterinary visits and explain the importance of them.

3. Reporting to the EU network

	Signal management reportings			Other reportings	
	Annual statements (section 3.1.1)	Signals (section 3.1.2)	PhV alerts (section 3.1.3)	Sales data & dose factor (section 3.2.1)	Regulatory measures worldwide (section 3.2.2)
Frequency and timing	Annually (due date), or higher frequency, if applicable	Action required: within 30 days of assessment no action: at the latest by due date	Within 3 days of detection	Annually (end of February)	Within 30 days
Where	IRIS-VSM	IRIS-VSM	IRIS-VSM	UPD	IRIS-VSM
Relevant links	IRIS portal Due date list	IRIS portal BPG AR template	IRIS portal	UPD portal Dose factor guidance	IRIS portal

Table 3: Reporting to the EU network

3.1. Signal management reporting obligations

MAHs are responsible[21] for continuously monitoring the benefit-risk balance of their VMPs, conducting the signal management process in compliance with the pharmacovigilance guidelines and recording their conclusions in the UPhV-database (IRIS-VSM).

There are two main reporting responsibilities for MAHs; the annual conclusion on the benefit-risk balance (annual statement), which needs to be submitted at least annually for all VMPs with a valid marketing authorisation and the submission of all validated and assessed signals as applicable.

Signal management submissions and annual statement submissions are also accessible by the public on the IRIS platform (public register)[22].

3.1.1. Annual statements

As laid down in the regulations, MAHs shall at least annually record a conclusion on the benefit-risk balance for each of their products in the UPhV-database and confirm that the signal management process has been conducted[23]. This should be done irrespective of whether any signals were detected throughout the year. Furthermore, it applies to all VMPs with a valid marketing authorisation, regardless of the marketing status. Where MAHs are responsible for the same or a similar veterinary

[21] Article 77 of Regulation (EU) 2019/6 and Article 18 of CIR (EU) 2021/1281
[22] https://iris.ema.europa.eu/publicregistersignal/
[23] Article 81(2) of Regulation (EU) 2019/6 and Article 19 of CIR (EU) 2021/1281

medicinal product[24], authorised in different Member States through different authorisation procedures, the signal management process may be performed at active substance level for all the products combined.

At the time of submission of the annual statement, the MAH will have to confirm that all validated signals have been submitted following assessment accordingly in the UPhV-database (IRIS-VSM).

All MAHs shall conduct at least one signal detection analysis per year for each of their active substances or products in the UPhV-database[7]. This signal detection analysis should be performed within 2 months before the annual due date (see section 2.1).

3.1.1.1. Marketing authorisation holder's responsibilities

The responsibility for the MAH to submit an annual statement in accordance with Regulation (EU) 2019/6 is independent of the marketing status. Even if an authorised VMP is not marketed after authorisation, the annual statement should be submitted annually.

In order to limit administrative burden, it is permitted to group same or similar products[25] from the same MAH and submit a grouped annual statement. However, it is not permitted to group products that are not the same or similar e.g. pharmaceuticals and immunologicals.

If the marketing authorisation of a VMP is suspended this does not affect the requirement to submit an annual statement, since this situation corresponds to a temporary marketing cessation which could be lifted. The usual requirements in terms of annual statement submission apply. In this case the option in the annual statement 'The marketing authorisation is currently suspended for reasons related to safety' should be chosen.

In all other cases, the MAH is asked to confirm that the benefit-risk balance remains favourable. This option should also be chosen in case a variation is ongoing concerning the safety of the VMP.

For VMPs for which the marketing authorisation has been withdrawn, revoked or surrendered, there is no need to submit annual statements after cessation of validity of the marketing authorisation.

3.1.1.2. Timelines for annual statement submissions (recommended due dates)

Annual statements should be submitted in accordance with the list of recommended due dates[26] for VMPs including homeopathic medicinal products.

The due dates are allocated to ATCvet codes and spread throughout the year with the aim to even out the submission of annual statements.

MAHs with VMPs with an ATCvet code that is not already included in the list of due dates are advised to send a proposal for a due date to EMA via the 'Send a question to EMA online form'[27]. The proposed new due date may take into account similar ATCvet codes with their assigned due dates. The MAH will be informed about the allocated date in due course.

[24] Article 17(2) of Commission Implementing Regulation (EU) 2021/1281
[25] https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl24-guideline-pharmacovigilance-veterinary-medicinal-products-management-adverse-event-reports-aers_en.pdf
[26] https://www.ema.europa.eu/en/documents/other/recommended-due-dates-submitting-annual-statements-centrally-non-centrally-authorised-products-caps-non-caps-homeopathic-medicinal-products_en.xlsx
[27] https://www.ema.europa.eu/en/about-us/contacts-european-medicines-agency/send-question-european-medicines-agency

At least once a year the list of recommended due dates will be updated with the new ATCvet codes as applicable and published on the EMA website[28].

MAHs are reminded that the conclusion on the benefit-risk balance shall be recorded at least annually[23]. 'Annually' should be understood as within a 12 months' time period and it is strongly recommended to submit them according to the due dates in order to facilitate the predictability of the annual statement submissions and to even out the workload of all involved stakeholders.

It should be emphasised that the annual submission of all results and outcomes of the signal management process, including a conclusion on the benefit-risk balance, is the default option. However, some VMPs can have a higher frequency as a requirement of the marketing authorisation[23] or recommended by competent authorities/the Agency. In such cases, the annual statement should be submitted in accordance with the requested frequency.

3.1.1.3. EU network/NCAs' responsibilities

Although the main responsibility for the assessment of the benefit-risk balance lies with the MAH, the regulators may perform an analysis following a risk-based approach to determine whether the MAH has detected and submitted all relevant signals in accordance with section 3.1.2.

Any identified discrepancies and recommended risk minimisation measures (see section 2.6) will be communicated to the MAH.

Furthermore, in some Member States, additional national legal requirements may exist for national competent authorities to perform safety surveillance/pharmacovigilance especially for nationally authorised VMPs, which may translate into specific requests to MAHs.

3.1.2. Signal submissions

3.1.2.1. Marketing authorisation holder's responsibilities

It is the responsibility of the MAH to continuously monitor the benefit-risk balance of their VMPs.

The MAH should notify any change to the benefit-risk balance or a new risk to the competent authorities or to the Agency as applicable without delay and no later than within 30 days and take the necessary action[29].

The notification of a signal should be done through the IRIS-VSM platform[30] for all validated signals once the assessment has been finalised, regardless of the MAH's conclusions. Detailed guidance on the functionality is available on the IRIS platform page[31]. In addition, the Veterinary Union Pharmacovigilance Database - Best Practice Guide**Error! Bookmark not defined.** provides further practical guidance for signal submissions.

The MAHs are advised to send separate signals for VeDDRA terms that are not medically linked, as well as for each target species. Same or similar products from the same MAH as well as medically linked VeDDRA terms (even if they are included in different SOCs) can be grouped in one signal submission. However, separate signals should be submitted for different proposed outcomes.

[28] https://www.ema.europa.eu/en/veterinary-regulatory-overview/post-authorisation-veterinary-medicines/pharmacovigilance-veterinary-medicines/signal-management-veterinary-medicines
[29] Articles 81(2) and 77(10) of Regulation (EU) 2019/6
[30] https://iris.ema.europa.eu/
[31] https://iris.ema.europa.eu/homeguidance/

The signal submission should be accompanied by an assessment report[32] outlining the pharmacovigilance data and their evaluation, as well as the conclusions of the MAH. In certain cases, several related signals are assessed in one assessment report. In such a case the same assessment report can be uploaded for several signal submissions.

Once a signal has been submitted via the IRIS-VSM platform it can, in general, not be amended. However, in case of a mistake, the MAH can request a correction via the EMA IT service desk[33].

Changes to a submitted signal should not be done after the regulatory assessment has been concluded and the outcome has been published in IRIS, unless there is a specific request for a correction by the responsible competent authority.

For further information on the possible conclusions of the signal evaluation, please see section 2.5.

In general, when the outcome of a signal leads to an amendment of the product information, it is expected that a signal with the MAHs conclusion 'Amendment of the product information' is submitted in IRIS.

However, in case the amendment of the product information has been requested by the responsible competent authority/ the CVMP following assessment of an already existing signal, then a variation can be directly submitted.

For VMPs for which the marketing authorisation has been withdrawn, revoked or surrendered it is strongly recommended that the MAH continues to perform pharmacovigilance activities, taking into consideration the recommendations in the VGVP module on collection and recording of suspected adverse events for veterinary medicinal products[8].

3.1.2.2. Timelines for signal management submissions

For validated signals for which the MAH identified a change to the benefit-risk balance or a new risk (e.g. the MAH proposes regulatory or other actions in accordance with section 2.5.3), the legal notification time[34] is no later than 30 days after finalisation of the signal assessment. As the benefit-risk balance of a product needs to be monitored by the MAH continuously, the signal management submission can therefore occur at any time throughout the year.

When submitting a signal, it is recommended that the data lock point (DLP) in the assessment report is not older than 3 months.

For assessed signals for which the MAH proposes a refutation or close monitoring, the corresponding signals can be submitted by the time of the submission of the annual statement (see also section 3.1.1).

Pharmacovigilance alerts (see also sections 2.2.1.1 and 3.1.3) should be notified as soon as possible and no later than 3 working days following their identification by the MAH.

3.1.2.3. EU network/NCAs' responsibilities

The competent authorities and the Agency evaluate the results and outcomes of the signal management process, consider options for risk management and recommend appropriate measures referred to in Articles 129, 130 and 134 concerning marketing authorisations[35].

[32] https://www.ema.europa.eu/en/documents/template-form/veterinary-signal-assessment-report-marketing-authorisation-holders_en.docx
[33] https://support.ema.europa.eu/esc
[34] Article 81(2) of Regulation (EU) 2019/6
[35] Article 79 of Regulation (EU) 2019/6

All submitted signals by the MAH will be evaluated by an assigned responsible competent authority and the proposed regulatory outcome agreed with other competent authorities where the affected VMPs are authorised or adopted by the CVMP as applicable.

In the situation where the regulatory outcome is in agreement with the proposed outcome by the MAH, the outcome will be published on the IRIS platform. In case of differences to the MAH's outcome, these will be outlined in an assessment report and communicated to the MAH before publication of the regulatory outcome on the IRIS platform.

3.1.3. Pharmacovigilance Alerts

Pharmacovigilance (PhV) alerts (see section 2.2.1.1.) should be reported to the relevant competent authority(ies) of the Member State(s) where the VMP is authorised and the Agency without delay and no later than 3 working days after its identification.

The notification of a PhV alert should be done through the IRIS-VSM platform[30] specifying the type of signal as 'Pharmacovigilance alert'.

When notifying a PhV alert, the MAH should describe the safety issue, the source(s) of information, actions taken or any planned actions with timelines and should provide any relevant documentation available at the time of initial notification. Any further information relevant to the issue should be provided to the Agency and relevant national competent authorities as soon as it becomes available.

Upon being notified of a PhV alert, the national competent authorities or the Agency as appropriate will promptly assess the urgency and potential impact of the issue and agree on appropriate next steps and the potential regulatory procedure to address the matter raised. This may involve consultation with the incident review network, if warranted (see incident management plan for medicines for veterinary use[36]). The MAH should collaborate with the Agency and national competent authorities in the assessment of pharmacovigilance alerts.

3.2. Other reporting obligations

3.2.1. Reporting of sales data and calculation of dose factor

The Union Product Database shall contain the annual volume of sales and information on the availability for each VMP[37]. It is the responsibility of the MAH to record in the UPD the annual volume of sales for each of its VMPs[38].

The sales data should be recorded in the UPD by the end of February of each calendar year[39, 40].

In addition to sales data, the MAH is also obliged to calculate and submit a dose factor; please see guideline on the calculation of dose factor[41]. Documentation should be maintained within the MAH's pharmacovigilance system.

[36] https://www.ema.europa.eu/en/veterinary-regulatory-overview/post-authorisation-veterinary-medicines/pharmacovigilance-veterinary-medicines/incident-management-plan-veterinary-medicines
[37] Article 55(2d) of Regulation (EU) 2019/6
[38] Article 58(12) of Regulation (EU) 2019/6
[39] UPD - Questions and Answers
[40] https://www.ema.europa.eu/en/documents/other/eu-implementation-guide-ig-veterinary-medicines-product-data-union-product-database-chapter-7-submission-other-post-authorisation-data_en.pdf
[41] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-calculation-dose-factor-be-submitted-union-product-database-upd_en.pdf

As described in Article 75(3) from Regulation (EU) 2019/6, the annual incidence data from suspected adverse events for each VMP by animal species and type of suspected adverse event should be made available for access to the general public in the UPhV-database (ADR website).

3.2.2. Notification on regulatory measures from non-EU regulatory agencies/Information from other regulatory authorities worldwide

Article 78(1)(k) of Regulation (EU) 2019/6 tasks the QPPV to communicate any regulatory measure taken by a competent authority in a third country and that is related to pharmacovigilance data to the competent authorities and to the Agency within 21 days of receipt of such information.

These notifications should be submitted via the IRIS-VSM platform[30] as signal type 'Submission of regulatory measure acc. to Art.78 1(k) of the Regulation 2019/6'.

4. Targeted signal management by the competent authorities and the Agency

As described in Article 81(3) from Regulation (EU) 2019/6, the competent authorities and the Agency have the option to perform a targeted signal management process for a given VMP or group of VMPs.

Regulators can start a Targeted Signal Management (TSM) procedure at any time throughout the year. The start of a TSM will be published on the EMA website[42] and concerned MAHs will be informed accordingly. MAHs should collaborate with the Agency and national competent authorities in any TSM initiated by the competent authorities and provide any requested information in a timely manner.

More detailed guidance on the targeted signal management procedure will be published separately.

5. Documentation requirements related to the Signal Management Process

Signal management is considered a critical process and shall therefore be well documented. MAHs shall ensure that their processes, procedures and policies to fulfil their obligations related to the signal management process and its related tasks are functioning properly and efficiently and are appropriately documented as outlined in EU Regulation 2019/6 and CIR (EU) 2021/1281. A quality management system shall be applied throughout. Please also refer to VGVP module: Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files[43].

It is important that the roles of all staff members involved are clearly defined and the individuals tasked with these responsibilities have the necessary qualifications and expertise to do so. Documentation regarding qualifications and training of relevant staff members should be kept up to date and available. It is expected that any IT-System used for and in conjunction with the signal management process and adverse event analysis is validated, approved and deemed as 'fit for purpose' by the QPPV and IT personnel. The relevant documentation for this is to be kept available for pharmacovigilance inspections.

When the MAH opts to use its own database for signal detection and analysis, detailed description of the data collection process, the data-tables and statistical measures available and routinely used shall be made available on request or at the time of pharmacovigilance inspections.

Upon inspection it is required that the entire process is not only described theoretically but also backed up with the appropriate documentation of its application. This includes the rationale for the method and periodicity of signal management activities and the individual steps applied throughout. Through a tracking system, all organisations should keep an audit trail of all signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale.

In summary, as a minimum, MAHs are expected to have procedures describing in details the overall signal management process and, for each step, how signal management is effectively carried out, i.e. for signal detection, signal prioritisation, signal validation, signal assessment, handling of potential pharmacovigilance alerts, submission of outcomes (signals and outcome statement to the EU network

[42] https://www.ema.europa.eu/en/veterinary-regulatory-overview/post-authorisation-veterinary-medicines/pharmacovigilance-veterinary-medicines/signal-management-veterinary-medicines#targeted-signal-management-by-regulators-14572
[43] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-pharmacovigilance-systems-their-quality-management-systems-and-pharmacovigilance-system-master-files_en.pdf

and relevant NCA). The level of details expected in procedures should be sufficient to allow, theoretically, any new employee to perform the corresponding tasks, should they have the relevant expertise.

- Overall signal management process.
- Procedure for signal detection (both in the UPhV-Database and MAH databases, if applicable).
- Overall policy and procedure for the remaining individual steps of the signal management process, namely:
    - Signal prioritisation,
    - Signal validation,
    - Signal assessment,
    - Handling of potential Pharmacovigilance Alerts,
    - Submission of the outcomes of the signal management process (signals and annual statements) to the EU Network and relevant NCAs.

Documentation of the application of above-mentioned procedures including their outcomes should be kept available. This includes, but is not limited to;

- Established risk-based monitoring criteria for each product or group of products (how often and by which methods is monitoring performed for each product/product group and why?).
- Compliance with established monitoring criteria.
- Signal validations performed, their outcome and rationale.
- Signal assessments performed.
- Reporting of the outcome of the signal management process (signals and annual statements) to the EU Network and relevant NCAs.

Documents and pharmacovigilance data relating to individual authorised veterinary medicinal products shall be retained as long as the product is authorised and for 5 years after the marketing authorisation ceases to be valid.[44]

[44] CIR (EU) 2021/1281 Article 5(3)