A Flexible Signal Management Framework for Animal Health Pharmacovigilance

Animal Health Institute

June 5, 2024

CONTENTS

ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AER	Adverse event report
AH	Animal health
AHI	Animal Health Institute
ANADA	Abbreviated new animal drug application
API	Application programming interface
ATCVet	Anatomical Therapeutic Chemical classification system for veterinary medicinal products
BARK	Banfield applied research and knowledge
CT	Clinical trial
CVM	Center for Veterinary Medicine
DME	Designated medical event
DPA	Disproportionality analysis
DWH	Data warehouse
EEA	European Economic Area
EMA	European Medicines Agency
EPA	U.S. Environmental Protection Agency
ESI	Emerging safety issue
EVMR	Electronic veterinary medical record
EVV	EudraVigilance veterinary
FDA	U.S. Food and Drug Administration
GL	Guideline
HH	Human health
ICSR	Individual case safety report
IMI	Innovative Medicines Initiative
JSON	JavaScript object notation
LLT	Low level term
MA	Market authorization
MAH	Marketing authorization holder
MIT	Medically important VeDDRA term
NADA	New animal drug application
NPS	New product surveillance
PDER	Periodic drug experience report
PEC	Product-event combination
PMSS	Post-marketing surveillance study
PSUR	Periodic safety update report
PT	Preferred term
PV	Pharmacovigilance
RA	Regulatory authority
RADR	Recognizing adverse drug reactions

Abbreviation	Description
ROR	Reporting odds ratio
SDR	Statistic of disproportionate reporting
SM	Signal management
SME	Subject matter expert
SRS	Spontaneous reporting system
USA	United States of America
USDA	U.S. Department of Agriculture
VeDDRA	Veterinary Dictionary for Drug Related Affairs
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP	Veterinary medicinal product

DEFINITIONS

Term	Definition / Explanation
Action	Activity taken based on the outcomes of the signal management process that support a change in the benefit-risk profile of a product.
Assessment	Process to determine if a new risk or a change to a known risk exists, what the cause or mechanism of action is, and what the appropriate next steps are to mitigate the risk.
Detection	Applying processes to data sources for identification of safety or efficacy observations. Detection includes triage of the detected observations.
Enhanced monitoring	Heightened surveillance consisting of increased frequency of analyses, depth of analyses, or both of PV data for a targeted period.
Evaluation	Application of appropriate data interrogation tools and expertise to the appropriate data to draw conclusions on the validity of the safety observation and confirmation of a new risk, a change to a known risk, or reassurance about the absence of a risk.
Index case (CIOMS VIII)	One well-documented ICSR with an unusual striking feature that can sometimes be interpreted as a signal even though in practice, in most situations, strong suspicions about possible drug-event associations are usually based on a series of cases with similar reported features.
Non-validated signal	A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis is not warranted.
Routine surveillance	The regular practices a PV unit follows for monitoring PV data for signal detection purposes as defined in an organization's standard operating procedures, guidelines, or work instructions.
Safety observation	A safety (or efficacy) observation is information from any source that differs from what is known about a product, either quantitatively or qualitatively. It has the potential to affect the risk profile of that product. A safety observation is preliminary and not equivalent to a safety signal. A safety observation may or may not become a signal after applying relevant clinical/scientific context and medical judgment.
Signal (CIOMS VIII)	Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
Signal (Meyboom)	A set of data constituting a hypothesis that is relevant to the rational and safe use of a drug in humans. Such data are usually clinical, pharmacological, pathological, or epidemiological in nature. A signal consists of a hypothesis, together with data and arguments.
Triage	The review and application of clinical/medical judgment to a safety observation to determine whether the safety observation merits further verificatory action.
Validated signal	A signal for which the signal evaluation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

INTRODUCTION

Signal Management in Animal Health Pharmacovigilance

The primary purposes of signal management (SM) in the post-approval lifecycle phase of a veterinary medical product (VMP) are early identification, characterization, communication, and mitigation of new risks that were not detected in the pre-approval phase, or changes to known risks (i.e., benefit-risk profile) such as changes in severity, frequency, or identification of an at-risk subpopulation. These risks may include rare or very rare adverse reactions that were undetectable during pre-authorization studies for several reasons including, but not limited to, the relatively small numbers of animals enrolled in these studies, the narrow population of enrolled animals, indications under study, or other protocol-specified inclusion or exclusion criteria. [1,2]

While SM concepts have been entrenched for years in animal health (AH) pharmacovigilance (PV) practices for early detection of new potential risks associated with VMPs,[3-5] formal approaches to SM are continually evolving as the practices and expectations of regulatory authorities change and as advances in data science and digital technology are adopted by the pharmacovigilance community.[6] It is vital to ensure that these ongoing changes improve or enhance the ability of AH PV processes to detect new risks rapidly and efficiently.

History of 'Signal'

The term "signal recognition" arises from electronic engineering. With radio or radar waves, a real signal exists but it is accompanied by "noise" in the background, and there is a need to detect the signal, distinguishing it from the background.[7] The word 'signal' has been used in pharmacovigilance (PV) for decades. M.D.B. Stephens (2000)[8] provided a definition of 'signal' referring to the World Health Organization (WHO; 1991) and a publication by T. Delamothe (1992)[9] as the origin of the definition.

> *A signal is reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.*

Meyboom et al. (1997)[10] provided an alternative definition.

> *Although pharmacovigilance is especially concerned with adverse effects, a signal is more broadly defined as a set of data constituting a hypothesis that is relevant to the rational and safe use of a drug in humans. Such data are usually clinical, pharmacological, pathological, or epidemiological in nature. A signal consists of a hypothesis, together with data and arguments.*

Hauben et al. (2005)[11] framed 'signals' as early hints that suggest the possibility of novel adverse events but then employed the definition provided by Meyboom et al. The authors further stated that a 'signal' is more than just a statistical association and used the term 'signal of disproportionate reporting' (SDR) when discussing statistical disproportionalities in Spontaneous Reporting System (SRS) databases without clinical,

pharmacological or (pharmaco)epidemiological context. SDRs indicate differential reporting and not necessarily differential occurrence.

In 2009 Hauben and Aronson[12] proposed a definition of 'signal' that aligned more with "real-world" PV processes at the time, noting that signals can be of both harmful and beneficial effects.

> *Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions.*

These authors further defined 'unverified signal', 'indeterminate signal', 'verified signal', and 'refuted signal' as qualifiers in the verification process.

In 2010 the authors of CIOMS VIII[1] noted that the definition provided by WHO (and included in Stephens' chapter) served the PV community well when most information about adverse events was obtained from individual case reports submitted by healthcare professionals or patients. They went on to describe how safety information is increasingly coming from a variety of sources and that the nature of signal detection has changed. They adapted the definition provided by Hauben and Aronson.

> *Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.*

The authors of CIOMS VIII also used the term 'statistic of disproportionate reporting' (SDR) for the potential outcome of disproportionality analyses and noted that an SDR does not mean that a signal of suspected causality exists.

The EMA in both human and veterinary good pharmacovigilance practices guidelines (GVP, 2017; VGVP, 2021) use variations of the CIOMS VIII definition.

> *GVP: Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.[13]*

> *VGVP: A signal is defined as information that arises from one or multiple sources, including observations and experiments, which suggests a potentially new causal association, or a new aspect of a known causal association between an intervention and an adverse event or a set of related adverse events, that is judged likely to justify further investigation of possible causality.[14]*

In this Flexible Signal Management Framework for Animal Health Pharmacovigilance, the authors include both the CIOMS and Meyboom et al. definitions of 'signal'.

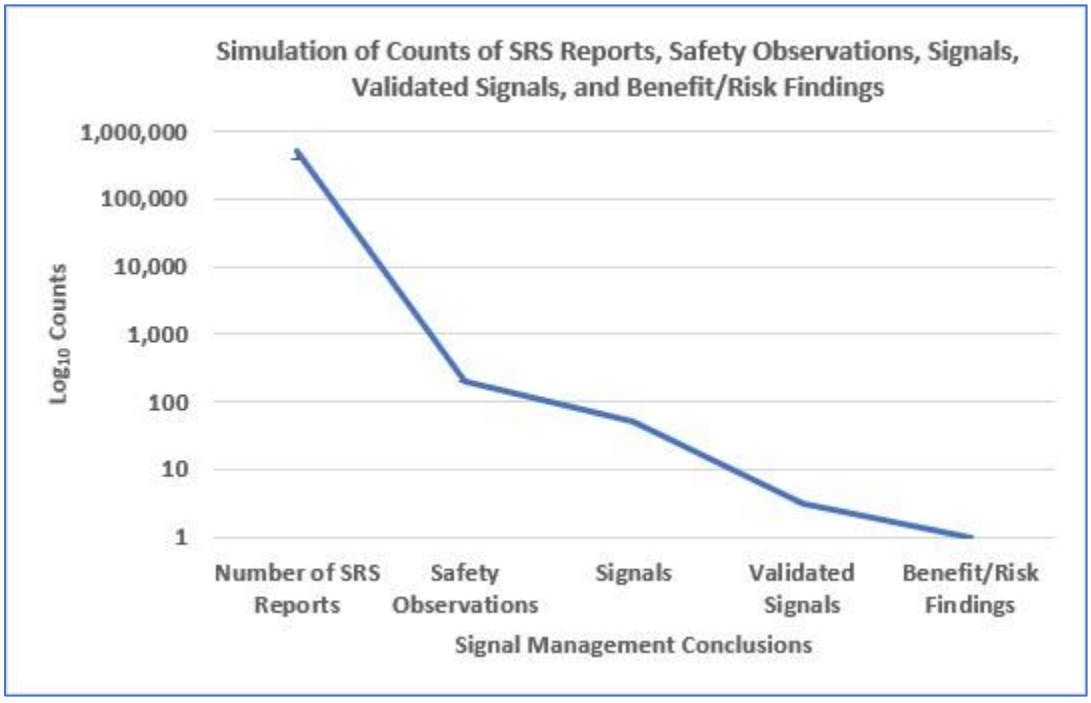
Risks, Resources, and Return on Investment

Experience in human health (HH) PV suggests that from the 10,000 to 100,000 SDRs that may have been identified, less than ten resulted in validated signals.[15,16] Fewer resulted in actionable safety outcomes. Applying a similar paradigm to AH PV, a theoretical model can illustrate this concept for an SRS database containing 500,000 adverse event (AE) reports for an animal species. In this SRS database, 200 safety observations might be identified and further evaluated, resulting in 50 signals, three validated signals, and one benefit-risk finding (Figure 1).

This theoretical model approximates what is expected during the SM process: a large number of safety observations but very few benefit-risk changes, particularly for products with established safety profiles. This illustrates the importance of adopting a risk-based and judicious approach to signal management. Without application of criteria to prioritize the most important safety observations, each observation would need to be investigated to determine that, 199 times out of 200, no action is needed.

There is an opportunity cost of time and resources spent to evaluate a large volume of false positive "signals" which could be better focused on activities that effectively monitor the safety and efficacy of VMPs. The answer is not to simply increase the resources available to evaluate signals because this added cost, which eventually impacts customers, is not justified if these activities do not meaningfully improve outcomes. This concept underscores the importance of having a flexible and efficient SM process in place.

Figure 1. Simulation of Signal Management Conclusions



Goal

This paper presents a risk-based signal management framework which is adaptable to meet the unique needs and challenges of AH PV, and which may be customized for the standard procedures and available resources of each Marketing Authorization Holder (MAH). This structured, yet flexible, framework enables MAHs to optimize their resources by focusing on the validated signals of greatest relevance to patient safety. The goal of this approach is to expeditiously identify changes in the benefit-risk balance while striking the proper balance between potential risk and the value derived from signal management activities.

OVERVIEW

Framework Principles

The main principles of this SM framework are listed below. MAHs may follow variations of the framework while still encompassing the general principles.

- Individual MAHs may adapt signal management processes based on their company's product portfolio.
- Scientific context and medical judgment should be applied and prioritized throughout all stages.
- MAHs can choose the methods and frequency best suited for identification of observations and answering specific questions.
- Information from multiple relevant sources and detection methods should be appropriately utilized throughout application of the framework while considering the respective benefits and limitations of each data source and detection method.
- Safety reviewers/evaluators should have a process for rapid and efficient triage based on review of readily available data before a safety observation is declared a signal while maintaining flexibility, as a "one-size process" is not likely to fit all safety observations.
- Statistical measures using various approaches are applied when case volume makes comprehensive review of individual case safety reports (ICSRs) impractical. Observations resulting from these analyses are not equivalent to safety signals and must be triaged and validated.
- An observation need not progress linearly through all stages of the framework or through all elements within a stage.
- The approach to signal assessment is situation-dependent based on the nature of the signal and the available data.
- Analysis of quality AE data,[17] using the most appropriate tools or analytical approaches and expertise, should strike the proper balance between potential risk and value derived from the analyses given the limited resources an organization may have.

Framework Structure

The overarching structure of the signal management framework consists of three stages (detection, evaluation, and action) and three processes (triage, validation, and assessment).[6] Stages and processes within this framework are flexible depending upon the characteristics of an observation or signal as well as the MAH's standard procedures and available resources. Activities and decisions in all stages should be justified, documented, tracked, and available for review or inspection.

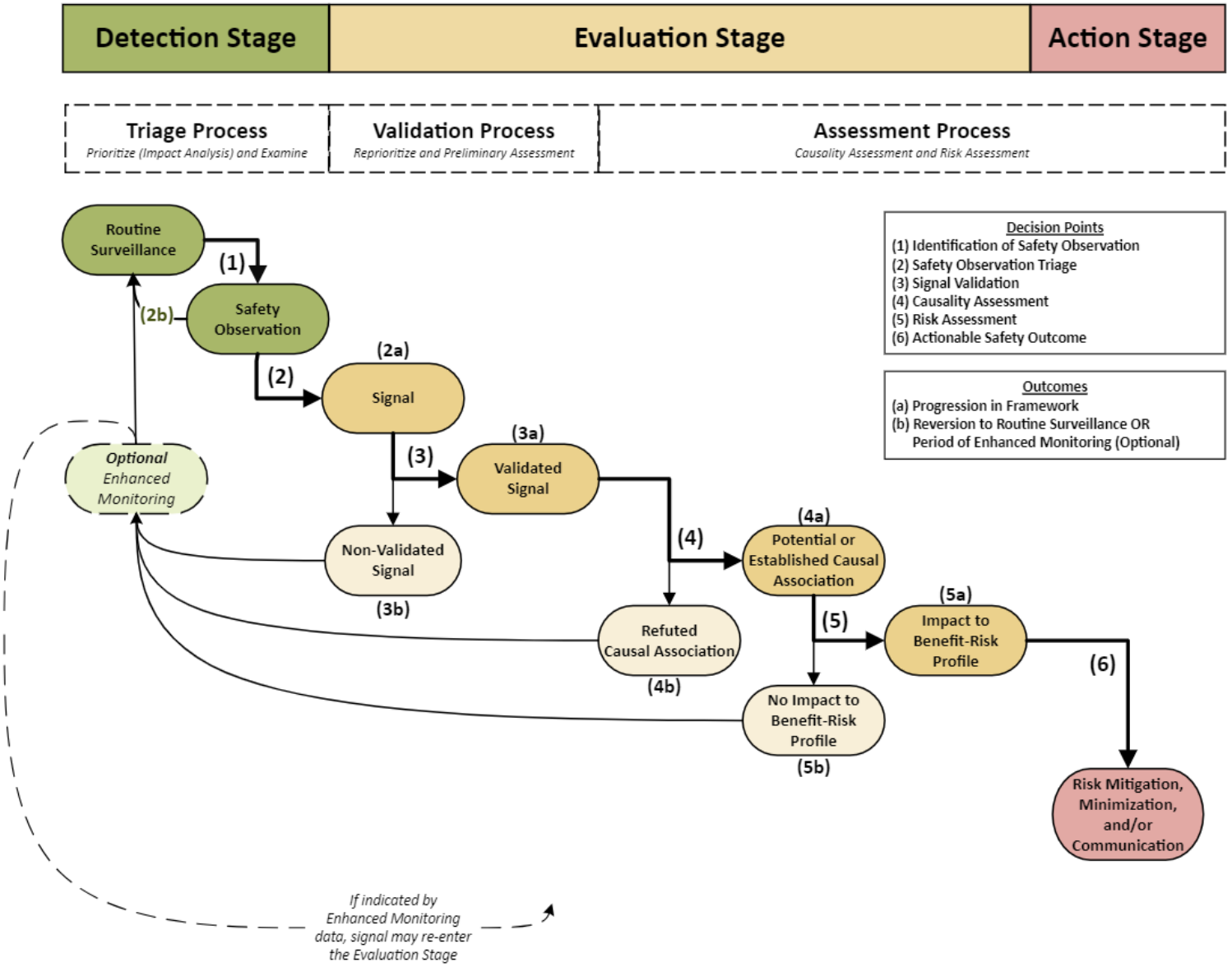
Reviewer discretion is essential when applying clinical, medical, and scientific elements throughout the signal management framework's stages and processes. Some processes and resources are shared across the framework stages (e.g., consideration of the ICSRs suggesting a potential safety signal) while other evaluation processes may be tailored to the situation, based on the availability, source, and quality of information.

Formal approaches to SM are continually evolving, as will this flexible framework. Organizations should periodically review and adjust their signal management practices, improving the efficiency and effectiveness in the interest of patient safety and the VMPs developed for the benefit of these patients.

The SM framework stages, processes, and progression along with decision points are illustrated in **Figure 2**. Labels used in the figure are referenced in parentheses throughout the text in subsequent sections. Steps one through six in the framework represent decision points, with an outcome of '**a**' indicating progression toward the action stage and an outcome of '**b**' indicating that the observation or signal will return to routine surveillance.

Alternatively, a signal with an outcome of **'b'** (a non-validated signal, a validated signal with a refuted causal association, or a validated signal with no impact to the benefit-risk balance) may enter a period of enhanced monitoring after which the signal either returns to routine surveillance or re-enters the evaluation stage for further review.

Figure 2. Signal Management Stages, Processes, and Decision Points



FRAMEWORK

Detection Stage Overview

The detection stage consists of applying processes to data sources for identification and triage of safety or efficacy observations. A safety (or efficacy) observation is information from any source that differs from what is known about a product, either quantitatively or qualitatively, and which has the potential to affect the risk profile of that product.[6] A safety observation is preliminary and is not equivalent to a safety signal.

Safety or efficacy observations are detected from many possible data sources of varying quality and consistency and using a variety of approaches. The potential benefits and limitations of each data source and detection approach must be considered (refer to section "*Observation Source Factors*" for a detailed discussion).

In this framework, a safety observation is first identified **(1)** in the detection stage from the available safety data. After the safety observation is identified, it undergoes triage **(2)** and will either qualify for progression to the evaluation stage as a signal **(2a)** or will revert to routine surveillance **(2b)**.

Detection Stage Processes

Triage Process (Prioritize and Examine)

Not all safety observations will represent risks and an initial prioritization process (i.e., impact analysis) is required to determine which observations have a high potential impact and require immediate attention.[1] Key determinants of risk may include (but are not limited to): the medical significance of the event (e.g., potential for prevention, severity, reversibility, outcomes, estimated frequency, novelty of the product-event association, consequences of treatment discontinuation and availability of other treatment options); product factors (e.g., type of medicinal product or active substance, length of time on the market, stability of the PV profile, potential class effects); the potential impact on public health or the environment; and other risk factors such as media attention or public concerns.[1,14,15]

Priority during the triage process should be placed on emerging safety issues (ESIs), which may require urgent regulatory action and communication, and medically important terms (MITs). An ESI or MIT might be progressed directly to a validated signal designation or to the action stage based on scientific context and medical judgment.

Observations which have been prioritized are further examined[6] to establish whether there is sufficient information for the observation to qualify as a signal and progress to the evaluation stage. The triage process may be viewed as a "noise-filtering step" that should be completed expeditiously. The focus should be on determining if the available information contains sufficient evidence, based on the source and data elements specific to the safety observation under review, to justify further analysis. Factors which may be reviewed to determine the strength of evidence include (but are not limited to): number of supportive ICSRs, case quality, case source(s), DPA scores, reporting rates, co-reported events, and previous analyses. Clinical and medical judgment are applied to determine whether the safety observation merits further verificatory action.[6]

During the triage process, most safety observations are quickly reconciled and downgraded, returning to routine surveillance. A small proportion of safety observations qualify as signals and move from the detection stage to the evaluation stage. Safety reviewers/evaluators should have a process for rapid and efficient triage before a safety observation is declared a signal. Triage does not entail an extensive review of all potential elements upon which safety observations may arise. Rather, the process should be based on a review of readily available data while maintaining flexibility, as a "one-size process" is not likely to fit all safety observations.

Triage Approach

A structured, yet flexible, pragmatic approach to the triage of safety observations (and later, to the validation of safety signals – see "*Validation Approach*") may consider an initial safety observation in the context of categories for the data supporting the detected observation (Table 1) that the reviewer can "jump to" or select in any order. The approach used by the reviewer should be based on fundamentals of good pharmacovigilance practices, focusing on the most appropriate and available data elements related to the safety observation and selecting from available elements those that are relevant and supportive of a quality triage decision.

Not all categories or elements within a category need to be considered. The reviewer selects, based on the source and nature of the safety observation, which categories and elements to consider. A rapid and efficient triage process will generally focus on a few elements.

Table 1 lists five common data categories and elements which may be referenced by the reviewer. Elements may be classified under more than one category and may contribute to prioritization and/or to establishing the strength of evidence. This list is not all-inclusive; other data categories and elements may also be considered.

Table 1. Data Categories and Elements

Data Categories	Data Elements
Safety Observation/ Clinical Sign Factors	Expectedness *Is the sign listed, or conceptually listed, in product literature?* *Is the adverse event reported from development/clinical studies at the recommended dose; target animal safety studies at multiples of the recommended dose; toxicology studies; or in vitro or in silico data?*
	Medical significance of clinical sign *Consider potential for prevention, severity, reversibility, outcomes, estimated frequency, novelty of the product-event association, consequences of treatment discontinuation, availability of other treatment options* *ESI, MIT, designated medical event (DME), or conceptually related term?*
	Time-to-onset (TTO) and duration *Include changes to TTO and duration from a known adverse reaction*
	Co-reported clinical signs
	Technical factors (e.g., VeDDRA coding) *Has there been a VeDDRA coding dictionary update or a VeDDRA coding practice change such as those requested/required by a regulatory authority (RA)?*
	Trends *Case counts, proportional report rates, DPA scores, frequency-based statistical measures*
	Potential or likely confounding by disease under treatment

Product Factors	Time on market *Newly launched product with an emerging post-marketing PV profile (which may yield wide swings in case reporting and variability in DPA) vs. mature product with more end user familiarity and stable PV profile?* *Introduction of the product in new markets?*
	Geographical, species, or indication expansions *May alter AE reporting for the product*
	Change in registration status *Prescription to over-the-counter*
	Seasonal reporting patterns
	Sales volume and reporting rate based on sales
	Market factors *Product support programs or satisfaction guarantees?*
	Manufacturing factors *Consider manufacturing site, formulation, or lot/batch*
	Product quality factors *Product handling or storage* *Product adulteration or counterfeit product*
	Labeled or extra-label use of the product *Any changes to the labeled regimen (e.g., dosing)*
	Labeled adverse reactions, precautions, warnings, indications, or contraindications
	Consequences of treatment discontinuation and availability of other treatment options
	The effect on prescribing behavior that occurs with changes in availability of a competitor's product with the same or similar indications
	Post-approval adverse reaction additions to product labeling *May affect both reporting and prescribing behavior*
	Concomitantly administered products *Possible product interactions?* *Confounding due to multiple products administered?*
	Pharmacology/toxicology, pharmacokinetics, pharmacodynamics
	Class effects *Prior experience with the same product or products from the same class.* *Consider differences from other products in the same class (which may influence prescribing behavior), client use, or characteristics of the treated population*
	Reporting biases *Biases to consider may include (but are not limited to): social media attention; notoriety bias; specific surveillance recommendations (e.g., Dear Doctor letter)*
	Additional risk factors *Public health or environmental implications*
Observation Source Factors*	Individual case safety reports (ICSRs) *Index case* *Case counts, reacting animal counts, proportional report rates, exposure-adjusted reporting rates, disproportionality statistic scores, frequency-based statistical measures, etc.* *Changes or trends in counts/rates/scores* *Thresholds: below, above, and magnitude of exceeding thresholds* *Case seriousness* *Causality assessment* *Case quality and completeness* *Opinion of the reporting veterinarian, if applicable* *Co-morbid medical conditions* *Confounding factors described in the case(s)* *Reporting biases* *Proportion of cases reporting strong temporal association, positive dechallenge or positive rechallenge, and of these the number that are free of confounding factors*

	Sufficient/insufficient historical information or diagnostic testing *Reporter (lay vs. medical professional)*
	Biomedical literature *Peer review status of the journal* *Quality of the published article* *Author(s) (a single article from one author/investigator or multiple articles from independent authors/investigators)* *Isolated study data analysis versus cross study meta-analysis* *Original research versus review article* *Contemporaneousness/timeliness of publication* *Journal editorial standards and impact* *Likelihood of yielding duplicate reporting (publication based on a clinical trial or development study? Co-reporting of individual cases/patients in a case series or review article directly to an organization's PV database as well as in the literature article?)*
	Studies conducted by organizations other than the MAH *Study design (including masking, randomization, and control group(s))* *Hypothesis being tested (purpose of the study and planned endpoints)* *Appropriateness of the data collection and analyses supporting the hypothesis or concluding the null hypothesis (e.g., statistical power and analysis)*
	PV Database **See detailed discussion on AH SRS databases in section "Observation Source Factors"*
	Environmental or epidemiological factors
Patient Factors	Labeled species, age, weight, gender, production class, reproductive status
	Listed precautions, warnings, or contraindications
	Disease under treatment, including its progression
	Population disease prevalence data
	Breed predispositions
	Subpopulations with differences from the general patient population such as proportion of younger, older, or reproducing animals
	Patient demographic subsets (e.g., gender, age, weight, breeds)
	Patients with comorbid conditions or pre-existing health factors
Subject Matter Expert	Internal organization SMEs *Medical officers or equivalent* *Toxicologists* *Product safety experts* *Manufacturing/quality experts* *Cross-discipline safety committees or councils*
	External expert consultation

*See section "*Observation Source Factors*" for a detailed discussion.

Theoretical scenarios illustrating potential application of this approach may be referenced in the Appendix (*"Application of Framework – Theoretical Scenarios"*).

Evaluation Stage Overview

After a safety observation has been triaged and has qualified as a signal, it progresses to the evaluation stage and enters the validation process **(3)**, where measures are taken to determine if the signal is valid or not.

The possible outcomes of the validation process **(3)** are: a validated signal **(3a)** or a non-validated signal **(3b)**.

Non-validated signals **(3b)** will revert to routine surveillance or, less commonly, may enter a period of enhanced monitoring.

For all possible outcomes throughout the evaluation stage and processes, enhanced monitoring is an option at the discretion of the safety reviewer or PV organization and dependent upon the nature of the signal. After a period of enhanced monitoring the signal may re-enter the continuum, subject to further review, or it may be reverted to routine surveillance.

For validated signals **(3a)**, a signal causality assessment **(4)** is performed to determine if there is a potential causal association between the safety signal and the VMP.

The possible outcomes of the signal causality assessment **(4)** are: the validated signal has a potential or established causal association with the VMP **(4a)**, or a causal association is refuted **(4b)**.

If a causal association is refuted **(4b)**, the validated signal may either revert to routine surveillance or enter a period of enhanced monitoring.

Although it may not be possible to definitively establish a causal relationship between the validated signal and the VMP, if the assessment is inconclusive but a causal relationship is possible, then the signal will generally progress in the framework. For validated signals with a potential or established causal association with the VMP **(4a)**, a risk assessment **(5)** will be performed.

The possible outcomes of the risk assessment process **(5)** are: there is a confirmed impact to the benefit-risk profile **(5a)** or there is not a confirmed impact to the benefit-risk profile **(5b)**.

If there is not a confirmed impact to the benefit-risk profile **(5b)**, the validated signal may either revert to routine surveillance or enter a period of enhanced monitoring.

With a confirmed impact to the benefit-risk profile **(5a)**, there will be an actionable safety outcome **(6)**. The validated signal moves to the action stage for consideration and implementation of risk minimization, mitigation, and/or communication measures.

In summary, validated signals with a refuted causal association or validated signals with a potential or established causal association but without an impact to the benefit-risk balance will either revert to routine surveillance or enter a period of enhanced monitoring. Only validated signals for which there is a potential or established causal association with the VMP and for which there is an impact to the benefit-risk balance will move to the action stage.

Evaluation Stage Processes

Validation Process (Reprioritization and Preliminary Assessment)

Signal validation is an ongoing reprioritization process which drives a signal toward assessment. Validation is not a process for confirming a safety issue and does not establish a causal relationship. Signal validation is a preliminary assessment of a signal and its associated evidence. The focus should be on evaluating the data supporting the detected signal to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis (i.e., assessment) of the signal.[13]

Validation Approach

The review method which was previously described for the triage process (see "*Triage Approach*") may also be applied to the signal validation process, with the reviewer considering five common categories for the data supporting a signal as well as multiple elements within each data category (Table 1). Again, not all data categories or elements within a category need to be considered, and the reviewer can "jump to" or select the most applicable categories and elements in any order.

Although a similar review method may be used for both processes, validation is a more in-depth review than triage, considering a broader set of elements from the associated data. While triage focuses on the rapid and efficient review of only a few elements to determine if sufficient information exists to justify further analysis of the signal, validation determines whether the existing information contains sufficient evidence of a new potentially causal association to justify a complete signal assessment.

Assessment Process (Causality Assessment and Risk Assessment)

The objective of the assessment process is to further evaluate a validated signal to determine if there is a potential causal association (causality assessment) and if a change to the benefit-risk profile has occurred (risk assessment).

Once a signal is determined to be valid, the assessment process should be as complete as possible, evaluating a broader scope of data, leveraging more resources, and using information from multiple relevant sources. Assessment is the process which either refutes or confirms whether a validated signal is associated with a new risk or a change to known risk. For confirmed risks, the validated signal that affects the benefit-risk profile will move to the action stage.

Assessment decisions are based on data from the available sources but also judgment of the various subject matter experts (SMEs) involved in the decision-making, including (but not limited to):

- Pharmacovigilance veterinarians and scientists
- Other product safety specialists and clinical veterinarians within the organization
- Toxicologists
- Regulatory affairs specialists
- Product technical services veterinarians/specialists
- Cross-disciplinary safety committee/council/board members

Assessment Approach

The approach to signal assessment is situation-dependent based on the nature of the validated signal and the available data. It is judgment based, although (semi-)quantitative tools (i.e., risk matrix or scorecard) may be used. Decisions are qualitative in nature and are generally made by senior multidisciplinary teams and specialists.

Action Stage Overview

Validated signals which are associated with a new risk or a change to a known risk will move to the action stage for determination of the appropriate actionable safety outcome(s) (6) including risk minimization, mitigation, and/or communication.

Cross-disciplinary safety committee/council/board members and other experts will likely determine the appropriate actions based on signal assessment. Individual organizations may have several rounds of expert discussions during the signal management process with different levels of decision-making.[13]

Action Stage Processes

The action stage is situation-dependent; many potential factors including (but not limited to) the nature of the risk and its severity, results of the analyses used to identify and characterize the risk, and the population at risk should be considered. Thus, the assessment process continues throughout the action stage.

Actions to consider include:

- Escalation or notification to the organization's management
- Regulatory authority notification
- Variation of the terms of the marketing authorization (i.e., update product information/labeling)
- Communication of new safety information to veterinary health professionals and others
- Market actions such as product recall or market withdrawal
- Prioritization and timing of executing actions
- Developing a strategy for monitoring the effectiveness of the risk minimization, mitigation, and/or communication
- Other targeted PV measures including, but not limited to, enhanced monitoring

Consideration may be given to actions more common to human health PV, including:

- Post-authorization study
- Risk management plan
- Patient support program

A theoretical scenario illustrating application of the entire framework from the detection stage to the action stage may be found in the Appendix ("Application of Framework – Theoretical Scenarios").

OBSERVATION SOURCE FACTORS

Understanding the distinct characteristics of safety data sources is critical prior to drawing any conclusions about a safety observation or signal.[1] The following discussion focuses on the potential limitations and confounding factors related to sources of safety observations. The discussion includes factors related to the original source data (e.g., SRS databases, clinical trials, literature, epidemiologic studies, longitudinal data) as well as data resulting from observation/signal detection methods such as statistics of disproportionate reporting. Observation source factors should be considered throughout the triage, validation, and assessment processes as they may influence decision-making.

SRS Databases

SRS databases have been and will continue to be the primary source of most safety observations. However, both MAH and external SRS databases have clear limitations, [11,18-22] many of which are summarized in Table 2. Despite these limitations, ICSRs from spontaneous reporting remain a primary source of data for identification of safety observations, particularly rare and unexpected potential adverse reactions.

MAH SRS Database

Depending on the number of reports and diversity of products, a MAH's SRS database may provide the most comprehensive and contemporary data for analysis with the application of selected methodologies, however influenced by the number and rate of reporting of certain products or product categories. MAHs have the responsibility to develop and defend risk-based methods with a frequency best suited for routine signal detection and evaluation, investigation of *ad hoc* safety or efficacy observations and signals, enhanced monitoring, and benefit-risk evaluation using the MAH's database. With the available and accepted signal detection tools and processes, MAHs can choose the methods and frequency best suited for answering specific questions.

Table 2. Potential Limitations and Confounding Factors of SRS Databases

SRS Database	Potential Limitations and Confounding Factors
MAH SRS	• Under-reporting, stimulated reporting, differential reporting (e.g., higher reporting of serious signs, effects of case reporting and receiving practices), coincidental reporting, duplicate reporting • Assessment of causality at the case level rather than the clinical sign level • May be influenced by the number and rate of reporting of certain products or product categories • Do not provide the number of animals receiving the medication, which precludes incidence calculations • Estimated animal exposure based on sales data and assumptions regarding number of animals treated may or may not be valid • Do not include the natural prevalence of a particular clinical sign in a specific species, so it cannot be determined if the reporting rate of an adverse event for a VMP is higher, lower, or the same as that without VMP exposure • Limited temporal information regarding duration of exposure and time order of exposure and condition • ICSRs are generally qualitative in nature and often have multiple confounding factors, which may include (but are not limited to): poor case quality, incomplete data, reporting biases (e.g., veterinarians or animal owners leveraging marketing guarantee programs or seeking diagnostic or treatment reimbursement), concomitant product administration, and/or concomitant medical conditions • Inconsistent quality of information • Reporting may be influenced by multiple factors including (but not limited to): time of VMP on market, event seriousness, and reporting biases (e.g., notoriety bias, specific surveillance recommendations)
External SRS (e.g., openFDA, EudraVigilance)	All limitations as described above for MAH SRS, **PLUS:** • Composition of database may be influenced by factors such as jurisdiction reporting requirements and time of products on the market • May be more susceptible to duplicate cases due to receiving reports of the same case from multiple companies • See '*External SRS Databases'* for detailed discussion

External SRS Databases

External SRS databases are vulnerable to the same potential limitations and confounding factors as MAH SRS databases plus additional factors which are unique to the external SRS itself. Two of these databases, EudraVigilance Data Warehouse and openFDA, are discussed below.

EudraVigilance Data Warehouse

Starting in 2022, the EudraVigilance Veterinary (EVV) data warehouse (DWH) has been available for MAHs to use for signal detection.[23] The database contains products that are approved within the European Economic Area (EEA). The DWH is updated daily, which has the advantage of having contemporary data but the disadvantage of continual change, for example, in background case data for purposes of conducting DPA.

The EVV DWH provides limited access and functionality. Data interrogation follows a pre-specified methodology and format. The available signal detection dashboards (Overview of AERs per product/active substance/ATCVET, Signal detection with 2 RORs [reporting odds ratio] up to Date 2 and up to Date 1, and Static ROR Evaluation) return relatively static, pre-defined reports that consist essentially of the ROR as the disproportionality statistic. In addition to ROR statistics, the reports return the number of cases and reacting animals by VeDDRA term. No additional statistical measures can be applied within the EVV DWH.

The ROR DPA results in the EVV DWH dashboards appear to include cases reported from clinical trials (CTs) and the biomedical literature, including literature reports from CTs. MAH users of the EVV DWH dashboards cannot exclude CT and literature cases from DPA.

Historically, the EVV DWH contained mostly cases that were assessed as serious according to VICH GL 24.[24] Thus, for older products the EVV DWH contains only a subset of the total cases that may be in a MAH's database.

An EVV DWH line listing returns multiple date configurations. The one used for filtering the signal detection dashboards is the "message received" date. This date may not reflect the date a case was first valid and for some cases the message received date can be months or years after occurrence of the adverse event. This date configuration for dashboard queries can confound trending.

For product-event combinations (PECs) reporting the VeDDRA Preferred Term (PT) Death, the number of animals listed as dead is the number of animals that reacted in the case, which includes both the number that died or were euthanized and the number of animals that did not die but experienced some other adverse event and therefore are counted as "reacted and died" for that case.

The reports available are inflexible in that no additional measures or restrictions can be applied other than the available filters (i.e., lack flexibility to perform ad hoc queries and analyses). There is no option, for example, to perform trending of case counts or DPA statistics over multiple temporal subsets. There is no option to adjust comparator groups such as restricting the analysis to biological or pharmaceutical products only. Signal detection is limited to case counts, reacting animal/patient counts, and the ROR disproportionality statistic and does not provide for other means of signal detection, including relative reporting based on proportional report rates, exposure-adjusted reporting rates, use of other disproportionality statistics, or other statistical measures for detecting signals.

The EVV DWH cannot be extracted by an MAH as an external source for applying alternative or more flexible approaches or PV analytical tools.[25-26]

openFDA

An open-source AH PV database is the FDA/CVM openFDA "Animal & Veterinary API [application programming interface] Endpoints."[27] The source of data in the database is animal drug adverse events

(AEs) reported to FDA/CVM. The period covered is from 1987 to the present with updates performed quarterly. The data are in JSON format.

Cases reported to FDA/CVM are those regulated by this agency. It is predicted that the database is comprised mostly of FDA/CVM approved pharmaceutical products with lesser numbers of reports for products regulated in the USA by USDA (vaccines/biologics) or EPA (topical animal pesticides). Reports from foreign (third country) sources are not required to be reported to FDA/CVM unless the product is specifically registered with FDA/CVM (i.e., has a NADA or ANADA number). Therefore, the database cannot be considered "global" or comprehensive for same or similar products marketed in other countries.

Products in the openFDA database are listed by generic name, including combination products, and adverse events are listed by the VeDDRA Low Level Terms (LLTs). Various filters can be applied to the data including species, drug sponsor, administered by, country, and drug trade name. Through 2023, openFDA compiled more than one million reports (termed "records"), with canine (~80%) and feline (~10%) reports comprising the highest proportion of these reports.

The website provides instructions on how to build ad hoc API queries of the database. There is not a provision for MAHs to conduct signal detection using the openFDA database.

Lack of product diversity and global scope, the time lag for obtaining openFDA data based on quarterly updates, missing or inconsistently entered data fields, and the inability for MAHs to view narratives are among the limitations of using openFDA for signal detection.

Other Data Sources

Clinical trials conducted during product development are the first source of adverse reaction data. These include laboratory efficacy and safety studies, including target animal safety studies, as well as controlled CTs in patients. Data from these studies may also be "revisited" as a potential source of supportive evidence during signal evaluation. However, such studies have multiple confounding factors such as small sample size and restricted patient populations and may not necessarily reflect real-world use of a product following approval. CTs are typically conducted under Good Clinical Practices (GCP) or Good Laboratory Practices (GLP) and therefore, study subjects are closely monitored and thoroughly documented. Furthermore, there is often a non-treated or alternatively-treated contemporaneous control group, which may allow estimation of incidence of observations in the absence of VMP treatment and/or a sense of relative frequency of observations between subjects treated with the VMP against those not exposed to the VMP. Because of the different nature of data collection in CTs compared to SRS systems, frequency comparisons between CTs and SRSs are not possible.

Post-marketing surveillance studies (PMSSs) may be conducted as a requirement at the time of product registration or to gather additional data to confirm the existence of a new risk or change to a known risk. PMSSs are performed less frequently in AH compared with HH.

Published biomedical literature is an increasingly important source of safety information in HH PV due in part to improved literature data mining tools. However, this may not be the situation in AH PV. Literature reports can be confounded by publication of poor-quality research, publication bias, flawed analyses, or improper or out-of-context interpretation of SRS data by authors lacking expertise in PV. The literature as

a source of safety observations/signals is also affected by latency of writing, reviewing, and publishing of articles. The principal uses of biomedical literature in AH PV are as part of the aggregate reporting process (i.e., Periodic Safety Update Reports (PSURs), Periodic Drug Experience Reports (PDERs)) and in SM at the signal evaluation stage during which broad sources of supporting data are considered.

While AE references in general social media datasets may complement more established AE sources, analysis of these datasets has demonstrated limited contribution to the SM process.[15,28] Some challenges include improper descriptions of drug names, poor characterization of AEs making coding to standard dictionary terms challenging, poor grammar, spelling mistakes, use of abbreviations and slang, and nonspecific characterization of AEs. The value in mining general social media as a tool for safety surveillance is limited by the volume of data, noise, unstructured text, linking verbatim text to medical AE dictionary terms, and duplication of posts.[28-30] One of the key points from the IMI WEB-RADR consortium[1] was that the performance of all DPA statistical detection algorithms tested poorly in social media-derived datasets compared with a traditional SRS database and that sample data from social media are not recommended for broad statistical signal detection.[28]

Structured longitudinal data are a source for signal detection and evaluation, including epidemiologic studies. Electronic veterinary medical records (EVMRs) facilitate big data collection platforms like VetCompass,[31] SAVSNET,[32] CAVSNET,[33] BARK,[34] and PETscan.[35] While providing additional data sources for signal detection, validation, and assessment, they may also be used to estimate background rates of medical conditions in the general population or in specific subpopulations. These sources provide a denominator to the signal scores, allowing more conventional statistical analyses including relative risks, odds ratios, or rate ratios. They also offer the potential to enable surveillance for specific products and conditions or add depth of knowledge at the signal evaluation stage. Limitations of these data sources may include questionable accuracy and completeness of the data and structural bias related to products included or excluded from the hospitals' formularies.

Disease epidemiology data may be leveraged during the signal assessment/risk evaluation process, providing context to the reports, observations, or signals. A reported AE for a product could be within expected background rates of the event in the general population, especially for very rare events. Epidemiological data put the event(s) in question into perspective by providing background rates of the event(s) in the population at risk that can be used as a point of reference.[1] However, disease epidemiology data have limited availability in animal health. Some sources include VetCompass, SAVSNET, CAVSNET, and occasional publications, mostly from veterinary colleges/teaching hospitals.

More recently, availability of big data, together with the development of analytical techniques, created new opportunities and challenges for signal detection in AH PV.[36] Big data is characterized by large volumes of diverse and dynamic data that are structured or unstructured. Both the opportunities and challenges stem from its complexity, content, and size. Constraints on application to AH PV include availability/accessibility, volume, and validation of data interrogation tools (e.g., machine learning models).

[1] The IMI WEB-RADAR consortium was a public-private partnership supported by the IMI Joint Undertaking. Participating members were from European regulatory agencies, the pharmaceutical industry, academia, patient groups, and other organizations with an interest in PV.

Qualitative Signal Detection Methods

Qualitative signal detection methods rely on review of ICSRs or case series development in a database or the biomedical literature applying clinical, scientific, and medical judgment. Aggregate review of spontaneously reported ICSRs and development of case series and summaries remain the "gold standard" for signal detection, triage, and validation[4,13,17,37] and are key components of safety observation evaluation. The ICSRs should be evaluated for the strength of evidence to support or refute a potential safety observation or signal. Factors to consider include, but are not limited to, temporality, biological and pharmacological plausibility, alternative causes, and dechallenge/rechallenge.[38] Among questions to consider are[15]:

- Is the safety observation new?
- Is it unusual?
- Is it occurring more than expected?
- Is it serious?
- Is it known to be linked to drug/product treatments (e.g., designated medical events (DMEs))?

For some AH MAHs with small PV databases or for certain species with low case volume, but often high numbers of reacting animals per case (e.g., poultry or fish), ICSR review and case series development may be the most reliable and appropriate approach to signal detection.

Other qualitative processes may include aggregate report preparation, assessment of a potential index case, and evaluating queries from regulatory authorities (RAs) or veterinary health care professionals.

Quantitative Signal Detection Methods

While qualitative review of ICSRs and data summaries remain regular activities for safety observation detection, the collection of ICSRs over time has resulted in large safety databases. The volume and complexity of data held in these databases has led to computational tools and quantitative algorithms to translate these data into meaningful knowledge. Quantitative data summaries may include absolute case counts, proportional report rates, or exposure-adjusted reporting rates.[4,15]

Statistical measures using various approaches are applied when case volume makes comprehensive review of ICSRs impractical. Descriptions and applications of DPA have been detailed in numerous papers in HH PV over the last 25 years[6,13,39,40] and to a much lesser extent in AH PV.[41,42] Examples of frequency-based measures include threshold-based statistics relative to a reference period,[2,15,43] change point analysis,[41,44] and sieve analysis.[45] Trending over time can be applied to most of these quantitative measures.

Questions to consider for quantitative detection methods may include:

- Type of measure to employ?
- Frequency of use?
- Reference period selection?
- Thresholds for outlier selection?
- Stage in product lifecycle?

Most signal detection and interrogation tools and related analyses have shortcomings. A few of these shortcomings are summarized.

Most quantitative methods lack clinical context and require expert knowledge, technical capacities, data availability, performance standards, testing, and validation. Simple statistics, such as case counts or proportional report rates (clinical sign report rates)[2] do not account for changes that may occur, for example, in sales and patient exposure. However, exposure-adjusted reporting rates based on sales or distribution data often apply assumptions that may or may not be valid such as, but not limited to, time between distribution and exposure or number of units to which one patient is exposed. The number of ICSRs (the numerator) is affected by limitations of SRS reporting, such as under-reporting, and assumptions to derive an estimate of the number of animals treated may not necessarily be valid. A dose sold or distributed may or may not be prescribed or administered to a patient.

The thresholds associated with disproportionality statistics are not justified based on statistical theory or empirical judgment but define a filter for the generated SDRs. Animal health SRS databases may be of limited size and diversity for evaluating disproportionate reporting. DPA approaches may not detect increased reporting without a change in the types of reported events. DPA cannot be used for comparative drug safety analysis beyond basic hypothesis generation because measures of disproportionality are missing incidence denominators, are subject to reporting bias, and are not adjusted for confounding.[46] Frequency-based approaches may not take seasonal use patterns into consideration without additional, possibly complicated, adjustments. Also, frequency-based approaches relying on a reference period can be used for mature products but would not be appropriate for new product surveillance (NPS). Sieve and change point analysis are relatively new approaches to quantitative signal detection and only recently has their potential value for AH signal detection been considered.

CONCLUSION

This flexible signal management framework consisting of three stages (detection, evaluation, and action) supports divergent practices and interpretation based on the situation and processes leading to identification of a safety or efficacy observation and its triage, validation, and assessment with implementation of appropriate actions. Priority is placed on the use of high-quality AE data analysis approaches applied to high-quality AE data to rapidly identify safety observations and validated signals that may be associated with new risks or changes to known risks. This risk-based approach enables MAHs to optimize resources for rapid identification of risks which are of greatest relevance to patient safety.

AUTHOR

This paper was authored by the Signal Management Subcommittee of the Animal Health Institute (AHI) Pharmacovigilance Working Group. AHI represents companies that develop and produce animal medicines that help protect and improve the health of nearly 10 billion companion animals and food-producing animals in the U.S. As sponsors of animal drugs all companies are required by law under 21 CFR 514.80 to report adverse events.

[2] The proportional comparison using the number of times a given clinical sign was reported divided by the total number of cases for that species, presented as a percentage.[4]

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APPENDIX

Application of Framework – Theoretical Scenarios

These scenarios are fictional examples which have been created to illustrate potential applications of the flexible signal management framework.

Application of Triage Process to a Safety Observation that Reverts to Routine Surveillance

The MAH instituted a marketing campaign with a satisfaction guarantee for product X. Afterward, routine surveillance detected an increase in the relative reporting frequency of event A following exposure to product X.

- Preliminary review of cases reported during the surveillance period revealed that some cases co-reported other events with no consistent patterns, 92% had causality assessments [3] of O-Unclassifiable/Unassessable or N-Unlikely (Observation source category/ICSRs/causality), most were reported by the animal owner and not medically confirmed (Observation source category/ISCRs/reporter), and 98% of cases were assessed as non-serious (Observation source category/ICSRs/seriousness).
- Review of cases assessed as serious revealed that the reporting was historical or coincidental as the reporter's intent for contacting the MAH was to take advantage of the product guarantee program with death or euthanasia mentioned coincidentally and for unrelated reasons (Product category/market factors-satisfaction guarantees).
- Review of some of the non-serious cases revealed a similar intent for contacting the MAH with cases reporting limited information (Observation source category/ICSRs/case quality and completeness) or alternative causes for the occurrence of event A.

The safety reviewer rapidly concluded there was sufficient evidence to support a conclusion that the observation was not a signal and reverted the finding to routine surveillance. The finding, factors considered in the triage process, and outcome were documented in the MAH signal management records system.

Application of Framework from Detection Stage to Action Stage

Routine surveillance was performed for product X and a new SDR was detected for clinical sign A. The new SDR was determined to be a safety observation which should be triaged.

- During the triage process, the reviewer noted that product X had been marketed for less than one year and that clinical sign A was a severe sign. The reviewer quickly determined that this observation had a potentially high impact/risk and should be prioritized. An overview of the ICSRs revealed that 30% of cases were assessed as ABON A, 40% as ABON B, 20% as ABON O or O1, and 10% as ABON N. 80% of cases were reported by a veterinarian. The observation was designated as a signal which should enter the validation process.

[3] Causality assessment is based on the ABON system where category A is Probable, B is Possible, O1 is Inconclusive, O is Unclassifiable/Unassessable, and N is Unlikely.[47]

- During the validation process, a preliminary assessment of the cases was performed. A detailed ICSR review of cases reporting clinical sign A determined that 40% of the cases were supportive of a potential product association due to factors including: complete historical information, extensive diagnostic testing to rule out alternate etiologies (and with test results provided), consistent co-reported clinical signs, a strong temporal association, and a lack of confounding factors such as pre-existing medical conditions. The signal was validated.
- The validated signal entered the assessment process for evaluation of a potential causal association. Cases were analyzed in greater detail to search for any contributing factors such as differences in sub-groups (such as higher incidence in a certain age group, breed, or sex), possible product interactions, or manufacturing/quality factors such as a batch issue, but no additional predisposing factors or potential causes were detected. Consultation of literature and epidemiological studies revealed that clinical sign A is exceedingly rare in the general population, and that even accounting for factors such as possible under-reporting, clinical sign A was occurring at a significantly higher incidence than would be expected due to background rate. Experts were consulted and determined a plausible pharmacologic mechanism by which clinical sign A could be causally associated with administration of product X. A meeting was held with multiple SMEs and representatives from the pharmacovigilance, regulatory affairs, clinical, safety/toxicology, and manufacturing departments to determine if there were any other factors which needed to be investigated and if the existing evidence was sufficient. It was agreed that there was sufficient evidence of a potential causal association for the validated signal to proceed to the action stage.
- Additional cross-functional meetings were held, including executive-level representatives who could approve/decide on next steps. It was agreed that a causal association of product X with clinical sign A could impact the benefit-risk profile of the product and that actionable safety outcomes should be initiated to minimize and mitigate risk. Communication of the risk was initiated, notifying the appropriate regulatory authorities, and the MAH began the process of adding the sign to the product label(s). Field veterinarians distributed educational materials to veterinarians and clients to inform them of the risk and ways to minimize the risk. Enhanced monitoring was initiated for clinical sign A in order to collect additional information about the outcomes of the risk minimization, mitigation, and communication measures.