PHARMACOVIGILANCE IMPLEMENTATION SYSTEM GUIDELINE FOR VETERINARY MEDICINES
Index

1. INTRODUCTION .................................................................2
2. DEFINITIONS ..................................................................2
3. PHARMACOVIGILANCE OBJECTIVES AND SCOPE .............3
4. NOTIFICATION SYSTEMS ..................................................4
5. CAUSE ANALYSIS ...........................................................12
6. SIGNALS DETECTION .......................................................14
7. COMMUNICATION ............................................................15
8. PHARMACOVIGILANCE SYSTEM DETAILED DESCRIPTION ....16
9. BIBLIOGRAPHY ...............................................................19
1. INTRODUCTION

Pharmaceutical companies carry out clinical and preclinical tests prior to commercialize a veterinary medicine, which allows proving their products efficacy, for the proposed use and with a better risk/benefit relation for animals, environment, worker and final consumer. All of these must be assessed by governmental regulatory authorities for each country within a sanitary registration routine process. However, clinical and preclinical test results come from a limited number of animals, and often not all variables encountered in the post-commercialization stage are considered, for instance, interactions with medicine administered in parallel, use in diverse breed, body conditions and age ranges, safety condition, among other variables. Even more, the limited number of animals included in preregistration tests, reduce the possibility of detection of less frequently reported or slowly developing adverse reactions.

Based on the above mentioned facts, it becomes necessary to implement a pharmacovigilance system for veterinary medicine, with an objective to identify adverse reactions in the post-commercialization stage, and in this way to continue to assess the veterinary medicine risk/benefit relation and safety/efficacy profile.

2. DEFINITIONS

2.1 Adverse Effects (EA):

Un-intentional damaging effects that may occur following consumption of a veterinary medicine on following or not the use recommendations indicated in the labels. It includes secondary damaging effects on animals (adverse reactions), as well as possible inefficacy of a medicine or adverse effects on the humans after the product exposure, final consumer and environment.

2.2 Serious Adverse Reaction (AR):

It provokes death, endangers life, produces significant incapacity or disability that may transform into a congenital malformation or birth defect, or may trigger permanent or prolonged symptoms in treated animals. The adverse reaction that results in euthanasia is also considered a serious AR, even if by itself, has not generated death. For animals managed and treated as a herd, only an increase in the incidence of serious adverse events that exceed the levels usually expected in that particular group are considered a serious adverse event.

2.3 Notification:

An action through which an authority and/or person in charge is informed about a patient, person or environment that has developed an adverse effect supposedly originated by a veterinary medicine. Consists of a format duly completed by the notifying officer in order to confirm causality, and it can be send by any way the local competent authority defines.
2.4 Off label use:

Utilization of a medicine different to the one authorized in labels intentional or not, including different dosage, intended species, use indications, administration form, among others.

2.5 Competent Authority: CA

Authority with professional proficiency in the area of Pharmacovigilance.

2.6 Unexpected adverse effect: (UAE)

Any adverse effect unknown up to date and, therefore, veterinary labels does not describe its nature, seriousness and consequences.

2.7 Periodic Safety Report (PSR):

A report of the adverse effects that have been notified to the CO during a specific and predefined period that provides an assessment of the benefit / risk balance of a veterinary medicine, which is sent periodically to the CA by the CO in order to provide an update of the safety and efficacy data of the veterinary medicine.

2.8 Commercialization Owner (CO):

Depending on each countries legislation, it is a natural or legal person, authorized to carry out primary commercialization of a veterinary medicine in a determined country.

2.9 Pharmacovigilance Accountable Professional (PVAP):

is a professional accountable on behalf of the CO, to coordinate and implement all activities related to Pharmacovigilance according to current regulations and is the valid interlocutor with the competent authority.

3. PHARMACOVIGILANCE OBJECTIVES AND SCOPE:

Pharmacovigilance objectives are:

1. To detect unknown adverse effects and interactions.
2. To detect any increase in the frequency of a known adverse effect.
3. To identify risk factors and possible mechanisms, which trigger adverse effects.
4. To permanently assess the veterinary medicine risk/benefit relation and safety/efficacy profile.

Pharmacovigilance scope:

1. Adverse reactions under authorized use conditions, i.e., observing the label recommendations.
2. Adverse reactions associated to off label use.
3. Alleged inefficacy of a veterinary medicine registered in a determined country.
4. Alleged insufficiency of the established control periods.
5. Adverse effects in people handling veterinary medicine.

6. Adverse effects manifested in the environment due to veterinary medicine use and/or its final disposal.

7. Infectious agents transmission by contaminated veterinary medicine.

It is recommended to implement the pharmacovigilance systems gradually in the country and according to the type of products applied.

4. NOTIFICATION SYSTEMS:

a) Private persons or citizens, cattle farmers or animal owners

They can notify about an AE, although they are not obliged to report or to fill any specific form.

In the event that there is a suspicion of an AE, a person can report by any means to the medicine Commercialization Owner (CO), to a veterinary doctor, to the technical director of the company where the product is available or directly to the competent authority.

b) Veterinary Doctors:

Veterinary Doctors should inform every AE suspicion they come to know in their routine clinical practice by observing a set of signs or symptoms, which cause suspicion about an eventual association with the administration of a veterinary medicine.

They shall notify any suspicious AE information they receive from private persons, cattle farmers or animal owners.

Regardless of the information source, veterinary doctors should notify the Commercialization Owner of the suspicious veterinary medicine, or to the Competent Authority by using the Green notification form, which must be sent to the CO of the suspect veterinary drug and / or directly to the competent authority, as defined by each country.

In the event that an AE appears in more than one animal species, a separate notification for each species is recommended, but it must indicate that both notifications are related. This also applies whenever the AE occurs in animals and in humans.

Whenever an AE appears in a non-treated animal that was exposed to a treated one, even though they are different species, a single notification must be submitted related to the animal affected by AE. In this case, the animal that received treatment with the veterinary medicine must be identified clearly. Further, information about the route of administration shall reflect the way in which the animal was exposed, i.e. orally (if the contact was by licking or by mutual grooming) or by cutaneous way (if there was skin contact between the animals).

Whenever AE appears in the descendants, it will be informed as follows:

• Spontaneous abortion or fetal death: notification should consider only the mother.
Whenever the AE is shown only in progeny (example: malformations) but the father is not affected: notification should only consider descendants. The number of affected litter descendants and the quantity of treated adults should be notified in order to know the proportion of affected animals. The latter is particularly important whenever there is inefficacy suspicion.

In the event that AE is observed both in the mother and the progeny (fetus intrauterine exposure): there should be one notification both for the mother and the progeny. Animal details notified should be the mother’s and the quantity of treated animal should be one (1): reported clinical signs should consider the mother and progeny.

To proceed with notification, suspicion must fulfill the following four minimum requirements:

- Notifying party identity: name, initials and contact information. It can be an individual, cattle farmer, owner or veterinary doctor.
- Affected party identification: (who or what has shown the AE): animal (specie, sex, age) humans (name or initials, sex, age) or environment (location).
- To identify at least one veterinary medicine suspicious of causing AE (example: name of the product, number of sanitary registration, commercialization owner or serial number, among others).
- AE Description

To have a valid notification, a great effort should be done to get complete and required information.

In cases of incomplete notifications, mainly in cases of serious or unexpected AE, there must be a follow up in order to get additional information from the initial notifying party or from other available documents or sources (results of laboratory analysis)

Additionally, veterinary doctors’ responsibilities are the following:

- To respect the truthfulness of the data received whenever registration of AE takes place.
- To protect confidentiality of data, which may lead to the identification of the person, in order to respect the privacy. In exception of the competent authority and/ or CO, so that it is possible for them to obtain additional information.
- To safeguard AE clinical documentation in order to complete or follow up cases.
- To collaborate with the Pharmacovigilance accountable professional PVAP at the Commercialization Owner CO, by providing any requested information in order to notify afterwards the Competent Authority CA
- To collaborate with the CA by providing all requested information to expand or complete AE information
- To keep himself updated about safety and efficacy data on prescribed or consumed medicine.

c) Technical directors at retail stores (TDRS)
TDRS are obliged to notify all AE they come to know, from individuals, cattle farmers or animal owners by filling out the Green notification form which must be forwarded to the CO for the suspicious veterinary medicine or directly to the Agriculture and Cattle Farmer Department (ACFD)

To proceed with a notification, those four minimum requirements detailed in previous section (b) must be fulfilled.

d) **Commercialization Owners** (import companies and domestic production laboratories)

Whenever the CO receives information about an AE suspicion, it should confirm previous data and, if necessary, contact the notifying person to obtain more or to complete information. In addition, he should contact the notifier and ask for supplementary background data, such as laboratory test results, necropsy in case of death and follow up history of cases.

In all cases where the CA receives a notification of suspicion of AE, it must be sent to the CO; who must have the capacity to avoid duplication of information received from the same source (notifier) through different channels.

i. **Individual Notification:**

The COs who receive information related to an AE suspicion, should report it to ACFD by filling out a yellow notification form no later than 15 working days after receiving the notification, in cases of:

- Serious AR suspicion in animals (both expected and unexpected) that have occurred in the country.
- AE suspicion in humans exposed to veterinary medicine that have occurred in the country.
- AE suspicion in the environment and a possible transmission of infective agents that have occurred in the country.

AE suspicion should be considered after the drug consumption according to the approved use and the off label use.

All of these AE, are classified as “expeditious or serious”

The yellow form must be filled out, and sent to the CA.

When no information is available, it should be indicated “unknown” or “it does not apply” in the corresponding items.

In cases of a serious AR suspicion in animals (expected and unexpected), that have occurred in the country, and at the same time there is suspicion of quality failure of the veterinary medicine, it must be reported no later than 72 hours since the time of reception of the notification.

Suspected serious adverse reactions, occurring in third countries, should be included in the periodic safety report.
ii. Periodic Safety Report

The AEs not included in the previous paragraph (i) are considered as “not expeditious or not serious”, and there is no obligation to report them individually, however, they must be reported to the CA in a Periodic Safety Report (PSR).

Regarding reports of events occurring in third countries, such as suspicions of unexpected serious AR, suspicion of AE in humans or in the environment and the possible transmission of infectious agents, they should also be included in the periodic safety report.

The Purpose of PSR is to provide an update on the safety and efficacy information to the world veterinary community. Even when there is no AE reported in a period, the CO must prepare and present the PSR.

The safety information must be gathered, analyzed, and assessed by the CO to define whether additional tests or changes in valid label are required.

Each PSR is defined by a data block point (DBP), matching the report closing date. At this point, all PV information known by the CO must be gathered and analyzed.

To initiate a PSR

- Starting from the sanitary registration date or the International Registration Date, as it is suitable.
- For administrative effects, the last day of each month must be considered.

Submission frequency

- Every six months, starting from the registration date up to effective commercialization date.
- Every six months, 2 years after effective commercialization in the country.
- Annually, during two consecutive years
- Every three years, starting from the last yearly report.

CA will define for every case the PSR modification frequency, for instance, whenever registration is changed including a new target species, dosage, use instruction, consumption forms, new excipient lacking a safety profile or whenever a closer continuous monitoring requirement about the product safety emerges.

PSR Cycle:

- It should start the following day after the previous PSR data block point. There cannot be any uncovered day by the PSR nor data overlapping.

Delivery date:

- Up to 60 days following DBP.

PSR Scope:
- PSR should cover all species, indications and commercialized presentations, either as originally registered or added in subsequent changes.

- It should include those AE reported within the country and in third countries.

**PSR content:**

1. **Veterinary Doctor’s information.**
   - Generic and commercial name
   - Pharmaceutical form
   - Sanitary Registration number
   - Registration date
   - PSR correlative number
   - PSR formulation date
   - PSR covered period
   - First effective commercialization date
   - PVAP’s name and signature
   - Number of countries in which the product has been approved

2. **CO’s name and address**

3. **Regulatory measures update or actions taken from the CA in any country of the world due to safety reasons, since the last report, such as registration denial, general or for a specific indication; registration or market withdrawal; registration renewal denial, registration change, risk management plan imposed by the CA, inter alia.**

4. **Presentation’s estimate**
   - Sales volume: for the reported period, both domestically and in third countries, expressed as:
     - Vaccines: dose quantity or volume in case the vaccine indicates different doses according to type of animal.
     - Liquids: liters
     - Powder: kilograms
     - Tablets: Tablet quantity
     - Collars: collars quantity
     - Paste: kilograms
Pipette: Pipette quantity

- Treated animal estimate: Even though each CA must define it, it is recommended that the PSR includes the estimated number of treated animals and incidence. Regardless of the AE appearance, in some cases the number of treated animals (for each authorized target species) corresponds to the number of sold dose, however in other cases the standard treatment period should be taken into account or the worst scenario (maximum recommended dose and longest treatment period) considering a standard weigh for each target species.

<table>
<thead>
<tr>
<th>Species and subcategory</th>
<th>Standard average weight (kg)</th>
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</thead>
<tbody>
<tr>
<td>Equine</td>
<td>550</td>
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<tr>
<td>Canine</td>
<td>20</td>
</tr>
<tr>
<td>Cat</td>
<td>5</td>
</tr>
<tr>
<td>Bovine</td>
<td>550</td>
</tr>
<tr>
<td>Veal</td>
<td>150</td>
</tr>
<tr>
<td>Unweaned Calf</td>
<td>50</td>
</tr>
<tr>
<td>Sows/Boars</td>
<td>160</td>
</tr>
<tr>
<td>Pigs (fats)</td>
<td>60</td>
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<tr>
<td>Piglet</td>
<td>25</td>
</tr>
<tr>
<td>Ovine</td>
<td>60</td>
</tr>
<tr>
<td>Lambs</td>
<td>10</td>
</tr>
<tr>
<td>Chicks broilers</td>
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</tr>
<tr>
<td>Laying Hens</td>
<td>2</td>
</tr>
<tr>
<td>Turkeys</td>
<td>10</td>
</tr>
<tr>
<td>Rabbits</td>
<td>1,5</td>
</tr>
</tbody>
</table>

* for those species and subcategories in which a standard average weight is not included, the CO must define and report the average weight that will be used to perform the calculations, having to use the same data consecutively.

For drugs intended for several species or subspecies, the OC should make a general estimation of the proportion of animals treated per species or subspecies; in order to calculate the incidence as detailed below.

5. AE Incidence

- Spontaneous AE general percentage incidence (A, B, O including O1. See definition in point 5: CAUSE ANALYSIS) after indicated and off label use, for all authorized target species, in relation to the sold volume. Those AE detected in post registration safety tests should be excluded.

- Percentage of lack of effectiveness incidence, after recommended use, in relation to volume sold.

- Proportion of animals with AE: in general and for each target authorized species.

- Proportion of animals that have EA: in general and for each target animal species authorized and commercialized.
o Quantity of animals with AE (A,B,O including O1) during the period/Dosages quantity sold during the period.

- **Incidence**
  o Quantity of animals affected by AE (A,B, O including O1) during the period/estimated quantity of treated animals during the period x 100.
  o An Incidence Estimation for each reported country shall be prepared.

6. **Data Check**
   - All individual AE reported during the period, highlighting main findings and AE types (foreseen, unforeseen, serious and not serious).
   - Reported AE in animals (including for inefficacy and off label use)
   - AE reported in humans
   - Other Pharmacovigilance areas: environment, vigilance period, infectious agent transmission
   - Presentation, analysis and assessment of new safety data, which change known data in terms of frequency and severity.
   - Charts summarizing main findings will endorse analysis.

7. **Ordinary Reports**
   - If the CA determines it, to attach data from other sources, like post registration analysis, AE published data, users experience studies; those should be reviewed and discussed.
   - To attach bibliographic list of published scientific articles that report AE for the same PSR period, and a brief discussion of results.

8. **Other information**
   - AE due to medical prescription, treatment mistakes (name change or veterinary medicine with similar appearance), misuse and/or abuse.

9. **Safety General Assessment**
   - Summary of all AE contained in the report.
   - A critical analysis on presented data and a critical assessment on the risk/benefit relation, particularly about frequency changes of known AE, occurrence of unexpected AE, interaction with other drugs, inefficacy and AE in humans
   - An assessment must indicate whether:
     o Safety information remains in line with accrued experience up to the date and the label.
10. Important information after DBP.

- Summary of all AE contained in the report.
- Any information received after the DBP should be included if relevant and may cause modifications to the general evaluation informed in the previous point.

11. List of cases

- It must contain all AE occurred throughout the world and spontaneously reported to CO or to CA.
- It should contain all individual cases classified as A, B, O, O1 and N.
- To report all measures taken by the CA or by the CO
- Standard information must contain:
  - Treatment/vaccination date
  - Use indication
  - Off label use
  - AE date
  - Quantity of treated animals
  - Target species
  - Age (s)
  - Quantity of animals which reacted
  - Quantity of death animals
  - Other accompanying drugs administered (Commercial names and active substances)
  - Case description and symptoms
  - Symbols list
  - Allocated causality assessment

- For AE in humans, the following should be included:
  - Patient identification
  - Occupation
Shorten PSR:

A shorten PSR is submitted whenever the veterinary medicine has not been commercialized in any country of the world, and when no AE has been reported in any additional post registration tests.

PSR content must include:

Generic and commercial name, pharmaceutical type, Sanitary Registration No.; Sanitary Registration No. date; PSR correlative Number, PSR covered period, non-commercialized and un-existing AE statement (in animals or in humans) for which risk/benefit balance remains unchanged, commercialization estimated date, CO’s name and address, PVAP’s name and signature.

In addition, CO are accountable for the following:

• To keep detailed registration of all AE that have been notified.
• To have a PVAP permanently available.
• Avoid sharing with clients any PV data, which has not been communicated beforehand or in parallel to the CA
• To monitor International references about AE caused by an active principle that is a component of a drug for which he is the authorized commercialization owner CO.
• To report to veterinary doctors on new data regarding safety or efficacy whenever CA ponders as required. The report content should have the CA agreement beforehand.
• To report immediately to the CA about urgent restrictions adopted due to PV.

5. CAUSE ANALYSIS

Regardless of the AE notification source, CO must assess or relationship between the veterinary medicine consumption and the notified AE appearance. Conclusions from causality assessment should be included in yellow format or PSR, depending on an expeditious or non-expeditious AE respectively.

The analysis of causality is an individual analysis for a given notification, which does not intend to study the risk potential of the drug globally or the importance of the risk induced by the drug in the population.

In order to determine causality, the following aspects must be considered:
• Manifestation of a temporary association (including non-exposure and re-exposure) or association in treated and affected anatomical exposure.

• Pharmacological or immunological explanation, blood levels, active principle previous knowledge.

• Manifestation of pathological phenomena or clinical features.

• Exclusion of other potential causes.

• Reported case complete and reliable data

• Quantitative measurement on the veterinary medicine impact to the AE development (dosage-effect relation).

Cause analysis is performed throughout ABON methodology, which studies five categories:

Category A: Probable

• There is a reasonable temporary association between the veterinary medicine administration and the AE occurrence and period.

• The clinical phenomenon description should be consistent with the AE, or at least credible according to the known veterinary medicine pharmacology and toxicology.

• There is no other credible AE development explanation.

Category B: Possible

• Veterinary medicine causality is one of many possibilities or it is a plausible cause, but available information does not comply with Category A’s inclusion principle.

Category O: Non-classifiable

• Available data is not reliable or sufficient to determine causality.

Category O1: Non Conclusive

• Association cannot be dismissed, however, there are factors preventing the allocation of a determined causality.

Category N: Unlikely

• Cases with enough information to establish beyond any reasonable doubt that there is AE alternate explanation and which is unrelated to veterinary medicine.

6. SIGNALS DETECTION

The causality assessment carried out by the CO must be evaluated by the CA.
When the causality analysis results determine an AE pattern associated to the medicine utilization, depending on the conditions under which AE have appeared and seriousness, CA might introduce corrective actions aimed to improve veterinary medicine risk/benefit relation.

Information about a possible cause relation between an AE and a veterinary medicine, unknown or insufficiently documented, constitutes a signal. Whenever there is a suspicion of a signal either from CO or from CA, causal relation and any AE aspects that could be relevant, must be assessed.

AE ordinary review and analysis by CO and CA may contribute to detect potential signals, such as:

- AE increase in a short period of time.
- An increase in the frequency of clinical sign(s).
- Whenever a new clinical sign stands out.
- Public health or animal sanitary impact suspicion.

When the CA or the CO detects any of the following situations, the CO must start an investigation:

- AE reaching an incidence level higher than basal (i.e. 1:10,000).
- Serious or unexpected AE appearing in 3 different sites in a week or there is a serious and unexpected AE incidence increase.
- Whenever there are more than 3 AE in farm animals with above normal mortality rate, and within the first 3 months of a new product commercialization.
- A suspicion about the vigilance periods is insufficient to confirm the residue levels lower than the maximum residue level.

When a signal that might affect the benefit / risk balance of the medicine is detected, there must be a formal communication between the CO and the CA or vice versa, depending on which entity identifies it.

When the above occurs, the signals must be validated by the CO and the CA; and in this case the assessment of the benefit / risk balance can be modified by the following actions:

- To increase benefit: including more information for medicine use improvement.
- To reduce risk: counter-indicate usage under certain circumstances, changing dosage, adding special usage precautions, etc.

In an enunciative and non-restrictive way, CA may take the following regulating measures:

- To include contraindications, usage warnings or precautions on the labels.
- To make changes in authorized usage conditions (use indications, dosage, time schedule, target species, vigilance, among others).
• Agreement to carry out post-registration studies by the CO, in case it is essential to obtain additional and relevant information.

• Increase in the periodicity on sending the PSR in order to evaluate the results of the actions taken.

• Based on the benefit / risk assessment of the medicine, temporary suspension and / or immobilization of the veterinary drug registration, until the safety / efficacy issues have been resolved.

• Cancellation of veterinary drug registry.

7. COMMUNICATION

The purpose is to keep veterinary doctors, suppliers technical directors (wholesale and retail) cattle farmers, animal owners and general public informed about any significant change in the information about any medicine (technical specification and graphic label), registration suspension or removal due to PV, in addition to any confirmed concern or suspicion which requires vigilance.

A communication must include the following aspects:

• The right message must be sent to the right group and at the right time.

• The appropriate terms should be used, having in mind diverse target groups.

• Communication should be clear, brief, and unbiased, without any commercial or promotional information.

• A contact person or place to receive any additional information request should be identified.

• Before a regulatory measure is taken, a communication should be delivered, except whenever there is an urgent prohibition due to safety reasons.

• CO or CA prepares communication, upon co-ordination and agreement from both parties regarding content, distribution plan, target group and implementation deadline.

• Distribution of a communication is carried out through different setups, like:
  o Press Release
  o CA web page
  o CO web page
  o Annual PV bulletin from CA
  o Other digital media

Direct communication with Veterinary Doctors (VDDC)
By general rule, relevant new or emerging information must be communicated first to veterinary doctors, before the rest of target groups, so that they can be better prepared and clarify any doubts from cattle farmers, animal owners or public in general.

The previous paragraph refers to the need to take actions or either to adapt their clinical practice.

VDDC does not provide answers to veterinary doctors’ requirements, or educational material for routine risk minimization activities.

When there is more than one CO with registered products manufactured under the same active principle, a single and consistent message should be issued.

A VDDC shall be distributed in situations when an immediate action is needed or a change in current uses of a veterinary medicine is required:

- A significant change in a veterinary medicine usage condition, due to a usage restriction indication, a new counter-indication, or a dosage change recommended due to safety reasons.
- A restriction in a veterinary medicine availability, that may cause potential effects in animals, humans or environment.
- Suspension, withdrawal or cancellation of a registration due to safety reasons.

Other situations whenever a VDDC must be considered are the following:

- New warnings, drug interactions or special usage precautions.
- New information that identifies a previous unknown risk or a frequency or seriousness change.
- Substantial knowledge that a veterinary medicine does not conform the registered efficacy.
- New recommendations to prevent or treat AE or to avoid medication misuse or mistakes, associated to a veterinary medicine.
- Ongoing assessment of a significant potential risk, for which all available data are insufficient to take regulatory action (in this case VDDC should encourage close monitoring about the risk in question; also encourage report making and delivery of information about ways to minimize this risk).

CA can distribute or request the distribution of a VDDC, in any situation when it may be necessary to keep address the safety and efficacy of a veterinary medicine.

8. PHARMACOVIGILANCE SYSTEM DETAILED DESCRIPTION

CO shall have a suitable and documented PV system and the required infrastructure to compile and notify AE occurring in any country where the veterinary medicine is marketed. The PV system should ensure close supervision of veterinary medicines so that appropriate corrective measures are applied when required.
CO shall have a PV professional in charge, of suitable profession, which must be informed to the CA and who will be accountable for the following:

- To set up and maintain a PV system.
- To carry out a continuous and periodic PV system assessment.
- To warrant an accurate AE registration.
- To inform to CA about any AE suspicion.
- To elaborate and submit Periodic Safety Reports PSR.
- To assess and allocate causality.
- To warrant a prompt, timely and correct answer to any information request from CA.
- Provide any information to de CA that may be of interest to evaluate the risk/benefit relation.
- To supervise data base, quality control system, contractual agreements in PV and internal audits matters.
- To be aware of the continuous process that is carried out for the detection of signals and its validation.
- To provide training to the company staff in PV related issues, as well as the staff of exclusive distributors if applicable.

It is preferable, although not obligatory, to appoint a Professional who will be accountable for all PV system matters (PVAP), and there should be a documented procedure to follow in the absence of the profesional.

PVAP must be properly qualified and with accredited experience in all PV’s matters to perform his duties; and a professional with similar qualifications should be available to substitute him whenever he needs to take a leave of absence.

Some or all PVAP duties may be transferable to a hired person or institution; however the CO should have the overall responsibility.

CO shall provide to CA a detail description of the implemented system, including monitoring of various functions and training of various parties for proper functioning of the Pharmacovigilance system content:

1) Information of the PVAP
   - Name, Profession and contact information
   - Summary of his Curriculum Vitae, with special emphasis on his education and PV background
   - Short description of his position and delegation of his duties
   - PVAP’s Substitute background information
• List of PV duties delegated to another professional

2) PV system organization

• Description of functional duties and responsibilities for all units involved in PV

• Organization chart showing the PVAP position within the organization and relationship with head office, branches and outsourcing companies.

• Summary of PV activities performed by each organization unit.

• Flow chart of AE notification activities, relating the manner in which AE and PSR are compiled, processed and notified.

• PV activities and data base location.

3) Standardized functional procedures.

• Available procedures list

• PVAP activities and back up procedure in his absence.

• AE collection, management, quality control, coding, classifying, assessment and notification.

• Data base management and utilization

• PV system internal audit

• Training

• Data storage

4) Data bases

• List of main available data bases, functional description and status validation.

5) PV areas subcontracts

• Contracts description, task and duties identification.

6) Training

• Training, documenting and registering system’s short description.

7) Documents

• PV document files brief location description.

8) Quality assurance system

• Implemented system brief description.

• Quality internal audits
9) Support documentation

9. BIBLIOGRAPHY
VICH GL24: Veterinary medicine pharmacovigilance. Adversed events reports management.

Standard 2001/82/CE: Determines a community code for veterinary medicine.

European Community Volume 98: Pharmacovigilance guideline for veterinary medicine.

SENASA Argentina: Pharmacovigilance system notification form
1. ADVERSE EFFECT IDENTIFICATION (AE)

<table>
<thead>
<tr>
<th>Safety Problem</th>
<th>Inefficacy</th>
<th>Vigilance Period</th>
<th>Environmental</th>
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<td>In Animals</td>
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<td>In Humans</td>
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2. NOTIFYING PARTY DATA

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<td>Telephone Number:</td>
<td></td>
</tr>
<tr>
<td>E-mail:</td>
<td></td>
</tr>
</tbody>
</table>

3. NOTIFICATION DATA

<table>
<thead>
<tr>
<th>Adverse Effect reception data (mm/dd/yy):</th>
<th>Follow-up report – if this option is selected, indicate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Initial Notification (mm/dd/yy):</td>
<td>Initial Notification Reference N°:</td>
</tr>
<tr>
<td>Name of the animal owner:</td>
<td>Pharmaceutical</td>
</tr>
</tbody>
</table>

Type of Notifier: Veterinary Doctor

Type of Notifier: Doctor

Type of Notifier: Other (specify):

4. VETERINARY DOCTOR/HUMAN DOCTOR/PHARMACEUTICAL DATA

<table>
<thead>
<tr>
<th>Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td></td>
</tr>
<tr>
<td>Telephone N°:</td>
<td></td>
</tr>
</tbody>
</table>

5. ANIMAL OWNER/PATIENT DATA

<table>
<thead>
<tr>
<th>Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td></td>
</tr>
<tr>
<td>Telephone N°:</td>
<td></td>
</tr>
<tr>
<td>6. ANIMAL (S) DATA</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>N° of Treated animals:</td>
<td>N° of animals with symptoms:</td>
</tr>
<tr>
<td>Species:</td>
<td>Breed/productive activity:</td>
</tr>
<tr>
<td>Reference (s) of animal (s) with symptoms:</td>
<td></td>
</tr>
<tr>
<td>Sex/Physiological Status:</td>
<td>Female</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Weight (kilograms):</td>
<td>Age:</td>
</tr>
<tr>
<td>Health status when treatment was prescribed:</td>
<td>Good</td>
</tr>
<tr>
<td>Reason for Treatment (preventive against an initial illness or diagnosis):</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. PRODUCT DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial/generic name:</td>
</tr>
<tr>
<td>Sanitary Registration Nº:</td>
</tr>
<tr>
<td>Serial Nº:</td>
</tr>
<tr>
<td>Description of real storage conditions:</td>
</tr>
<tr>
<td>Treatment details:</td>
</tr>
<tr>
<td>Dosage/Frequency:</td>
</tr>
<tr>
<td>Route and place of treatment consumption:</td>
</tr>
<tr>
<td>Starting of treatment (mm/dd/yy):</td>
</tr>
<tr>
<td>Accountable person for the medicine consumption: Veterinary Doctor owner of the animal, Other, (Specify)</td>
</tr>
<tr>
<td>Consumption according to approved label:</td>
</tr>
<tr>
<td>No (specify):</td>
</tr>
<tr>
<td>Action taken after appearance of adverse effect:</td>
</tr>
<tr>
<td>Other (specify):</td>
</tr>
<tr>
<td>Does the AE stopped when treatment was taken?</td>
</tr>
<tr>
<td>Does AE re-appeared when treatment is started?</td>
</tr>
</tbody>
</table>
8. ADVERSE EFFECT DATA (EA)

<table>
<thead>
<tr>
<th>Date of appearance of AE (mm/dd/yy):</th>
<th>Date AE ended (mm/dd/yy):</th>
</tr>
</thead>
</table>

Describe Sequence of events, including route of the product administration, clinical signs, location where AE reaction occurred, seriousness, laboratory tests conducted and its results, autopsy results, and other factors that could have contributed. Include details of treatment prescribed.
Or was the AE treated?  No  Unknown  
Yes (Describe):

Chronological tracking of the AE:

<table>
<thead>
<tr>
<th>Euthanasia</th>
<th>Dead</th>
<th>Under treatment</th>
<th>Alive with sequelae</th>
<th>Recovered</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quantity of animals

<table>
<thead>
<tr>
<th>dates (mm/dd/yy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

9. CRITERIA OF VETERINARY IN CHARGE OF TREATMENT

According to the Veterinary Doctor, to what degree the product has caused AE:

Probable  
Unlikely  
Without any Veterinary Doctor care

10. EXPOSURE TO PREVIOUS REACTIONS OF VETERINARY MEDICINE

Was there any previous history of exposure to the product?

<table>
<thead>
<tr>
<th>No</th>
<th>Unknown</th>
<th>Yes (specify a date (mm/dd/yy) if known):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Has there been a reaction to this medicine?

<table>
<thead>
<tr>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

Yes (Specify):

Has there been any reaction to ANOTHER medicine?

<table>
<thead>
<tr>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

Yes (Specify):
### 11. DATA ABOUT ALLEGED AE IN HUMANS

**Data about patient:**

- **Sex:**
- **Date of birth (mm/dd/yy)**
- **Occupation (relation with exposure):**
- **Veterinary Medicine exposure date (mm/dd/yy):**
- **Date of appearance of alleged AE (mm/dd/yy):**
- **Type and duration of exposure AE details (including symptoms), consequences and results:**
### 12. PRODUCT CAUSALITY ASSESSMENT

<table>
<thead>
<tr>
<th>Classification</th>
<th>A (Probable)</th>
<th>B (Possible)</th>
<th>O (Non-classifiable)</th>
<th>O1 (Non conclusive)</th>
<th>N (Unlikely)</th>
</tr>
</thead>
</table>

Justification of classification:
<table>
<thead>
<tr>
<th>13. DATA ON PRODUCT(S) CONSUMMED SIMULTANEOUSLY (whenever more than 2 medicine are taken simultaneously, duplicate this form)</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial/Generic name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical presentation and concentration (e.g.: 100 mg tablets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanitary Registration No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validity date (mm/dd/yy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage real conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route and place of consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose/ Frequency (dosage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Duration / Exposure Starting Date (mm/dd/yy):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Date (mm/dd/yy):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Who prescribed the medicine? (veterinary doctor, owner, other)</td>
<td>Yes Unknown No (Specify):</td>
<td>Yes Unknown No (Specify):</td>
</tr>
<tr>
<td>Was the medicine prescribed according to the approved label use?</td>
<td>Treatment Suspension Dose Reduction Other (specify):</td>
<td>Treatment Suspension Dose Reduction Other (specify):</td>
</tr>
<tr>
<td>Does the adverse reactions disappeared when the treatment stopped?</td>
<td>Yes No Does not apply Unknown</td>
<td>Yes No Does not apply Unknown</td>
</tr>
<tr>
<td>Does the reaction re-appears after treatment re-starts?</td>
<td>Yes No Does not apply Unknown</td>
<td>Yes No Does not apply Unknown</td>
</tr>
<tr>
<td><strong>14. NOTIFYING PARTY SIGNATURE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE notification date (mm/dd/yy):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location (City):</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Name of Notifying party:

Signature*: __________________
*Only in case this formulary is delivered
Printed.

**Contact (telephone Number)** (in case is different from the number indicated in page 1)
# GREEN NOTIFICATION FORM

**NATIONAL PHARMACOVIGILANCE SYSTEM**

<table>
<thead>
<tr>
<th>CA name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CA address</td>
<td></td>
</tr>
<tr>
<td>CA Phone No.</td>
<td>CA e-mail</td>
</tr>
<tr>
<td>CA web page</td>
<td></td>
</tr>
</tbody>
</table>

## ADVERSE EFFECT (AE) IDENTIFICATION

### SAFETY PROBLEM:

- In animals
- In human

### INEFFICACY

### VIGILANCE PERIOD PROBLEM

### ENVIRONMENTAL PROBLEM

## NOTIFYING PARTY DATA

<table>
<thead>
<tr>
<th>Role</th>
<th>Veterinary ID N°</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Technical Director at retail store</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>Telephone</td>
<td></td>
</tr>
<tr>
<td>E-mail</td>
<td></td>
</tr>
</tbody>
</table>

## PATIENT(S) DESCRIPTION

<table>
<thead>
<tr>
<th>Species</th>
<th>Breed</th>
<th>Sex</th>
<th>Status</th>
<th>Age</th>
<th>Weight</th>
<th>Reason for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td>Female</td>
<td>Castrated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>Pregnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>Unknown</td>
<td>Other (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### VETERINARY MEDICINE WAS ADMINISTERED BEFORE THE ALLEGED ADVERSE EFFECT APPEARANCE

*(whenever more than 3 medicine were prescribed simultaneously, duplicate this form)*

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterinary medicine commercial name</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical presentation and concentration (e.g.: 100 mg tablets)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanitary Registration Number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serial Number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route and place of consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose / Frequency (dosage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment / Exposure Starting date (mm/dd/yy):</td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
</tr>
<tr>
<td>Final Date (mm/dd/yy):</td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
</tr>
<tr>
<td>Who prescribed the medicine? (veterinary, owner, other)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you believe the AE is caused by the medicine?</td>
<td>Yes / No</td>
<td>Yes / No</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Has the relevant laboratory been informed?</td>
<td>Yes / No</td>
<td>Yes / No</td>
<td>Yes / No</td>
</tr>
<tr>
<td><strong>ALLEGED ADVERSE EFFECT DATE</strong> (mm/dd/yy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time passed between medicine administration and AE in minutes, hours or days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE duration in minutes, hours or days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N° of treated animals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N° of animals with symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N° of dead animals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REACTION DESCRIPTION</td>
<td>Please, specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety problems in animals / alleged inefficacy expected / Vigilance period problems / Environmental Problems</td>
<td>Also indicate whether the AE has been treated. How and which medication was used and what result(s) was obtained?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OTHER RELEVANT INFORMATION (e.g.: Completed or ongoing tests, relation of necrosis. Attach documents in timely manner).

<table>
<thead>
<tr>
<th>ADVERSE EVENTS IN HUMANS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact with treated animal</td>
<td></td>
</tr>
<tr>
<td>Oral intake</td>
<td></td>
</tr>
<tr>
<td>External exposure</td>
<td></td>
</tr>
<tr>
<td>Ocular exposure</td>
<td></td>
</tr>
<tr>
<td>Injection exposure</td>
<td></td>
</tr>
<tr>
<td>Other (specify)</td>
<td></td>
</tr>
<tr>
<td>Finger</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td></td>
</tr>
<tr>
<td>Joint</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Received Dose:</td>
<td></td>
</tr>
</tbody>
</table>

NOTIFYING PARTY SIGNATURE

Date (mm/dd/yy): / / 

I hereby declare the above information is true.

Full name:

Signature*: ____________________

- Only if this form is handed in

Contact (telefone No.) (only if is different from the number indicated in the first page):