GVPP
GOOD VETERINARY PHARMACOVIGILANCE PRACTICE

The Good Practice Guide for the European Animal Health Industry
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IFAH-Europe
Brussels, March 2004
FOREWORD

This IFAH-Europe1 Good Veterinary Pharmacovigilance Practice Guide is part of the animal health industry initiatives to promote veterinary pharmacovigilance. It follows previous industry contributions, including FEDESA2 reporting forms for adverse reactions and a joint workshop with authorities (EU and national) and veterinarians (FVE) in May 2002. The main conclusions of this workshop were that all interested parties must take their responsibilities and act towards promoting good pharmacovigilance, which industry aims to pursue herewith.

This Good Practice Guide provides a useful tool for anyone involved in veterinary pharmacovigilance, by explaining the obligations of each party responsible for the pre and post-approval surveillance of veterinary medicinal products. The guide should be read in conjunction with the legal texts, but does not bind industry or the relevant authorities or any other party involved. It is written in a Questions & Answers format, completed by 2 appendixes containing the links to the legal texts and official documents, and a reporting decision tree.

This document was elaborated by the IFAH-Europe pharmacovigilance ad hoc group, and coordinated by Sylvie Meillerais, with special acknowledgements to Bob Cornez and Erik De Ridder for their time and effort. The national associations and technical and regulatory IFAH-Europe committees also added some valuable contribution to finalising the document.

Moreover, the authorities responded positively to this initiative, described as a useful contribution to promoting veterinary pharmacovigilance in Europe.

Brussels, March 2004
Dr. Susanne Zänker
Technical and International Affairs Director
IFAH-Europe

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1 IFAH-Europe: A division of IFAH, International Federation for Animal Health
2 FEDESA: European Federation for Animal Health, became IFAH-Europe in January 2003
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1. INTRODUCTION: THE IMPORTANCE OF GOOD PHARMACOVIGILANCE PRACTICE

Pharmacovigilance is the systematic collection, collation and analysis of reports from veterinarians and animal owners, of adverse reactions or events connected to the use of a medicinal product. Its purpose is to identify unwanted properties in relation to substances and products that could not be observed in the development process since testing during development is always limited to a relatively small numbers of individuals compared to the real world. In that respect it is just another phase in the life of a medicinal product. This pre and post-authorisation surveillance also includes reactions in humans, lack of expected efficacy, off-label use, violation of residues and potential effects on the environment.

Pharmacovigilance was first addressed in the legislation in the framework of Directive 81/851 (now Directive 2001/82/EC). It is an essential part of the regulatory process and it should be the aim of all interested parties (i.e. animal owners, veterinarians and the animal health industry) to work together to ensure that it is implemented fully and consistently in all member states and within all companies. All interested parties must act towards promoting good pharmacovigilance within their organisations and to their customers.

In the forthcoming amendments to the pharmaceutical legislation, pharmacovigilance will receive renewed emphasis, as less is placed on the renewals procedure. An efficient and effective pharmacovigilance system will help to mould the future regulatory process by enabling the examination, validation and verification of pre-registration assumptions. One possible conclusion from this experience could be to reduce the reliance on large amounts of pre-registration data while delivering a more targeted and potentially higher level of product assurance via post-marketing surveillance.
The purpose of this good practice guide is to provide a useful tool for the animal health industry to apply a consistent pharmacovigilance system in line with the current legislative requirements. Companies are fully aware of the need to accurately monitor suspected adverse reactions, to collect and evaluate the information to be reported to the authorities, and take appropriate measures if needed to. This guide makes pharmacovigilance easy by answering the “what, when and how” questions often addressed. Above all, this guide demonstrates that the animal health industry is fully dedicated to running an efficient and fully operating pharmacovigilance system and is a reliable link in the reporting chain.

The animal health industry is also participating actively in the ongoing VICH process, which aims at harmonising technical requirements for veterinary product registration between the EU, Japan and the USA. The more homogeneous pharmacovigilance is performed, the more valuable will be the results.

2. LEGAL FRAMEWORK

2.1 What is the right terminology for Suspected Adverse Reactions?

Directives, guidelines and communications from authorities use different terminologies to describe a pharmacovigilance (PhV) case throughout these documents.

The most common denominations are:
- Adverse Drug Reaction
- Suspected Adverse Reaction
- Suspected Adverse Drug Reaction
- Adverse Event (to cover efficacy, residue and environmental problems, in addition to adverse drug reactions)

Only the term “Suspected Adverse Reaction” (SAR) is used in this guide, since it is most often the case in the documents prepared by EMEA. So no further connotation should be given to this choice.

2.2 Where can the relevant legal texts be found?

The links to the legal texts and other official documents are given in Appendix 1.
2.3 What are the obligations of an animal health company on pharmacovigilance?

1. Each company must have a system to collect and collate all the information about any suspected adverse reactions that are reported to the personnel of the company, including sales representatives. This system must have a point of access in the European Union (EU).

2. All companies must make sure to report:
   - Serious suspected adverse reactions within 15 calendar days.
   - Suspected adverse reactions in periodic safety update reports (see section 3.4).

3. Each company must ensure that any request from the competent authorities in any of the Member States (MSs) of the EU, for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a Veterinary Medicinal Product (VMP), is answered fully and promptly. This includes the provision of information about the volume of sales of the concerned veterinary medicinal product.

2.4 Who are the different actors in veterinary pharmacovigilance?

Pharmacovigilance involves several key players. The legal references clearly state the responsibilities of both Competent Authorities (CAs), in establishing an efficient pharmacovigilance system, and the Marketing Authorisation Holders (MAHs), in providing a Qualified Person (QP) to collect the data on SARs. All the relevant information is shared between the two, so they can fulfil their obligations and responsibilities, e.g. measures to be taken in relation to the use of a product. However, the whole system depends on the users of medicines fulfilling their ethical responsibility of reporting adverse reactions.

When sharing information, the issue of protection of privacy comes in the focus. Industry fully respects any legal obligation in that respect. Besides this, we should be aware that pharmacovigilance relates to public health and safety and that in any decision we take, public interest prevails.

– The reporter plays a major role in the chain, ensuring the relevant information reaches the CAs and the MAHs. It is the role of the veterinary health professional, or indirectly the animal owner, to report any adverse drug reactions following administration of a veterinary medicinal product to an animal.

– The Qualified Person (QP) is the key industry person. By collecting all relevant data, he/she is the main reference for all pharmacovigilance information within the company. He/She also informs the authorities and provides them with any additional information they might require.

– The Competent Authorities (CAs) are engaged in evaluating the reports received from the field in the light of the data available on the concerned product. They are also responsible for establishing a risk/benefit analysis and, if needed be, for taking appropriate management measures. Furthermore, they provide legal guidance.

2.5 What is the geographical area in which EU pharmacovigilance rules apply?

Pharmacovigilance rules prevail in the whole European Economic Area (EEA). The EEA is composed of the EU MSs plus Liechtenstein, Iceland and Norway. So if you read EU in European pharmacovigilance rules, you should in fact read EEA.

2.6 Is there a flow chart or decision tree available that reflects the reporting of SARs in veterinary pharmacovigilance?

A generic decision tree on the reporting and recording of SARs in veterinary medicines in Europe can be found in Appendix 2.
3. PHARMACOVIGILANCE CASES

3.1 Suspected Adverse Reaction: definition, scope and need to report

3.1.1 Definition

3.1.1.1 What is a Suspected Adverse Reaction?

An adverse reaction is defined in article 1 of Directive 2001/82/EC as follows: "a reaction (read "observation") which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function".

In order to fully understand what the European authorities mean by that definition, one must look at Volume 9 of "The rules governing medicinal products in the European Union". This volume updates and replaces any pharmacovigilance guidance published in the Community prior to 30th September 2001. Volume 9 mentions that the scope of veterinary pharmacovigilance covers not only clinical safety, but also other aspects of post-authorisation surveillance (see 3.1.1.2).

3.1.1.2 Is the scope of SAR in veterinary pharmacovigilance limited to clinical safety under normal use?

No, the system must also take into account any available information related to:

- Reactions in human beings related to the use of veterinary medicines.
- Lack of expected efficacy of a veterinary medicinal product for the registered indications.
- Off-label use (adverse observations linked to any use not according to the Summary of Product Characteristics (SPC) including misuse and abuse of the product). So positive experiences after "off-label use" do NOT need reporting.
The expectedness of a SAR has implications for those that do get reported from a so-called third country, i.e. outside the EEA, where serious and unexpected cases have to be reported in an expedited way (see section 3.3).

3.1.1.7 What is a ‘serious SAR’?
Any SAR which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect or results in permanent or prolonged signs in the animals treated.

Please note that all suspected reactions in human beings are considered to be serious.

3.1.1.8 How is the word ‘serious’ interpreted for each type of animal?
In veterinary medicine, the existence of a variety of animal species and husbandry conditions requires a modified approach to the classification of a ‘serious SAR’.

For example, in intensive animal production of species such as poultry, fish or bees, a certain level of mortality rate is considered as ‘normal’ or ‘expected’. These species are usually treated as a group and only an increased incidence of mortality, or severe signs, or variations of animal production levels exceeding the rates normally expected should be considered as a ‘serious SAR’.

However, in species like dogs, cats or horses, a single death constitutes a ‘serious SAR’. This also applies to cases of individual deaths in cattle, sheep, pigs, goats and rabbits even if they are kept in herds or flocks in intensive animal production because treatment is often performed on the individual animal and therefore a single death or severe symptoms have to be considered on an individual basis.

But remember, for any animal kept individually, a single death constitutes a ‘serious SAR’, whatever the species.

3.1.1.9 Is every unintended and harmful observation after an off-label use of the product reportable as a SAR?
In general, yes, however there are possible exceptions. For instance, a suspected lack of expected efficacy can only occur after normal use of the product. The expected...
3.1.1.13 Are human exposures that are reported to the company to be asymptomatic considered as SARs?

Human asymptomatic exposures are not SARs, as they do not fulfil the four criteria (see 3.1.1.4); they are only exposures and not reactions. It is however good practice to ensure a suitable follow-up of such reports with the reporter.

3.1.2 Investigation and reporting of a reported SAR by a company

3.1.2.1 What are the basics a company needs to do when receiving a SAR report?

Basically, a MAH needs to ensure that the SAR is:
- Recorded,
- Investigated,
- Reported and
- Causality assessed (section 3.2).

3.1.2.2 Do all SARs need to be RECORDED?

Yes, all SARs need to be entered in the pharmacovigilance system, which your company is obliged to have (see 2.3). It is also recommended to keep records of those reports that never met the four minimal data components (see 3.1.1.4). It will enable you to demonstrate, in a transparent manner, the way these reports have been handled.

3.1.2.3 Do all SARs need to be REPORTED?

Yes, but how and when you report differs depending on the serious and/or (un)expected character of the SAR and on the region where it took place. An overview of the reporting requirements is presented in the “decision tree” in Appendix 2.
3.1.2.8 Do serious SARs need much closer investigation?

MAHs are expected to fully validate and follow-up all serious reactions that have been reported. It is essential for MAHs to provide as complete data set as possible, including all relevant clinical information, for cases of serious SARs in order to facilitate the assessment. The original words used by the reporter should be provided even if they are subsequently classified or coded according to the MAH or the competent authority accepted terminology.

3.1.2.9 Are reports concerning the validity of the withdrawal period (residues above the MRL) to be reported as serious SARs?

Where investigation of drug residues in tissues or products of treated animals casts doubt on the validity of the withdrawal period of a veterinary medicinal product, it is important that this information is brought to the attention of the CA responsible for authorisation of the product. Such cases should be reported as SAR in the PSUR (see section 3.4).

3.1.2.10 How should reports on environmental cases be handled?

As environmental issues are often of complicated nature and do not easily fit in the classic procedures, it is advised to contact the concerned competent authorities.

3.1.2.11 How should mortality in a Suspected Lack of Expected Efficacy (SLEE) case be handled?

Mortality is normally reported as a SAR. However, if the company can demonstrate within two weeks that the mortality was caused by the lack of efficacy (e.g. by a post-mortem or other investigations), and that the mortality is therefore inherent to the lack of efficacy, the report should be submitted as a SLEE in the Periodic Safety Update.

In all other circumstances the case should be reported in an expedited manner.

3.1.2.12 What about SARs following the use of a veterinary premix?

SARs occurring on or after treatment with an in-feed medication are reportable.
under the pharmacovigilance scheme. In fact, when medicated premixes, which have been incorporated in the finished medicated feed, are suspected of causing a reaction in animals or humans, both the premix and the medicated feed should be investigated without delay.

3.1.2.13 What about reporting SARs for ‘generic’, copy cat and co-distributed products?

‘Generic product’ is a commonly used terminology for products whose Marketing Authorisation (MA) derives from a registration previously granted to another equal/comparable product. For a detailed definition, we advise you to refer to art. 13.1(a) of Directive 2001/82 and to the relevant sections of the Notice to Applicants.

For the purpose of this guide we will limit the discussion to the following types and descriptions:

- **True generic:** a MA obtained via an abridged procedure as described in Directive 2001/82 art. 13.1(a)iii.
- **Informed consent** (or copy cat): a MA obtained via an abridged procedure as described in Directive 2001/82 art. 13.1(a).
- **Co-distribution:** a product sold by two different companies under the same MA.

<table>
<thead>
<tr>
<th>Type of MA</th>
<th>Company responsible</th>
<th>Specific instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>True generic:</td>
<td>Each MAH is responsible for his own product.</td>
<td>Authorities will co-ordinate any action deemed necessary.</td>
</tr>
<tr>
<td>Informed consent (or copy cat)</td>
<td>1st scenario: The company holds both MAs and is therefore responsible for both products.</td>
<td>Any regulatory action will apply to both products.</td>
</tr>
<tr>
<td></td>
<td>2nd scenario: One MA is transferred, then each MAH is responsible for his own product.</td>
<td>Both MAHs must maintain close liaison and inform each other on reported cases. Any regulatory action will apply to both products.</td>
</tr>
<tr>
<td>Co-distribution:</td>
<td>The MAH is responsible.</td>
<td>The co-distributor must report the cases IMMEDIATELY to the MAH. The MAH will report to the authorities and will coordinate any further action.</td>
</tr>
</tbody>
</table>

3.1.2.14 Do SARS that already have been reported directly to the authorities need to be reported by the company as well?

If the MAH is aware that another person already has reported a reaction to one of its products directly to the authority of a member state, the MAH should still report that same reaction, informing the authority that his report is likely to be a duplicate of a previous one.

In such a situation, it is essential the MAH provides all the available details, including any reference number provided to the reporter by the authority, in order to help identifying the duplicate.
3.1.2.15 Do all clinical signs need to be coded according to the VEDDRA codes and terms?

There is no legal obligation yet, but you might want to check the current guidelines; however guidelines do not have any legal obligations.

3.2 Causality coding

3.2.1 What is causality coding?

MAHs may comment on whether they consider there is a causal association between the suspect product(s) and reaction(s) reported and should provide the criteria on which they have made the assessment.

3.2.2 How is this causality association expressed?

It is important that causality is expressed using the ABON system. For that purpose, the EMEA/CVMP has developed a guideline, which provides common understanding and uniform approach to performing causality assessment (see EMEA/CVMP/552/03).

According to this system, four categories of causality can be made:
- “A”: probable.
- “B”: possible.
- “O”: unclassifiable (cases where reliable data are not available or insufficient information is available to draw any conclusion).
- “N”: unlikely to be drug related.

3.2.3 What factors should be taken into account when assessing the causality of a SAR?

In assessing causality, the following factors should be taken into account:
1. Associative connection in time, including de-challenge and re-challenge following repeated administration (in clinical history), or in anatomic sites.
2. Pharmacological explanation, blood levels, previous knowledge of the drug.
3. Presence of characteristic clinical or pathological phenomena.
4. Exclusion of other causes.
5. Completeness and reliability of the data in the case reports.
6. Quantitative measurement of the degree of contribution of a drug to the development of a reaction (dose-effect relationship).

3.2.4 What is the minimum basis to consider a case to be “probable”?

For inclusion in category “A” (probable), it is recommended that all the following minimum criteria be met:
- There should be a reasonable association in time between the administration of the drug and onset and duration of the reported case.
- The description of the clinical phenomena should be consistent, or at least plausible, with the known pharmacology and toxicology of the drug.
- There should be no other equally plausible explanation(s) of the case (if such are suggested - are they validated? what is their degree of certainty?).
- The concurrent use of other drugs or the presence of disease should be taken into account in the assessment. If either of these could possibly be responsible for the signs, this makes it impossible to define the case as “probable”.
- Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information), then such reports can only be classified as “B” (possible), “N” (unlikely) or “O” (unclassifiable/not assessable).
- Where re-challenge is undertaken, a positive re-challenge is a strong indication. A negative re-challenge makes it likely that the case should be category “N”.

3.2.5 What is the minimum basis to consider a case to be “possible”?

Inclusion in category “B” (possible) is recommended when drug causality is one (of other) possible and plausible causes for the described case, but when the data do not meet the criteria for inclusion in category “A”.

3.1.2.15 Do all clinical signs need to be coded according to the VEDDRA codes and terms?

There is no legal obligation yet, but you might want to check the current guidelines; however guidelines do not have any legal obligations.

3.2 Causality coding

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- “B”: possible.
- “O”: unclassifiable (cases where reliable data are not available or insufficient information is available to draw any conclusion).
- “N”: unlikely to be drug related.

3.2.3 What factors should be taken into account when assessing the causality of a SAR?

In assessing causality, the following factors should be taken into account:
1. Associative connection in time, including de-challenge and re-challenge following repeated administration (in clinical history), or in anatomic sites.
3.2.6 What is the minimum basis to consider a case to be “unlikely”?
For inclusion in category “N” (unlikely), sufficient information should exist to establish beyond reasonable doubt that drug causality was not likely to be the cause of the case. Basically, you could say you need to be 95% sure that the case was not caused by the drug.

3.2.7 What is the minimum basis to consider a case to be “unclassifiable/not assessable”?
For inclusion in category "O" (unclassifiable/not assessable), reliable data concerning a SAR is unavailable or is insufficient to make an assessment of causality.

3.2.8 Must human cases be coded?
No, there is no obligation to code human cases.

3.2.9 In a case of concurrent use must other companies’ products be coded?
No, and it would probably be impossible since you have no access to the terms under which such a product was registered. The best way to address this concurrent use and to provide your opinion is in the narrative part.

3.3 Third country reporting

3.3.1 What is a third country?
A third country is a country outside the European Economic Area (EEA), which includes the EU countries, Iceland, Liechtenstein, and Norway.

3.3.2 Must a SAR occurring in a third country be reported?
While this is a highly debated issue and also addressed in the ongoing VICH process, this document can only reflect what the present guidelines foresee.

This is indeed prescribed by the European guidelines. In practice, it appears that the European authorities consider this information to be important especially for centralised products. Although this legal obligation also exists for national MAs (national and mutually recognised products), some competent authorities may not yet be prepared to receive and process these reports.

A general overview on the reporting of SARs for third country reporting is included in the decision tree diagram (Appendix 2).

3.3.3 Are all SARs occurring in third countries reportable?
Broadly speaking yes, however authorities allow, for practical reasons, some filtering in the reports to be submitted. Important aspects are:

1/ that the product within the EU or the concerned MS is “essentially similar” to the 3rd country product. For the similarity, we refer to the definition proposed in the VICH process, where:
   → the same pharmaceutical VMP is defined as originating from the same MAH being responsible for pharmacovigilance of this VMP with similar formulations and posology and the same indications.
   → the same biological VMP is defined as originating from the same MAH being responsible for pharmacovigilance of this VMP with similar formulations and posology and same manufacturing specifications and for the same indications.

2/ whether the case must be considered as expected or non-expected (with regards to the differences in the respective SPCs).

However several companies choose not to apply these filters and to submit all relevant data to the concerned authorities.

The most crucial information in addressing third country cases is whether the competent authorities of these countries deem it necessary to take any regulatory
action as a result of the reported cases. Obviously this information is of utmost importance to the competent authorities in the EU.

3.4.4 Who must these third country cases be reported to?
These serious and unexpected cases should be reported to the EMEA for all centrally approved products and to all MSs where the product is authorized nationally, thus immediately, and in no case later than 15 calendar days following receipt within the EU.

In addition, all unexpected adverse reactions from third countries should be reported as line listings in the PSUR (see 3.4.2).

3.4 Periodic Safety Update Reports (PSURs)

3.4.1 What is a PSUR?
A Periodic Safety Update Report is a report produced at set time by the MAH for a veterinary medicinal product.

It is intended to provide the competent authorities with an update of the worldwide safety experience of a VMP at defined times post-authorisation. At these times, MAHs are expected to provide succinct summary information together with a critical evaluation of the risk/benefit of the product in the light of any new or changing post-authorisation information.

3.4.2 What is the purpose of the PSUR?
While the purpose of reporting specific actual cases is mainly to gather information on new or unknown cases, or to evaluate whether any direct action is required, PSURs serve a different purpose. Their main purpose is to evaluate whether new data have become available or whether the incidence of known effects has increased. This data could lead to further investigations, which might in exceptional cases lead to a change in the registered use of the product. In most cases, it will confirm that the product is indeed safe and “fit for use”. It is important to keep this purpose in mind when establishing these reports.

Reporting is often limited to a line listing (see 3.4.5). It is however obligatory to make a narrative critical assessment and to classify the cases into the ABON system. This should not be a lengthy story, but should put the observed cases in the right perspective. It also gives the opportunity to outline if something, which has happened in field conditions, can explain certain changes in occurrence of cases. Moreover, a comprehensive explanation will enable the authorities to take the appropriate decision.

3.4.3 When must a PSUR be submitted?
Unless specified otherwise in your registration, PSURs should be sent as follows:
- First 2 years post-registration: every 6 months.
- 3 following years: every 12 months.
- After 5 years: at renewal (every 5 years).

In specific circumstances, authorities might require an additional PSUR.

The above schedule applies to all types of registrations. While this timeline is quite understandable for nationally and centrally registered products, it is often less obvious for mutually recognised ones. In such case, it is best defining the timeline upfront with the Reference Member State (RMS).

3.4.4 What data must be included in the report?
In order to make a good assessment, the report should not only contain data on the concerned cases, but also include the following:
- A copy of the latest approved SPC.
- An overview of any safety measures taken anywhere in the world in the period covering the PSUR (if any).
- The sales volume of the product (see section 3.4.9).
- General details, such as name of the registration holder, name of the product, registration number of the active substance… (most will already be included in the SPC).
- An overview of all the SARs reported worldwide.
Besides the classic “animal and human clinical safety” SARs, the following information must also be included, when available:

- Any SAR that has come to your attention in the literature.
- Cases where the MRL values in edible products have been exceeded, even when the registered withdrawal periods have been respected.
- Potential environmental problems.
- Cases from post-authorisation studies (including clinical studies using a marketed VMP).
- Lack of expected efficacy.

### 3.4.5 Which SAR cases need to be included in the line listing?

The following reports must be included: spontaneous reports from your own country, from any other EU country and even outside the EU. They include all spontaneous reports on SARs, which occurred either in animals or humans, all the reports from authorities. Cases noted in post-marketing studies should be dealt with separately.

Even if you do not agree with the link assumed by the reporter between the case and your product, it must be reported. All these data should be presented in the so-called “line listing” format, as proposed in the guidelines (see page 186 of Volume 9).

### 3.4.6 What data need to be included for a SAR reported in the line listing?

Focus should be made on the data of the reported cases. Whether a report should be considered as a real report depends on several parameters. The minimum data you should be able to retrieve from the reporter before a report is a ‘case’ is discussed in 3.1.1.4 above. The data you will need to have available to enter a case in a line listing are the following:

- Company case reference number.
- Date of treatment and date of reaction.
- Was the product used as recommended?
- Number of animals treated.
- Species and ages of the animals.
- Number of animals that reacted and eventually died.
- Concurrent use of other products.
- Narrative of the case, including symptoms and diagnosis.
- The ABON classification.

When listing the cases, you should clearly indicate whether reports were already submitted as separate cases or received from the authorities.

### 3.4.7 What time span should the report cover? What is the common birth date?

In order to streamline the reporting schedule and to prevent unnecessary reporting, the principle of the “Common Birth Date” has been established.

The first day of registration of a product in the EU is the European Birth Date. VMPs also authorised outside the EU have an International Birth Date (IBD). For medicinal products first authorised in the EU, the IBD may be designated as the last day of the same month.

This birth date sets the time when your database should be closed or locked (Data Lock Point - DLP) for establishing the PSUR. In order to harmonise periodic safety updates internationally, the MAH may use the IBD, rather than the EU Birth Date, to determine the DLPs in the EU; in such case, the first DLP must be within 6 months of the EU marketing authorisation Birth Date.

Each PSUR should cover the period of time since the last update report and must always be submitted within 60 days following the data lock point, only including the data received up to the DLP.

Dates for reports from nationally registered products will be defined by their national registration dates.
3.4.8 What language should be used?
Overall, English should be used. Also for decentralised and national MAs, English is the language of choice. Moreover most companies maintain their database in English. A translation into a national language is inconvenient and might even negatively influence the consistency of the submitted data to the different MAs. Some countries may insist on receiving reports in their national language, but you have no obligation to do so.

3.4.9 Must sales figures be provided for all Member States?
Yes, sales volumes must be given on a country-by-country basis wherever possible.

3.4.10 For multiple species’ products, how are sales attributed to one species?
Scientifically, it is difficult to identify the proportion of your sales to species. The most logical solution is to provide one sales volume without going into speculations. However, some authorities will refuse a single sales figure for a multiple species’ product. In such cases, a reasonable assessment should be possible, based on the information provided by your marketing department.

3.4.11 How can the number of doses applied be calculated?
In cases where you have a single dose product (e.g. vaccines) it is fairly simple, the number of doses is the number of animals treated.

If your product has multiple dosing schedules and is eventually used in different breeds and age categories, it becomes difficult to identify the number of doses sold. In order to make a consistent report, leading to a consistent assessment, it is necessary to define upfront how the sales could actually relate to the number of animals treated.

The advised way to achieve this is to put forward a justifiable formula taking into account the split of the sales over the different species and the different dosage regimens in each species. It is advised to comment on the formula used to obtain the number of doses in the report.

In case of repeated administrations, the formula should also reflect whether or not each administration has been considered to be a single dose.

Furthermore, it is advisable to use standardised live weights for the animal species under review (see 3.4.12 below).

3.4.12 What are the standardised body weights to be used in dose calculation formulae?
The European authorities propose the following standard weights:
- Adult horse: 550 kg
- Cattle:
  - Cow: 550 kg
  - Newborn calf: 50 kg
  - Beef calf: 150 kg
- Sheep:
  - Adult sheep: 60 kg
  - Lamb: 10 kg
- Swine:
  - Sow/boar: 160 kg
  - Waster: 25 kg
  - Finishing pig: 60 kg
- Dog: 20 kg
- Cat: 5 kg

For other species, IFAH-Europe proposes the following standard weights:
- Poultry:
  - Broiler: 1 kg
  - Layer: 2 kg
  - Turkey: 10 kg
- Pigeons: 30 pigeons/litre of drinking water
3.4.13 What SARs need to be included in incidence calculations?
Incidence rates should be based upon ABO animal safety cases. Human SARs, “N” coded animal cases, suspected lack of expected efficacy cases and environmental safety cases are to be excluded.

3.4.14 Do off-label SARs need to be included in incidence calculations?
It is common practice to include both off and on-label use cases. However, a company can separate off-label and on-label incidence when justified.

3.4.15 Is there a standardised terminology to describe incidence rates?
IFAH-Europe recommends using the following convention:
- Very common (>1/10);
- Common (>1/100, <1/10);
- Uncommon (>1/1,000, <1/100);
- Rare (>1/10,000, <1/1,000);
- Very rare (<1/10,000).

3.5 SARs in clinical studies

3.5.1 Must cases occurring in clinical trials be reported?
A clear distinction has to be made on whether the product(s) used in the trial, and which might have caused the effect, is registered or not. Cases occurring with registered products must be reported via the normal reporting schedules for every registered product. Special attention should be paid to trials with control products. It might well be that your own test product is not registered, but the control product is, especially on trials in more than one MS.

A specific problem arises when you are using a registered product in a clinical trial for a non-registered use (e.g. a new species). Such cases are under the scope of off-label use. For this kind of study, you need a specific trial exemption in most MSs. It is highly recommended that you address this topic upfront with the authorities of the MSs where you will do the trial.

Another specific issue arises when studies are set up to study specific safety issues related to a registered product. Such studies are normally set up based on findings and reports from the field. It is strongly recommended to discuss any such study upfront with the authorities. Furthermore a specific guideline on this kind of study exists and should be followed (EMEA/CVMP/044/99).

3.5.2 How must cases occurring in studies with unlicensed products be handled?
In principle, this is handled by the guidelines on Good Clinical Practice (GCP), which are based on the VICH guidelines. Detailed guidance can be found in the FEDESA GCP handbook, available from IFAH-Europe.

Furthermore, this issue is regulated by the national CAs when issuing trial clearances.

In general, it can be said that when drafting a protocol for a trial, it is essential that the SAR section is assessed thoroughly. Often immediate actions are required and good and clear instructions are paramount in such cases.

A good principle is to record as much as possible. In case of doubt: record and investigate it as a SAR. This data might be very helpful in the final risk/benefit assessment of your new product.
4. Tools

4.1 Qualified Person

4.1.1 Should every company have a Qualified Person?

It is a legal requirement to have a QP responsible for pharmacovigilance (article 74 of Directive 2001/82/EC). The EU legislation does however not define what his/her qualities should be. Most countries have their own system where focus is often on a scientific/medical background in combination with a certain experience with pharmacovigilance. The QP is the main contact point, both internally and externally, for all pharmacovigilance information within the company. He/She also informs the authorities and provides them with any additional information they might require.

4.1.2 Should a company have a Qualified Person in every EU Member State?

While you must have a QP for all your MAs, there is no obligation to have a QP in every MS. Nevertheless, it is often recommended to have a local contact person within the different countries. In pharmacovigilance, good communication with the different CAs is indeed imperative.

4.2 Database

4.2.1 Does a company need a database?

Yes, the guidelines state that a company needs to establish and maintain a system which ensures that information about all suspected adverse reactions which are
4.3.2 What considerations should be taken into account when writing a procedure on pharmacovigilance?

When writing a procedure, all legal requirements should be taken into account, as well as internal company requirements. Internal requirements can never overrule legal requirements.

Procedures should be developed in such a way that they fit the legal timeline requirements.

Procedures should at least address the definition of SARs, as well as the recording, investigating and reporting procedures for SARs within the company.

4.3.3 Is it necessary to train relevant company personnel in pharmacovigilance procedures?

Yes, training of relevant personnel will not only demonstrate to the CAs that the company is fulfilling its obligations, it will also contribute to a higher quality pharmacovigilance system. It should also be remembered that it is best having a flexible and practical SOP rather than one that will not be followed.

4.2.2 Does the pharmacovigilance system need to be digital?

No, the guidelines only make it obligatory to have a system, without specifying either digital or paper format.

However, experience tells that digital systems may be more convenient and reliable (prevent loss of data, facilitate data analysis...). Besides several company-owned digital systems, there are also different commercial database solutions available.

4.2.3 Must the system be accessible from within every single EU Member State?

No, the system should have at least one point of access within the Community, but one point is sufficient. The company can choose the location of this point.

4.3 Written procedures on veterinary pharmacovigilance

4.3.1 Should every company have a written procedure on veterinary pharmacovigilance?

Although there is no obligation to have a written procedure or Standard Operating Procedure (SOP), it is highly recommended. Written procedures help your company to ensure that the pharmacovigilance process is up to high quality standards. Furthermore, they help to overcome shortcomings in the process.

If you have a procedure, make sure everyone in the company is informed of the document and its implications.
Pharmacovigilance is no easy information to communicate. No one likes to discuss "unpleasant" experiences occurring with their products. Reporters do not always appreciate the benefit from reporting, or are even afraid to communicate these topics to the registration holder. Authorities sometimes have doubts as to whether everything has been done to get all available data and whether all reports were transferred accordingly.

For these reasons, it is important to assess what can be done to improve external communications and consequently the output of pharmacovigilance information.

5.1 How can reporting be generally improved?

In principle, anyone can report an adverse reaction. In practice, however, not only the number of reports, but also the quality of the data, should be taken into consideration. In this respect, it seems obvious that the emphasis of your efforts should be directed towards the veterinary profession. This group is scientifically qualified and also has an important interface with what is really occurring in field conditions. Their good support and understanding will increase both the number and the quality of reports.
5.2 How can customers and end users be convinced of the importance to report?

As already mentioned above, the most valuable partner is the veterinary profession. Unfortunately, it is not always easy to convince this group of the importance to report, as their daily priority is to give assistance to their customers and not to fill in forms. Nevertheless, for the success and effectiveness of pharmacovigilance, it is important to increase awareness and encourage the cooperation of the veterinary profession. The systematic reporting of adverse reactions will result in better treatments. This will benefit not only the veterinary profession, but also their customers and patients. Improved label information will reduce the incidence of adverse reactions, which has a direct benefit to animal welfare. Improving animal welfare falls within the high ethical value of veterinarians, but above all our own behaviour is the most important. Therefore, keep in mind the following aspects:

- A reporter is entitled to a fast and personalised reply.
- Good and scientific assistance is always appreciated.
- Provide the reporter with clear instructions on where and how your company can be reached in case of SARs.
- Always keep the reporter informed of the final outcome.
- Money should never encourage reporting!

5.3 How can the best information be obtained?

It is indeed crucial that good quality data is provided. Three major points must be taken into account by making sure of the following:

- Follow up the case personally.
- Obtain as much data as possible as quickly as possible. The best quality data is obtained when the case is “fresh”.
- Obtain all the data. Again a personal follow up is essential for this.
  ➔ The key issue is to “be open in your communication”.

5.4 What considerations should be taken into account when communicating with the authorities?

Obviously all the legal requirements, as described above, must be well respected. But good pharmacovigilance practice goes further. The key issue is again to be open and proactive. Therefore, when reporting cases, keep the following in mind:

- Report early. It is best sending in a very brief report at an early stage and completing the data later, rather than waiting until you think you have all the required information. By then, it is more difficult to retrieve additional data. Also if authorities consider an action is required, they should be informed early.
- Make sure all communication is clear and informative. Avoid standard statements.
- When optimising relationships with CAs by clear and open communication, companies will also increase the likelihood of (pro)active communication of potential problems by the authorities to the companies.

5.5 Is internal communication important?

Pharmaceutical companies are often large structures composed of different departments with different interests. It is important that the right information on pharmacovigilance circulates internally. Make sure this communication is positive. After all, good pharmacovigilance provides valuable information on your products, which is beneficial to the whole company.

Also make sure that good and clear instructions on your policy are given. It will enhance good reporting and will provide guarantees that reports are handled in the best possible way. This is best accomplished by formal training on the company pharmacovigilance procedures.
List of abbreviations

CA(s)  Competent Authority(ies)
CVMP  Committee for Veterinary Medicinal Products
DLP   Data Lock Point
EMEA  European Medicines Evaluation Agency (http://www.emea.eu.int)
EU    European Union
EEA   European Economic Area
FEDESA European Federation for Animal Health
FVE   Federation of the Veterinarians of Europe (http://www.fve.org)
GCP   Good Clinical Practice
GL    Guideline
GMP   Good Manufacturing Practice
IBD   International Birth Date
IFAH-Europe A division of IFAH, International Federation for Animal Health
MA    Marketing Authorisation
MAH(s) Marketing Authorisation Holder(s)
MIC   Minimum Inhibitory Concentration
MRL   Maximum Residue Limit
MS(s)  Member State(s)
Appendix 1: Links to the legal texts and other official documents


Commission Directive 91/412: which lays down the principles and guidelines of good manufacturing practice for veterinary medicinal products

Council Regulation 2309/93 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

Commission Regulations 1084/03 and 1085/03 concerning respectively the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State, or falling within the scope of Council Regulation 2309/93
Appendix 2: Decision tree when a report is received on an observation after treatment or exposure to a VMP

Was the observation after treatment or exposure negative and unintended?
- YES
  - Deal with according to company SOP's (e.g. on inquiries)
- NO

Were all four minimum criteria met to define it as an inspected adverse reaction (SAR)?
- YES
  - Investigate to try and get all the minimal criteria fulfilled.
  - Keep track for future reference.
- NO

Is the adverse observation within the scope of EU Veterinary Pharmacovigilance?
- YES
  - Investigate the adverse event to obtain enough information to make a (causality) assessment of the case.
- NO

Is the SAR involving off-label use?
- YES
  - Deal with according to company SOP's or procedures (e.g. on inquiries or complaints).
  - It is advisable to keep track for future reference.
- NO

Is the SAR serious? (Does it meet any of the following criteria?)
- YES
  - Life-threatening or deadly SAR
  - SAR in a human (note: some asymptomatic exposures are not events)
  - SAR leading to significant disability or incapacity
  - SAR leading to a congenital anomaly/birth defect
  - SAR resolving in permanent or prolonged signs in the animals treated
  - Residue issues should always be treated as non-serious (PSU only)
  - For group treatment in poultry, fish or bees only increased incidence of the above to be considered a serious adverse event
- NO

Is the SAR expected? (Expected, if already present in the SPC?)

<table>
<thead>
<tr>
<th>Expected SSAR</th>
<th>Not Exp. SSAR</th>
<th>Expected NSSAR</th>
<th>Not Exp. NSSAR</th>
<th>The SAR happened in? (Third Country?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. SSAR in Member State</td>
<td>1 3</td>
<td>Exp. NSSAR in Member State</td>
<td>3</td>
<td>Exp. SSAR in Third Country</td>
</tr>
<tr>
<td>Exp. SSAR in Member State</td>
<td>1 2</td>
<td>Exp. NSSAR in Member State</td>
<td>2</td>
<td>Exp. NSSAR in Third Country</td>
</tr>
</tbody>
</table>

1. As stated in PEP: “If a national licence reporting is not legally required, for a contracted licence reporting, depend on the requirements of the MA”.
2. Report within 15 calendar days to Member State where the SAR occurred.
3. Report within 15 calendar days to all Member States where the product is licensed and to EMEA (all 28 Member States if contracted licence).