UNIVERSIDADE DE LISBOA

Faculdade de Medicina Veterinária

Pharmacovigilance and the safety of veterinary medicinal products

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Dissertação de Mestrado Integrado em Medicina Veterinária

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To my family and friends (you know who you are) to making my life happy and full

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Farmacovigilância e a segurança dos medicamentos veterinários

Resumo

A farmacovigilância em medicina veterinária tem-se desenvolvido bastante nos últimos anos. O aumento de legislação na área do medicamento veterinário, bem como a maior sensibilização do médico veterinário para a necessidade de reportar os eventos adversos observados aquando da utilização do medicamento veterinário nos animais que estão a seu cuidado, têm resultado num aumento no número de casos reportados a nível europeu.

Para a elaboração desta dissertação de mestrado foi feita uma revisão das publicações existentes sobre o assunto da farmacovigilância nomeadamente o enquadramento legal, os requisitos para o titular de autorização de introdução no mercado do medicamento veterinário, bem como para o médico veterinário que prescreve os medicamentos aos animais que tem sob sua responsabilidade e tratamento.

Atualmente considera-se que a gestão de sinais é a melhor forma para realizar a vigilância dos medicamentos e esta segue uma metodologia específica. A gestão de sinais dos eventos adversos é o pilar da futura legislação quer do medicamento veterinário, quer do medicamento de uso humano.

Neste estudo os sistemas de farmacovigilância europeus, como de Espanha, França, Portugal e Reino Unido, são analisados e comparados, pois tendo como base a mesma moldura legislativa europeia, cada um deles tem as suas particularidades.

Também se faz uma reflexão sobre a subnotificação de eventos adversos por parte dos veterinários e algumas medidas que podem melhorar a notificação, como a utilização das novas tecnologias e uma melhoria nas respostas que se dão aos notificantes, entre outras.

Seja como médico veterinário clínico, como médico veterinário profissional do sector farmacêutico, bem como membro nas autoridades competentes, a figura do médico veterinário é fundamental no sistema de farmacovigilância veterinária, na monitorização contínua dos medicamentos veterinários, na manutenção do benefício-risco positivo e na proteção da saúde animal e segurança alimentar.

Palavras chave: farmacovigilância, farmacovigilância veterinária, gestão de sinais, eventos adversos, medicamento veterinário.

Abstract

Pharmacovigilance in veterinary medicine has developed considerably in the recent years. The increase in legislation in the area of veterinary medicinal products, as well as the increased awareness of the veterinarian regarding the need to report the adverse events observed during the use of the medicines in the animals in his care, has led to an increase in the number of cases reported at European level.

For the preparation of this master's dissertation, a review was made of the existing published references on the subject of pharmacovigilance, namely the legal framework, the requirements for the marketing authorization holder of the veterinary medicinal product as well as for the veterinarian prescribing the medicines to the animals which are under her/his responsibility and treatment.

Signal management is currently considered the best way to carry out drug surveillance and it follows a specific methodology. Signal management is the pillar of the future legislation on veterinary medicinal products as well as human medicines.

In this study the European pharmacovigilance systems, France, Portugal, Spain, UK, are analysed and compared because although having the same legislative frame, each one has different particularities.

There is also a reflection about the underreporting of adverse events by veterinarians and some measures that can improve notification, such as use of new technologies and improvement in the feedback to reporter, among others.

Whether as a clinician, as veterinarian working in the pharmaceutical industry as well as in the competent authorities, the veterinary professional is essential in the veterinary pharmacovigilance system, the continuous monitoring of veterinary medicinal products, maintaining the positive benefit-risk balance and in the protection of animal health and food safety.

Key words: pharmacovigilance, veterinary pharmacovigilance, signal management, adverse event, veterinary medicinal product.

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List of abreviatures

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios
ANSES-ANMV: L'Agence Nationale du Médicament Vétérinaire part of the Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail
CNITV: Centre National d'Informations Toxicologiques Vétérinaires
CP: Centralized Products
CPs: Centralized Products
CPVL: Centre de Pharmacovigilance Vétérinaire de Lyon
CVMP: Committee for Veterinary Medicinal Products
DCP: Descentralized Procedure
DDPS: Detailed Description of Pharmacovigilance System
DGAV: Direção Geral de Alimentação Veterinária
EEA: European Economic Area
EMA: European Medicines Agency
ERA: Environmental Risk Assessment
EU: European Union
EVVet: Eudravigilance Veterinary
FDA: Food and Drug Administration
FVE: Federation of Veterinarians of Europe
GLP: Good Laboratory Practices
GMP: Good Manufacturing Practice
MA: Marketing Authorisation
MAH: Marketing Authorisation Holder
MRLs: Maximum Residues Limits
MRP: Mutual Recognition Procedure
NCA: National Competent Authority
NOEL: No observed effect level
NSAIDs: nonsteroidal anti-inflammatory drugs
OIE: Office international des épizooties
PSURs: Periodic Safety Update Reports
RMS: Reference Member State
SARSS: Suspected Adverse Reaction Surveillance Scheme
SPC: Summary of Product Characteristics
UK: United Kingdom
USA: United States of America
VeDDRA: Veterinary Dictionary for Drug Regulatory Activities

VMD: Veterinary Medicines Directorate
VMP: veterinary medicinal product
VMPs: Veterinary Medicinal Products
WHO: World Health Organization

Pharmacovigilance and the safety of veterinary medicinal products

Introductory note

The student completed the veterinary medicine training in 1999, in the pre-bologna regime at Faculty of Veterinary Medicine in Lisbon.

There was a wish to obtain the master degree in veterinary medicine and after the curricular phase that started in 2017, the student decided to perform the necessary internship in the pharmaceutical company were the student works.

Elanco is a pharmaceutical company that markets veterinary medicinal products (VMPs) and other products such as biocides and feed additives for both farm animals and companion animals worldwide.

At Elanco, the student is responsible for Regulatory Affairs for both Portugal and Spain, and is the responsible for pharmacovigilance for Italy, Portugal and Spain. As a Regulatory Manager has the responsibility of registering new products and maintaining their life cycle by submitting variations, renewals and keeping the compliance of the products. There is a continuous interaction with the local authorities, in this case the Portuguese and the Spanish ones. The Regulatory Manager also has the responsibility of approving the products artworks and making sure they reflect the texts approved by the authorities. Another responsibility is the approval of the promotional materials developed by the company's marketing department. It is required that those comply with the European and local legislation and reflect the approved texts (target species, indications, etc.).

As Local Responsible Person for Pharmacovigilance for Italy, Portugal and Spain, there is the requirement to collect the reports of adverse events that took place after the administration of an Elanco product and report those to the Global Pharmacovigilance Organization for processing and inclusion in the databases. These reports come either from company's employees (sales representatives, for example) or directly from veterinarians or pet owners. When necessary, there is contact with local authorities, in order to clarify any detail on a case or when there is a safety concern with any of the products. There is also a need to coordinate with Global Pharmacovigilance Department the submission of the Periodic Safety Update Reports (PSURs). The training of the company's employees concerning pharmacovigilance is another of the responsibilities of the Local Responsible Person for Pharmacovigilance.

Being pharmacovigilance an area of interest, it was decided to make the internship and dissertation around the subject.

This thesis is the result of a study of the European pharmacovigilance regulation, available literature, and information available from the European Medicines Agency (EMA) and national competent authorities as well as knowledge the student has from her work experience.

It was also decided to analyse and compare five European pharmacovigilance systems: the EMA, France, Portugal, Spain and the United Kingdom (UK). Although having the same legislative framework, there are different setups and performance in the various systems. The rational for choosing these four member states has been the following: the UK system was chosen due to the continuous referencing in published literature and from previous knowledge about it, being considered a good example, the French was chosen due to the fact that it has a differentiated setup, with involvement of anti-poison centres and universities, the Portuguese and the Spanish because they are part of the daily work of the student in the company's functions, Italy is a recent assignment. Others, as for example the German system, were not chosen due to the lack of availability of published information in English.

Each pharmacovigilance organization is described and the annual reports from 2016 are compared, using the total number of adverse event reports per year, the proportion of adverse events per target species and the total number of reports by therapeutic class/class of product.

The objective is to make a comparison, understand what is working well in these systems and finally to make a proposal for what could be a good standard for a good pharmacovigilance system, ensuring the reporting of adverse events, maintaining the benefit-risk balance and reinforcing the participation of the various stakeholders.

1 The birth of pharmacovigilance

In the 30's there was an incident that caused 73 deaths (and associations with 20 other) in the USA due to a sulphonamide syrup that contained dietilenoglicol, known as Elixir of Sulphanilamide (Woodward, 2009). A causality was established and this event resulted in a change in the legislation, it started to be mandatory the submission of safety data in order to get a medicine introduced into the market (Geiling, 1938).

In the post war era (1960's), thalidomide was used to combat sleepiness and it was first introduced in Germany as an over the counter drug (non-prescription medicine) due to the fact that the manufacturer alleged its safety. It then started to be used in pregnant woman for morning sickness, as an off-label use. Nevertheless, due to the news around the possibility of the drug creating phocomelia in the delivered babies, it did not receive Federal approval by the Food and Drug Administration (FDA) and did not get into the market in the United States of America (USA), greatly due to the opposition of FDA's inspector Frances Kelsey (Fintel, 2009). This fact tremendously reduced the impact of the disaster by not exposing the USA population to the drug and the respective consequences. Nevertheless, there were around 4.000 cases of phocomelia in Europe (Batalha, 1993).

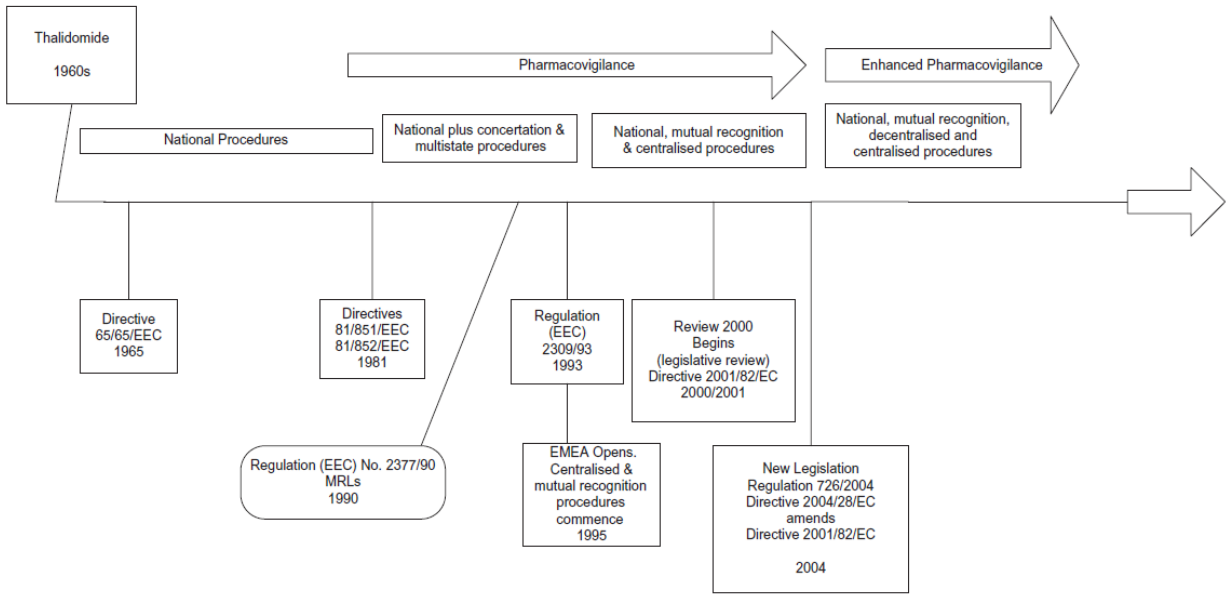
The thalidomide was the most widespread event related to the safety of a drug and created the need to regulate and control medicines in many countries (Woodward, 2009). European and

national pharmaceutical legislation was generated after this event. Figure 1 explains the evolution of the Medicines European Legislation since the thalidomide accident.

“Pharmacovigilance has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.” (European Commission, 2011).

The European Union (EU) Directive 65/65/EEC of 26 January 1965 was the first Directive in the pharmaceutical area and it established the first set of rules regarding medicinal products. In the case of the UK the Medicines act was approved in 1968 (Woodward, 2009). Later there were also published Directives 81/851/EEC and Directives 81/852/EEC, establishing basic regulatory framework for VMP and the testing requirements to ensure safety, quality and efficacy for VMP. It was considered important to harmonise the European Countries concerning the requirements as some countries had existing national legislation.

Figure 1 – The thalidomide event and the generation of Medicines European Legislation (Woodward, 2009)



When a VMP is registered, there is limited knowledge about its potential side effects because clinical trials only include a limited number of animals, the population exposed is limited and reflects its use under controlled conditions.

When the VMP starts to be used in field conditions like off-label use (e.g. non-target species), different breeds, and animals with concomitant pathologies, the adverse events that were not detected during the clinical trials start to emerge. In addition, the treatment of thousands of animals start to reveal reactions that have a very low incidence and were not present themselves in the clinical trials with a limited number of animals.

Thorough and robust monitoring of adverse events is a crucial part of future benefit-risk profile of the product. Therefore, pharmacovigilance is a requirement for the safe and efficacious use of VMPs (EMA, 2015b).

2 Legal Basis and Regulation

There is European Legislation defining the legal framework for VMPs in the EU and the pharmacovigilance requirements. Directive 2004/28/EC amending Directive 2001/82/EC, establishes the rules for the VMPs approved via National Procedure, Mutual Recognition (MRP) Procedure and Decentralized Procedure (DCP) (Woodward, 2005a). Regulation (EC) No 726/2004 that replaced Regulation (EC) No 2309/93 establishes the rules for Centralised Products (CP). While the Directive has been transposed by each Member State to the national legislation, the Regulation has a direct application to the EU Member States.

Besides the European legislation, there are other reference documents that serve as guidance on pharmacovigilance for the pharmaceutical industry, as well as for the National Competent Authorities (NCA). The most important document is “Volume 9B of The Rules Governing Medicinal Products in the EU – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use” (European Commission, 2011). These rules are considered “soft law”, and serve as guidance documents allowing the Marketing Authorisation Holder (MAH) to be able to establish its pharmacovigilance system, prepare documents for submission to the authorities (e.g. Detailed Description of Pharmacovigilance System (DDPS) and PSURs) and other routine activities necessary to ensure a good and robust pharmacovigilance system.

In this review about veterinary pharmacovigilance, focus is aimed at centrally authorised products because of the availability of published information about them.

The work also references some examples of European Member States pharmacovigilance systems. The UK pharmacovigilance system was chosen because it is considered a good example, because of availability of online-published documents (Woodward, 2005b) and the fact that the information is available in English and therefore understandable. Portugal and Spain are also present in this work due to the student’s work experience in the two countries and France due to the special set up, being an interactive system involving the veterinary university (Keck & Ibrahim, 2001) and therefore considered interesting to be reflected here.

3 The Pharmacovigilance system in the European Economic Area (EEA)

3.1 Registration of VMP in the EEA

VMPs need to have a registration in order to be marketed in the EEA. An “Agreement of EEA” was accepted in some European countries as Iceland, Liechtenstein and Norway, adopting the

complete *acquis communitaire* on medicinal products. They are therefore parties to the EU procedures (Woodward, 2009).

The applicant, future MAH submits a registration dossier with data on quality, safety and efficacy and this data is then assessed by European competent authorities and the decision is made on the approval (or not) of the VMP (European Parliament and Council, 2001, European Parliament and Council, 2004). Once the product gains approval, it can be placed on the market in one or several EU member states.

The dossier is constituted by four parts that are pre-defined in the European Legislation (European Commission, 2015).

Part I includes administrative information, product literature and the detailed and critical summaries (former expert reports).

Part II is the pharmaceutical file where there is information on the active substance, excipients, the manufacturing method, the tests and controls performed on the active substances, intermediate and finished product. There is also information on the manufacturing chain with the description of the manufacturers responsible for each steep of the process. Stability studies are conducted and include normal and accelerated studies and will allow the establishment of the product's shelf life: shelf life as packaged for sale, as well as in use stability, if applicable.

Part III includes safety and in the case of food producing animals, it also includes residues studies. The safety studies are conducted in the target species and include for example single dose toxicity, repeated dose toxicity, tolerance in the target species, reproductive toxicity including developmental toxicity, user safety, etc.

There is also an Environmental Risk Assessment (ERA) that will assess the potential harmful effects that the use of the VMP may cause to the environment, and to identify the risk of such effects. The assessment shall also identify any precautionary measures, which may be necessary to reduce such risk (European Commission, 2015). The ERA is constituted by two phases.

The first phase is mandatory and indicates the potential exposure of the environment to the product and the level of risk associated with any such exposure.

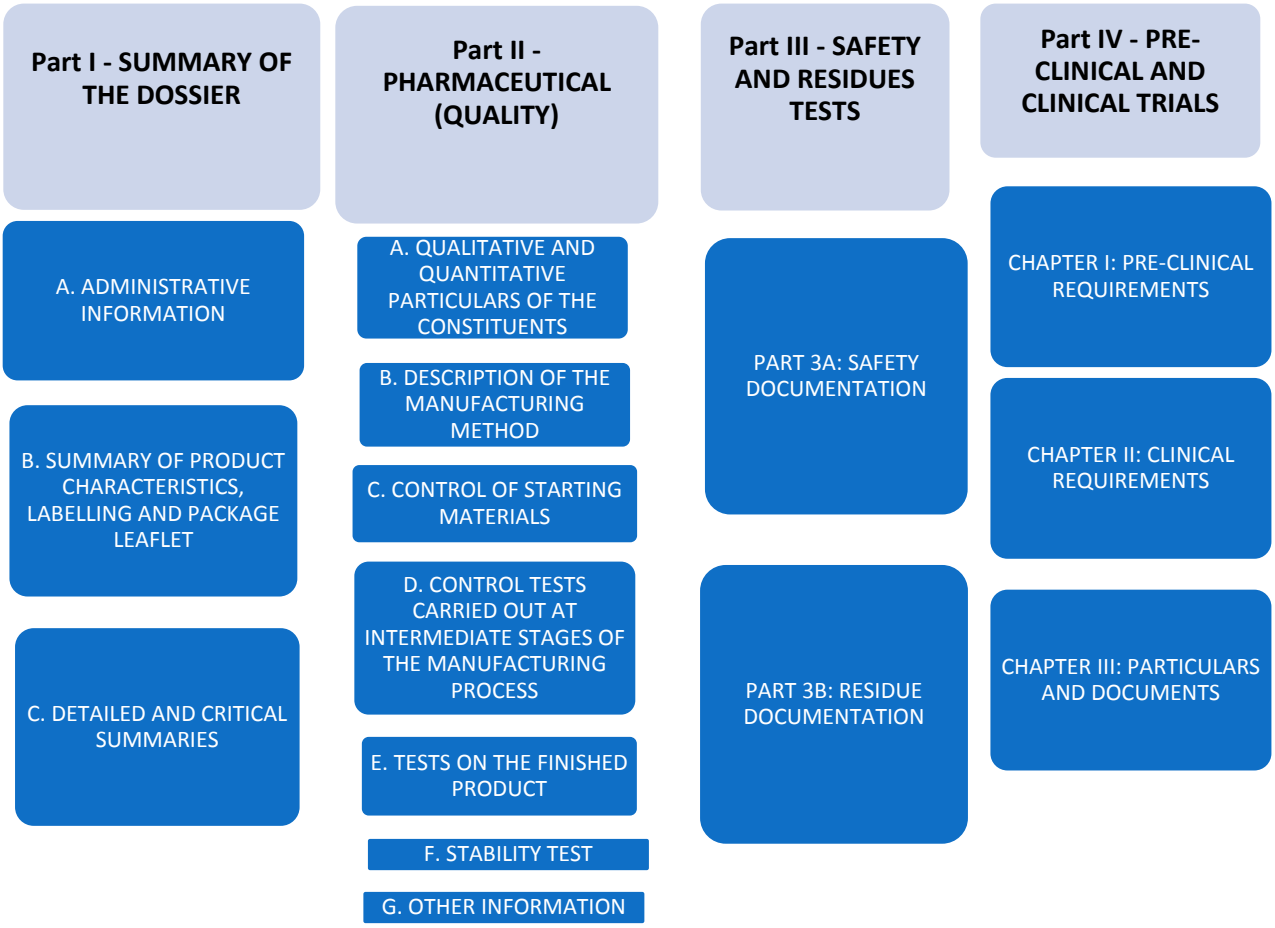
The second phase is necessary when the results of phase one indicate that there is a potential exposure of the environment to the product. The applicant will need to evaluate the potential risk(s) that the VMP might pose to the environment. It may be necessary to further investigate the impact of the product on the soil, water, air, aquatic systems, non-target organisms (European Commission, 2015).

Part IV of the dossier includes the pre-clinical and clinical trials. Pre-clinical studies are required to establish the pharmacological activity and the tolerance of the product (European Commission, 2015).

Pre-clinical studies include pharmacology with the pharmacodynamics, development of resistance (if applicable), pharmacokinetics and tolerance in the target animal species studies (EMA, 2008). Clinical trials will be conducted to demonstrate or substantiate the effect of the VMP after administration at the proposed dosage regimen via the proposed route of administration and to specify its indications and contra-indications according to species, age, breed and sex, its directions for use as well as any adverse reactions, which it may have. Experimental data shall be confirmed by data obtained under normal field conditions (European Commission, 2015).

Figure 2 enumerates the constitution of the registration dossier for a non-immunological VMP in the EEA.

Figure 2 – Constitution of the registration dossier (Adapted from European Commission, 2015)



The applicant submits the registration dossier either to the NCA (in the case of national, MRP/DCP) or to the EMA (in the case of CP) (European Commission, 2017). The dossier is analysed by experts in the areas of quality, safety, residues and efficacy.

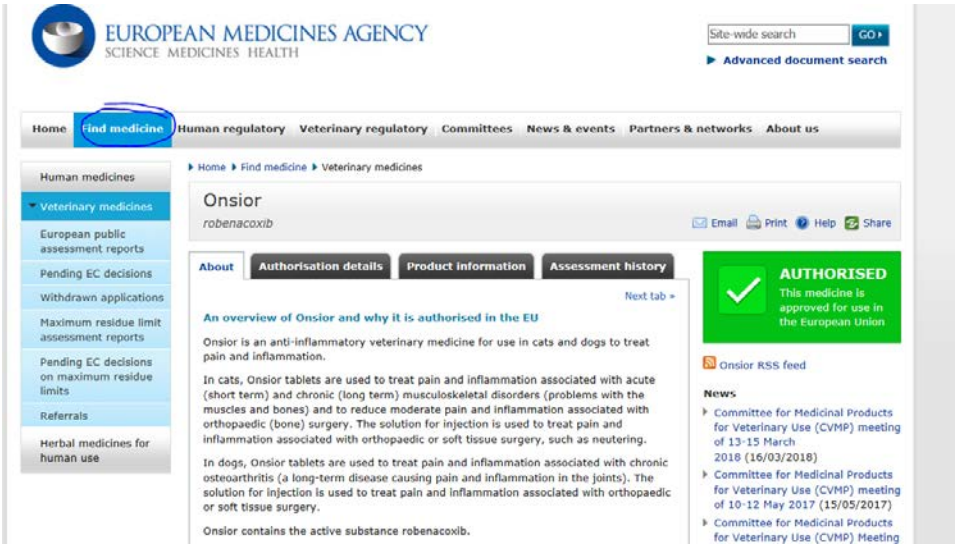
The NCA has experts available for the distribution of the dossier as well as a Committee responsible for issuing the opinions. The administrative bodies at the various agencies then issue the Decision. Some national authorities have Agencies responsible for VMP alone (Czech

Republic, Romania, Slovakia, UK), while others also have human medicines responsibility (Austria, Belgium, Netherlands, Denmark, Estonia, Finland, Greece, Liechtenstein, Norway, Poland, Slovenia, Sweden). In other cases there are departments inside the Ministry of agriculture (Croatia, Lithuania, Malta, Portugal) while others work under the Ministry of Health (Cyprus, Italy, Luxemburg). In some situations, VMP are the responsibility of a food safety authority (Bulgaria, France, Hungary, Iceland, and Latvia). There are also special cases like Germany where the pharmacological VMP are the responsibility of one agency, the BVL- Federal Office of Consumer Protection and Food Safety, while the immunological are under the responsibility of another agency, the Paul-Ehrlich Institut - Federal Institute for Vaccines and Biomedicines. Ireland also has a particular setup being the responsibilities shared between Health Products Regulatory Authority (HPRA) and Department of Agriculture & Food.

In the case of the CP, the Committee for Veterinary Medicinal Products (CVMP) has experts from all EU Member States and for each VMP there is one member that will act as Rapporteur and another as Co-Rapporteur in the evaluation of the dossier. They will generate an evaluation report that is approved by the CVMP and will issue a recommendation for approval (or rejection) of the application. The European Commission will issue a decision based on the opinion of the EMA.

The Commission Decision is published in the European Commission website while the Summary of Product Characteristics (SPC), package insert and labelling in all MS official languages, together with the list of all approved presentations and well as the European Public Assessment Report is published in the EMA website (Figure 3).

Figure 3 – Centralized product information available at the EMA website (EMA, 2018a)



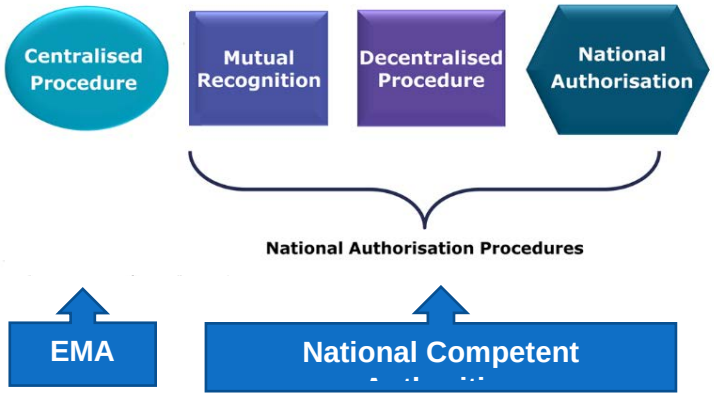
As mentioned previously, a VMP can be approved in the EU using three types of procedures (Table 1).

Table 1 – Types of procedures available for VMP registration in the EU (European Parliament and Council, 2001, European Parliament and Council, 2004).

Type of procedure	Geography	Applicable legislation and responsible authority
"Pure" national procedure. The future MAH registers the product in one Member State only.	Registration in one Member State	Directive 2001/82/EC amended by Directive 2004/28/EC. The National Competent Authority is responsible for assessing the veterinary medicinal product and decide on the grant of the Marketing Authorization.
Mutual Recognition Procedure/ Decentralized procedure. The MAH choses one Reference Member State (RMS) that will be responsible for the assessment of the VMP and the other MS will approve the VMP based on the RMS assessment. The MAH may decide to choose only some MS to register its VMP. These procedures are mandatory in the case a MAH wishes to register the same VMP in more than one MS.	Registration in more than one Member State	Directive 2001/82/EC amended by Directive 2004/28/EC. The National Competent Authorities are responsible for assessing the veterinary medicinal product and decide on the grant of the Marketing Authorization.
Centralized procedure. **The EMA receives an application, the CVMP gives an opinion and the EC issues a decision**	Registration in all EEA	Regulation (EC) No 726/2004 of the European Parliament and of the Council. EMA.

As mentioned earlier, the European system allows the VMP to be placed on the market by using the centralized procedure and the national authorisation procedures to obtain a MA (Figure 4).

Figure 4 – The various procedures and type of authorizations for VMP in Europe. (Adapted from Bere, 2016)



The centralised procedure has a mandatory scope and an optional scope.

Products that are considered innovative and those produced by means of biotechnological process have to follow the centralized procedure in order to obtain a MA and be placed in the European market. Recombinant Deoxyribonucleic acid (DNA) technology, controlled expression of genes coding for biological active proteins in prokaryotes and eukaryotes and hybridoma and monoclonal antibody methods are included in the mandatory scope. VMPs intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals also have to follow the centralised procedure (European Parliament and Council, 2004).

The optional scope allows the applicant to request the application to be submitted via centralized procedure, even if not qualifying for the mandatory scope. Products eligible for this scope contain a new active substance (an extensive list of examples is provided in the Regulation) or constitute a “significant therapeutic, scientific or technical innovation or that the granting of the authorisation in accordance with Regulation (EC) No 726/2004 is in the interests of animal health at Community level.” (European Parliament and Council, 2004).

“A generic or hybrid application veterinary medicinal product of a reference product veterinary medicinal product authorised via the centralised procedure has “automatic” access to the centralised procedure” (European Parliament and Council, 2004).

In case the VMP is granted an approval from the authorities, the SPC is agreed and it reflects the indications, posology, conditions of use, technical information about the VMP pharmacology or immunological properties. This document is in public domain and in case of the centrally authorised products it is published on the EMA website. Together with the SPC, the EMA also approves the package insert, secondary packaging and primary packaging texts. The package insert is supplied together with the VMP and provides the following information to the user: target species, posology, safety warnings, etc.

The pre-clinical and clinical studies performed for the purpose of registering the VMP will provide safety information that will be reflected in the products literature. For the conduction of the trials that will result later in the registration dossier, the applicant has to follow a number of guidelines, to be able to meet with EU requirements. In the case of the safety of the VMP, there are target animal safety, user safety and others specific guidelines.

Regarding target animal safety the guideline provides recommendation about following Good Laboratory Practices (GLP), number of animals present in the study, study design, dose, frequency, duration of administration (EMA, 2008). For example, animals should be administered the highest recommended dose and two multiples of this dose, usually three times the dose and five times the dose. There are recommendations for the observation of the animals and medical exams (e.g. blood analysis, urine analysis) during and after the trials. Additionally, there are also recommendations for the necropsy and histopathological exams. Finally, the statistical analysis should be performed in a standard way and study reports prepared in such a way that facilitates the evaluation of potential safety concerns. Specific studies may need to be presented in some pharmaceutical forms or type of products; injection site safety studies are needed for injectable VMP for food producing animals and reproductive studies are required for systemic use VMP intended for breeding animals (EMA, 2010). There are also guidelines regarding user safety (EMA, 2008).

Therefore, user safety risk assessment is aimed at protecting the user and the user is defined as “any person that may come into contact with the VMP or components of the product before its application to the animal… during its application, and after its application” (EMA, 2010).

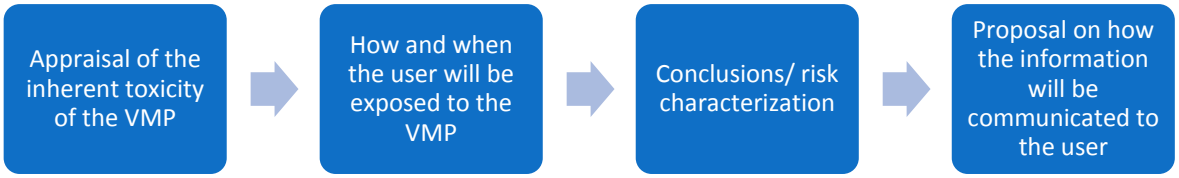
The user can be the veterinarian administrating the VMP to his /her patient or the pet owner that can also be exposed to the drug when administering a tablet or by contacting with a topical application VMP while petting the animal (EMA, 2014a). Figure 5 provides some examples of tasks and situations that may lead to exposure.

Figure 5 - Examples of tasks and situations that may lead to exposure (EMA, 2010)

Pre-application phase	Application phase	Post-application phase
• Storage • Opening or accessing the product: e.g., taking product out of packaging • Mixing and/or diluting of concentrates: e.g., mixing with feed & water • Loading application apparatus or system: e.g., dosing gun	• Administration to the animal(s): • Holding/restraining animal for treatment	• Cleaning equipment & preparation areas • Disposal activities: such as disposal of packaging, equipment & surplus product • Handling treated animals • Stroking/handling the coat of treated animals

This user safety risk assessment includes the following steps described in Figure 6.

Figure 6 – User safety risk assessment steps (EMA, 2010)



The results of the safety studies are compiled in the dossier and will be used for the preparation of the SPC and product literature.

The template used to construct the SPC reflects how the safety information will be included in points 4.3 to 4.8:

"4. CLINICAL PARTICULARS; 4.1 Target species; 4.2 Indications for use, specifying the target species; 4.3 Contraindications; 4.4 Special warnings for each target species; 4.5 Special precautions for use; Special precautions for use in animals; Special precautions to be taken by the person administering the veterinary medicinal product to animals; 4.6 Adverse reactions (frequency and seriousness); 4.7 Use during pregnancy, lactation or lay; 4.8 Interaction with other medicinal products and other forms of interaction; - common (more than 1 but less than 10 animals in 100 animals treated); - uncommon (more than 1 but less than 10 animals in 1,000 animals treated); - rare (more than 1 but less than 10 animals in 10,000 animals treated); - very rare (less than 1 animal in 10,000 animals treated, including isolated reports)." (EMA, 2017a).

For example, point 4.6 Adverse reactions (frequency and seriousness) will include "information on adverse drug reactions attributed to the product when used as recommended. The reactions listed should be based on an assessment of all observed adverse events and all facts relevant to their causality, severity and frequency." (EMA, 2006).

Results from the user safety risk assessment should populate point 4.5 Special precautions for use, ii) Special precautions to be taken by the person administering the medicinal product to animals, with information regarding preparation of the product, possible hypersensitivity reactions. In addition, safety information resulting from the reproductive studies should be included in point 4.7 Use during pregnancy, lactation or lay, of the SPC.

When an initial MA is granted, it is because the benefit-risk balance is considered positive based on available information on the products benefits covered by the approved indications and the respective adverse effects. The MAH has to continue to perform the benefit-risk assessment throughout the medicine's life.

After the launch of the VMP in the market, the MAH has to continuously monitor de behaviour of the product in field conditions. The adverse events or lacks of efficacy reports that may arise from the veterinary practitioners, pet owners, pharmacists or other involved persons, have to be complied and communicated to the competent authorities. The authorities will later assess and decide on possible actions; applying safety measures as for example adapting posology, inclusion of safety warnings, by addition of contraindications, etc. In case of a safety issue, these actions will allow the management of the risk benefit balance and maintain it positive.

According to current EU legislation, the CVMP at the EMA and its Pharmacovigilance Working Party (PhVWP-V) are responsible for the pharmacovigilance of centrally authorised VMPs i.e., the products that have been granted an EEA-wide MA, whereas the surveillance of non-centrally authorised VMPs is undertaken by the competent authorities, at Member State level.

3.2 Establishment of Maximum Residue Limits (MRLs)

In order to protect the health of the consumer of foodstuffs of animal origin, one of the most important principles laid down in the legislation is that foodstuffs obtained from animals treated with VMPs must not contain residues of the medicine or its metabolites, which might constitute a health hazard for the consumer (European Commission, 2005). Establishing the MRLs for the substance that will be used in the formulation of a VMP is mandatory according to the European legislation.

The MRL definition is "The maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or µg/kg on a fresh weight basis) which may be accepted by the Union to be legally permitted or recognized as acceptable in or on a food" (European Commission, 2005).

The major element underlying the elaboration of MRLs is the Acceptable Daily Intake (ADI) which is derived from the No Observed Effect Level (NOEL) identified in suitable toxicological, pharmacological and microbiological studies. This NOEL is then adjusted by way of a safety factor to give the ADI value (Woodward, 2009).

MRLs should be set for pharmacologically active substances used or intended to be used in VMPs placed on the market in the Community (European Parliament and of the Council, 2009).

The submission procedure is defined in Article 8 of Regulation (EC) 470/2009 and further described in Commission Implementing Regulation (EU) 2017/12. MRL application always needs to follow the centralized route.

Considering the status of the active substances, Commission Regulation (EU) No 37/2010 of 22 December 2009 contains two tables. Table 1 contains the allowed substances while table 2 contains the prohibited substances**.** The substances listed in the table 1 are allowed to be used in VMP intended for food producing animals while substances listed in table 2 are forbidden.

This Regulation replaced the previous Council Regulation (EEC) No 2377/90, and table 1 is a combination of the previous Annexes I, II and III, while the actual table 2 contains the substances that were listed in Annex IV, as reflected in Figure 7.

Figure 7 – Classification of the active substance in the four Annexes (Woodward, 2009)

Annex I	Full MRLs
Annex II	No MRLs required
Annex III	Provisional MRLs
Annex IV	No MRLs possible on consumer safety grounds

In the case of Annex I, a full dossier application for MRL had to been submitted and the MRLs were established. For Annex II it was considered that it was not necessary to establish MRLs, as the residues of the substance concerned were not considered to present a public health risk from the levels used. Annex III contained the substances for which a provisional MRL had been established, as there were no grounds for supposing that residues of the substance at the level proposed would present a hazard for the health of the consumer. This period of provisional MRLS could not exceed five years (European Commission, 2005). Annex IV contained a list of substances which residues, at whatever concentration, in foodstuffs of animal origin constituted a hazard to the health of the consumer. VMPs containing substances included in Annex IV were forbidden for treatment of food producing animals (European Commission, 2005).

The withdrawal period, defined as the period between the last treatment and the moment of slaughter, is established by trials. The animals are treated with the commercial formulation of the drug and are slaughtered at different intervals (Woodward, 2019). The moment when all the animal tissues have residues below the defined MRL, will establish the withdrawal period. The withdrawal period is of outmost importance to make sure that the foodstuff of animal origin does not contain

residues from the VMP that were administered to the animal. The withdrawal period is usually expressed in days.

MRLs also need to be established for milk, eggs as well as honey although the residues in this case to not deplete, they just need to be discarded until they are below the MRLs.

Withdrawal periods in fish have the particularity that are expressed in degree days as the temperature affects the metabolism, so need to consider time as well as temperature.

The withdrawal period will be established during the authorization process, no matter which procedure it will follow (National, Mutual Recognition, Decentralized or Centralized) and will appear of the VMP SPC and product literature. The veterinarian has the responsibility to follow the recommended withdrawal period and make sure it is respected as a safeguard to human health and food safety.

3.3 Spontaneous adverse events

An adverse event is “a reaction which is harmful, unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.” (European Parliament and Council, 2001).

The adverse events can be divided as expected or unexpected and serious or non-serious (European Commission, 2011). An unexpected adverse event is defined as a reaction that is not consistent with those described in the SPC. On the other hand, an expected adverse event describes an observation that is already mentioned in the SPC. The serious adverse events are the ones that result in death, life threatening, results in significant disability or incapacity, results in congenital anomaly/birth defect or in permanent or prolonged signs in the animals treated (European Commission, 2011). The classification of seriousness depends if the animal is an intensive animal production species (e.g. poultry, fish or bees) or companion animal (e.g. cats or dogs). In the first instance, there is a baseline level of mortality that is considered to normal, in which case the increase mortality rate, severe signs, or variation of animal production levels will be classified as serious. If the mortality rate is considered normal, it will be classified as non-serious. In the case of dogs, cats or horses a single death constitutes a serious adverse event. This rule will also apply to individual deaths in cattle, sheep, pigs, goats as well as rabbits, even kept in herds, the treatment is often performed on the individual animal and therefore individual death or severe signs have to be considered on an individual basis. In summary, in the case the animal is kept individually, a single death will be considered as serious adverse event, whatever the species (IFAH, 2011).

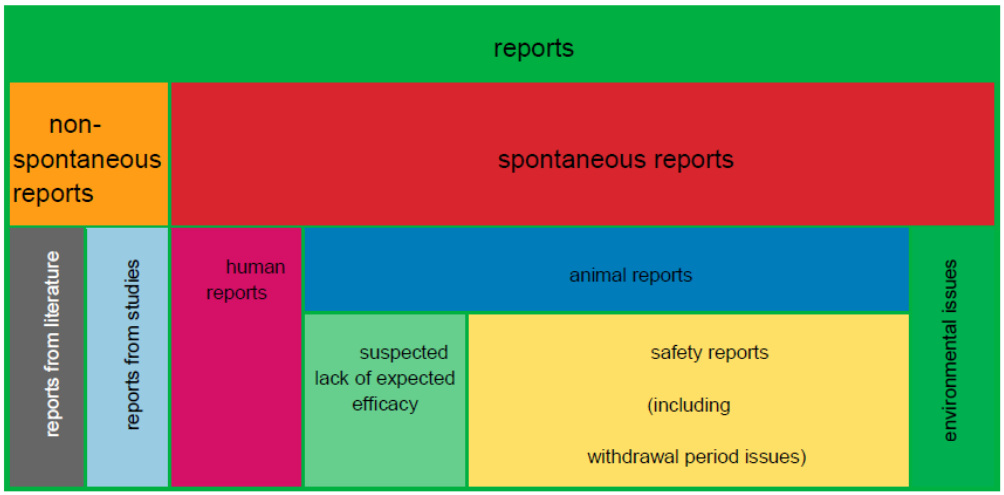
The adverse events reports can be classified into spontaneous and non-spontaneous reports. Spontaneous reports are the ones originated from the field and include events with animals,

humans and environmental incidents. The spontaneous adverse events may be reported by the veterinarian, the pet owner, pharmacist or other person involved.

These reports can be either from companion animal, food animal or withdrawal period issues. The non-spontaneous reports can originate from literature revision, or reports originated from clinical trials.

Figure 8 allows a better understanding of the type of adverse events that need reporting.

Figure 8: Types of pharmacovigilance reports (Adapted from VMD, 2016)

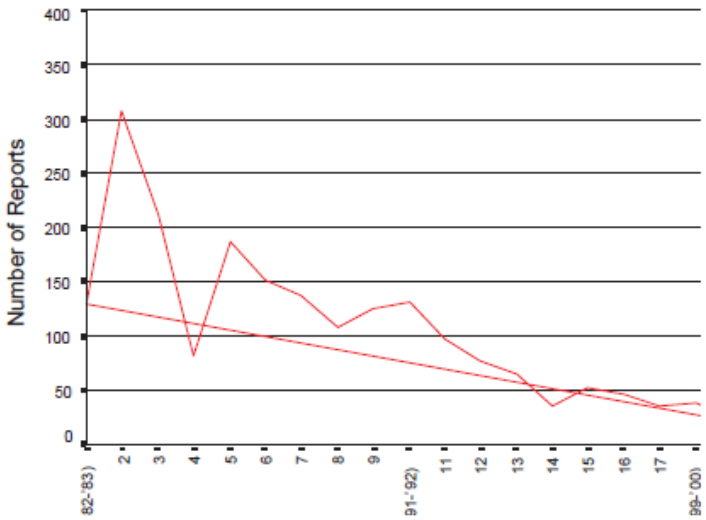


It is important to remember that the events: lack of efficacy, off-label use, validity of withdrawal periods, i.e. violations of MRLs, environmental problems arising from the use of VMPs should also to be reported as adverse event (European Commission 2011).

3.4 Importance of the product portfolio

Knowing the MAH portfolio allows a better understanding of the type and nature of adverse events. In the case of innovative products, new active substances, new indications, or target species, it is expected to have a peak of adverse event reports in the second year after marketing and then experience a decrease. This is called the Weber effect (Figure 9), (Weber, 1984 and Hartnell, 2004).

Figure 9 – Weber effect. Number of adverse event reports submitted each year from date of approval (Adapted from Hartnell, 2004)



Investigators speculated about the reason of the decrease after the initial years. Prescribers tend to report adverse events from newly available and less familiar products. The reason behind this being the fact that the population exposed to the new drug is different from the clinical trials and results in a greater variability of the individuals. Non-innovative products tend to lead to less reporting, as the users are more knowledgeable about these products and the way these are used. Regarding companion animals *versus* food-producing animal's products, it is expected to have more reporting in the case of companion animals. This marked difference results from the fact that companion animals are more closely observed by the pet owners when compared to food producing animals. In addition, there seems to be a difference in the acceptability of the level of suffering; the same event can be considered as unacceptable for a dog's pet owner while the same event in a farm animal may pass undetected or never considered for reporting purposes (Cornez, 2009).

3.5 Risk information originates from various sources

The overall surveillance of adverse events is carried out predominantly using following three processes: individual case reporting, PSURs, and continuous monitoring of all pharmacovigilance data is conducted via signal detection by national competent authorities, EMA and MAHs.

3.5.1 PSUR writing and submission

The PSUR is a product specific document that evaluates the safety of the product in field use. The PSUR is generated by the MAH of a VMP and has the objective of providing the NCA or the EMA with an update of the worldwide safety experience at predefined intervals post-authorisation and

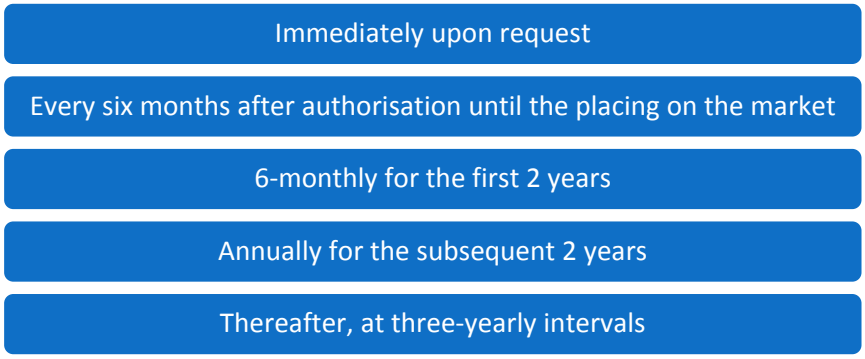
must contain certain specific information. Figure 10 shows the summary of the necessary information to be covered by the PSUR.

Figure 10 – Information contained in the PSUR (Adapted from European Commission, 2011)

The assessment of the PSURs allows the authorities to determine if the benefit-risk ratio of the product remains unaltered and if the current SPC is still appropriate. It also may lead to the conclusion that a safety trend needs to be further investigated and can potentially lead to regulatory actions as SPC changes for example.

Apart from the submission at the five-year renewal (still mandatory), the MAH has to submit the PSUR following a specific schedule. Until the placing on the market, PSUR needs to be submitted every 6 months (Figure 11).

Figure 11 – Schedule for PSUR submission (Adapted from European Commission, 2011)



The PSUR writing and the submission to the competent authorities are very time-consuming activities due to different interpretations from authorities (Cornez, 2009).

Nevertheless, PSURs are still one of the most important sources of pharmacovigilance information for the authorities and the basis for the decision-making in regards to risk management. In the future legislation soon to be published, the PSURs will be replaced by signal detection activities in a European database (European Commission, 2018). Future legislation and signal detection will be further developed in this document.

For the literature reviews, it is expected that the MAH performs a search via the major electronic databases. This information should also be included in the corresponding PSUR.

3.6 Risk Management System

In order to have a VMP registered, as already mentioned, the MAH needs to submit a registration dossier that contains several studies, in the case of VMP including pre-clinical (including toxicological testing), clinical safety and efficacy studies in the target species.

When a VMP is released into the market, the increase in the number of animals exposed as well as the sub-populations that are going to be treated will result in observation of new adverse events and special populations susceptibility to the drug, that were not noticed earlier in the investigation phase and during the clinical trials.

These adverse events resulting from the field use of a VMP will then be compiled and submitted to the authorities via expedited reporting of individual case reports and PSURs to the competent authorities, depending on the seriousness.

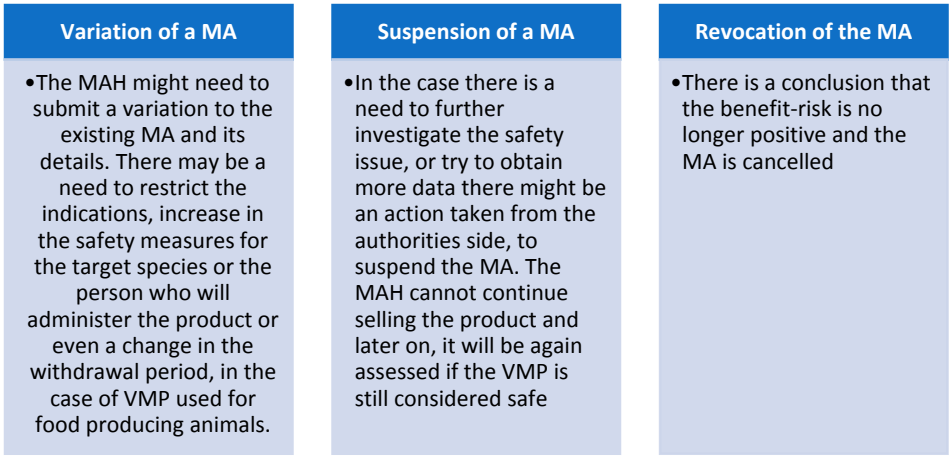
Safety information will be assessed by the EMA/NCA and regulatory actions may result from this assessment in order to maintain the benefit-risk positive.

This positive balance may be achieved by limiting indications, narrowing target population (breeds, age, weight, etc.), addition of safety warnings, for example (EMA, 2015b).

3.7 Change in the evaluation of the benefit-risk balance of a product

After assessing the pharmacovigilance data, conclusion can be drawn that the benefit-risk is no longer positive and regulatory actions might be necessary. There are several types of urgent safety restrictions (Figure 12).

Figure 12 – Types of urgent safety restrictions (European Commission, 2011)



4 The Pharmacovigilance System at the MAH

Pharmacovigilance is mandatory for MAHs and they must ensure to have "…an appropriate system of pharmacovigilance and risk management, in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken…" (European Commission, 2011).

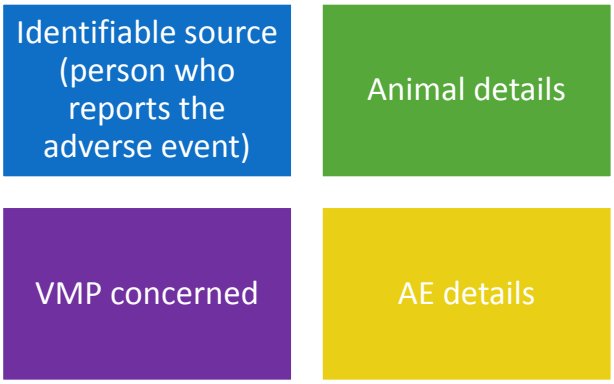
The MAH should have permanently and continuously at his disposal a Qualified Person Responsible for Pharmacovigilance (QPPV) residing in the EEA. This qualified person is responsible for "the establishment and maintenance of a pharmacovigilance system which ensures that information about all adverse events which are reported to any personnel of the MAH, is collected and collated in order to be accessible at least at one point within the EEA". The QPPV should also "…have oversight of the pharmacovigilance system in terms of structure and performance and be in a position to ensure in particular the above system components and processes, either directly or through supervision." (European Commission, 2011). Another responsibility of the QPPV is the training of the personnel in relation to pharmacovigilance.

All the employees need to be trained on basic information in regard to the pharmacovigilance system in particular the rules for the reporting of the adverse events (European Commission, 2011).

Usually the multinational pharmaceutical companies have a Global Pharmacovigilance Department that has oversight of the system as a whole, are responsible for the internal procedures, training of the employees, ensure the legislation and internal rules are followed. Then there may exist regional leaders per regions (ex. Europe, Asia, and North America). There is the legal requirement in Europe to have a QPPV that ensures the European legislation is followed and coordinates the work between Global and Local Teams. Finally, there is the Local Responsible for Pharmacovigilance that is responsible for the collection and reporting of the adverse events to the

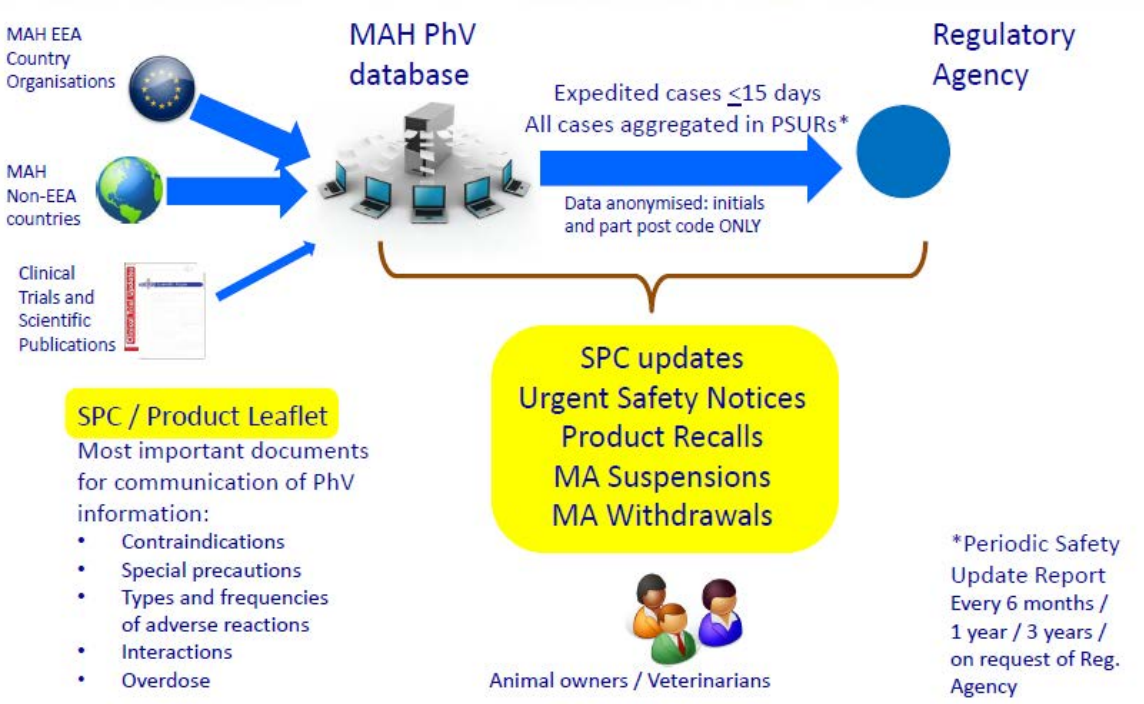
Global Department, training of the local employees, interaction with the local authorities and has knowledge of local requirements and provides input to the Global Department.
Employees need to be knowledgeable on how to report an adverse event, which information they need to recompile and send. There is a minimum information for being able to report an adverse event, as described in Figure 13.

Figure 13 – Four minimum criteria to report an adverse event (European Commission, 2011)



The adverse event needs to be classified as serious/non-serious, expected/non-expected and coded for causality, as mentioned previously. This classification can be proposed by the MAH and finally the authorities will decide on the final and definitive classification.
According to European Legislation, the quality defects and product complaints are not considered to be adverse events, they are handled under the Good Manufacturing Practice (GMP). These reports are therefore out of the scope of European Pharmacovigilance if they are not accompanied by observations that would be consistent with the definition of adverse event. In the case of multinational companies with the same products being licensed in the USA, there is a need to record these cases (IFAH, 2011).
In the case that the MAH is aware that a case has already been reported directly to the NCA, the case should still report the same reaction, stating in the report that it is likely the case is a duplicate of a previous one.
Figure 14 illustrates how the safety information enters the MAH pharmacovigilance database, how it is communicated to the EMA and the results in the MA and product literature.

Figure 14 – View of the MAH, where does the safety information go (Adapted from Simon, 2016)



4.1 Causality assessment

When an adverse event is reported, there is a need to establish if there is a causal association between the reaction and the use of a product. The causality assessment should be carried out using the ABON system. According to this system, five categories of causality can be selected, as described in table 2.

This classification is important as it will have an impact in the incidence calculation and consequently it may result in changes on the product literature and the conditions under which the product in authorised.

Table 2 – Causality assessment, ABON system (Adapted from European Commission, 2011)

Category A	**Probable** • There is a reasonable association in time between drug administration and onset and duration of the event • Positive challenge/dechallenge • Clinical or pathological phenomena should be consistent with the adverse reaction, or at least plausible, given the known pharmacology and toxicology • No equally plausible explanation. Concurrent use of other drugs or intercurrent disease, exclusion of other causes • Where any of the above cannot be satisfied, consider B, N or O or O1
Category B	**Possible** • Drug causality is one of the other possible or plausible causes but data does not meet inclusion criteria for A
Category O	**Unclassifiable/ Assessable** • Insufficient data to draw any conclusions
Category O1	**Inconclusive** • Other factors prevented a conclusion being drawn, but an association with product treatment could not be eliminated
Category N	**Unlikely to be product related** • All cases where there is no reliable or adequate evidence with which to make an assessment of causality

When assessing causality, the following factors should be taken into account, as described in the Figure 15.

Figure 15 – Factors to take into account for the assessment of causality (European Commission, 2011)

Besides the legislation available on causality assessment, there is also guidance provided from the scientific working groups at the EMA about how to harmonize the causality assessment at the authorities and the pharmaceutical industry individuals (EMA, 2013). This guidance is in the format of a questionnaire where questions are made about the case and will help to make the assignment of the causality.

4.2 Reporting timeframe

Depending on the adverse event, the reporting time to the EMA or NCA of an AE happening in the EEA is the following: all serious adverse events in animals and all human adverse reactions need to be reported expedited, send directly to the authorities, no later than 15 calendar days; all the rest of the adverse events should be included in the PSUR (European Commission, 2011).

5 Signal management in veterinary pharmacovigilance

5.1 Introduction to signal management

The definition of signal from the Report of Council for International Organizations of Medical Sciences (CIOMS) Working group VIII 'Practical Aspects of Signal Detection in Pharmacovigilance' CIOMS, (Geneva 2010) is the following: "a signal is information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action".

Another definition is “A signal is reported information on a possible causal relationship between adverse reaction and a drug, the relationship being unknown or incompletely documented” (O’Rourke, 2009).

The availability of adverse event databases, as for example Eudravigilance Veterinary (EVVet) allows the screening and the assessment of data reported for a particular VMP and/or active substance, defined as signal management process. This surveillance activity is often referred as “signal detection” and has to follow a specific methodology (EMA, 2015b).

Signals from spontaneous reports arise from adverse event reports, adverse event databases, articles from the scientific literature, PSURs or other documentation provided by MAHs in the context of regulatory procedures (e.g. variations, renewals, and post-authorisation studies) or their on-going benefit-risk evaluation of medicinal products (EMA, 2015b).

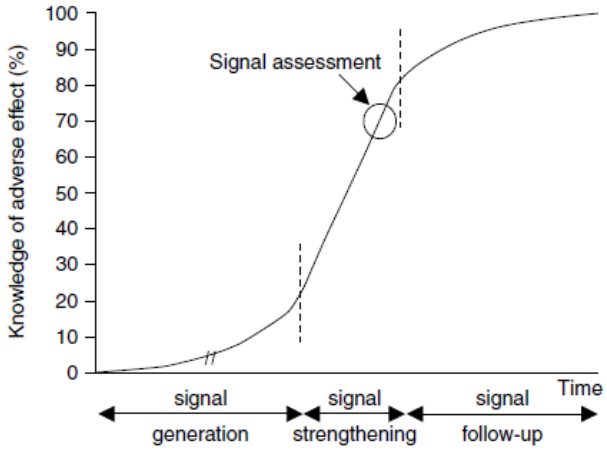
Informal sources of information include public websites, social networks, media reports or other systems through which practitioners and animal owners express adverse experiences with VMPs. These “new media” are increasingly used and are still developing further. Unfortunately, as the threshold for using them is low, so is the quality of information available and it has not been possible yet to include these sources as standard within the signal management process. Further reflection is ongoing and may lead to further specific guidance regarding the use of information available through the “new media” (EMA, 2015b).

Surveillance has already been implemented for centrally authorized products but not for the other products, as national approved licenses. This is due to the fact that the EVVet data does not have the majority of the cases of the nationally approved products.

5.2 Signal management process

“The discovery of a drug-induced disorder, from the earliest suspicion via a credible signal to a fully explained and understood phenomenon, is a lengthy process it may take years until the symptoms, frequency, mechanism and risk factors of an adverse reaction have been fully recognized and the causal connection has been definitely established.” (Figure 16), (Meyboom, 2002).

Figure 16: The process of the discovery of a drug-induced disorder (Adapted from Meyboom, 2002)



Due to the increase of the use of electronic databases and the sharing of adverse event data at global level, there has been an increase of data available. This increases the power of statistical and data mining techniques that allow the surveillance of the VMP. VMP have some specificities when compared to human medicinal products: one case can include adverse events in several animals, because of group treatment. This may cause a distortion in the case if this is not taken into account (EMA, 2015b).

The increase in signal detection performed by the authorities in the databases of spontaneous reports is due to the increase of adverse event reporting, the existence of electronic databases and the mandatory electronic transmission of expedited reporting from MAH to NCAs. An advantage of the databases is that it allows data mining and generation of statistical parameters.

The Figure 17 illustrates how the signal detection and evaluation are performed using the traditional methods as well as the computer enhanced data mining methods.

Figure 17 – Signal management using traditional and computer enhanced methods (Adapted from Almenoff, 2015)

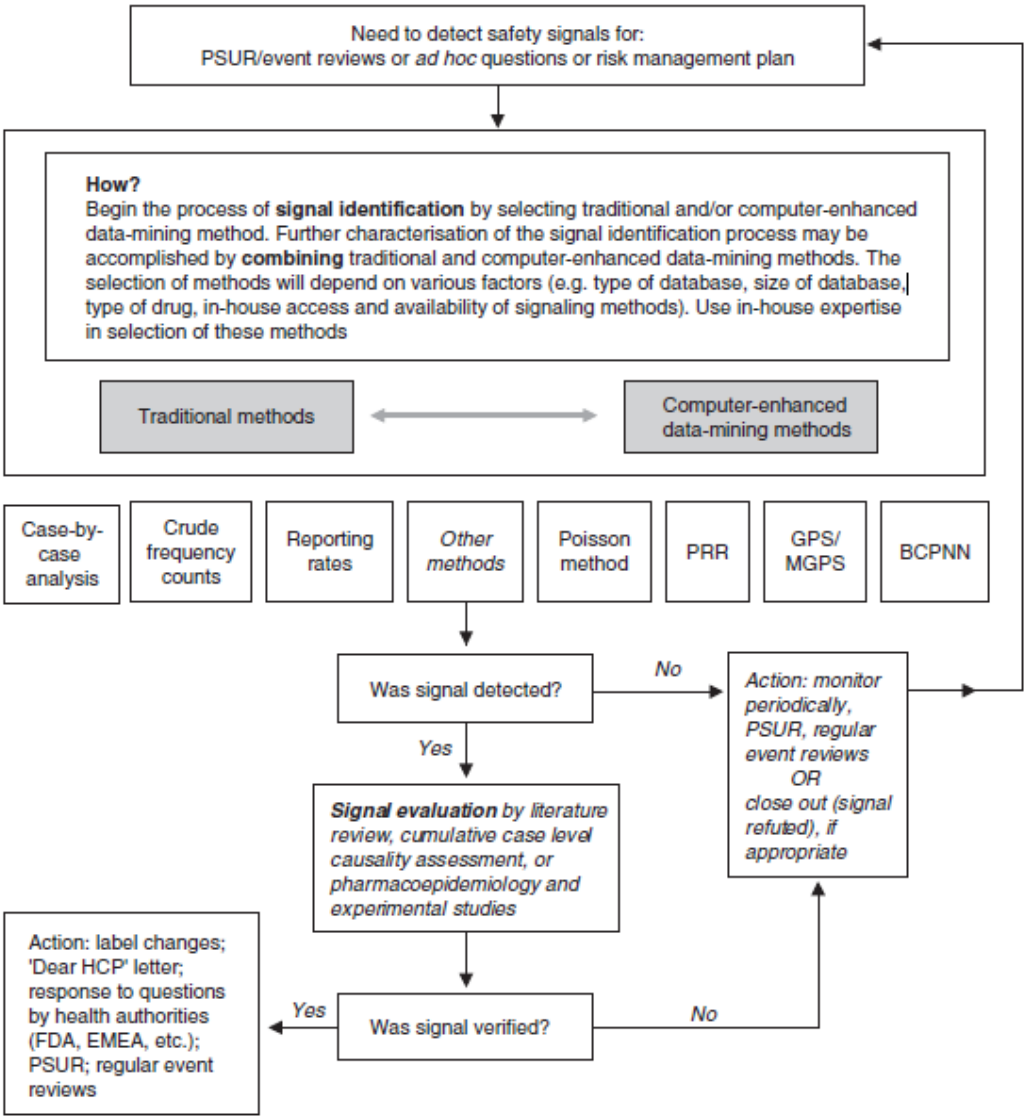


Fig. 1. Integrating computer-enhanced data-mining methods and traditional pharmacovigilance methods in process for signal detection. **BCPNN** = Bayesian confidence propagation neural network; **EMEA** = European Medicines Agency; **GPS** = gamma Poisson shrinker; **HCP** = healthcare provider; **MGPS** = multi-item gamma Poisson shrinker; **PRR** = proportional reporting ratio; **PSUR** = periodic safety update report.

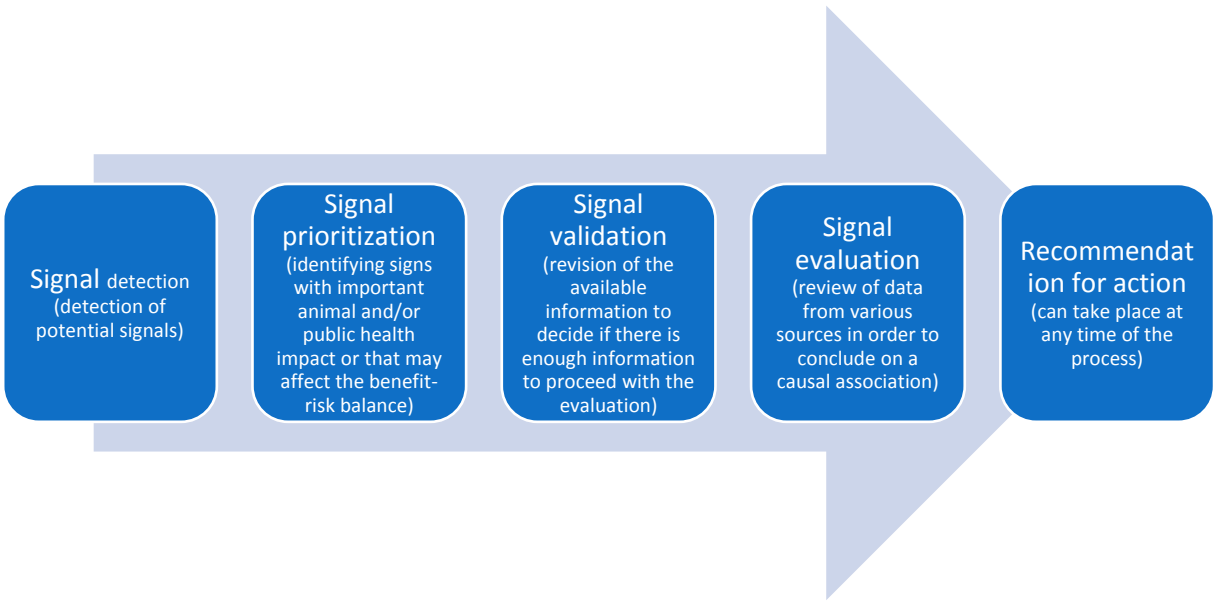
The authorities can perform signal detection in the EVVet database, which has other regions adverse event information, besides the information available in their own database allowing the increase of the power of the analysis.

The principle of the statistical analysis in the databases is to compare the frequency of a specific drug event association with the frequency of this specific event associated with other drugs, the last being considered as the baseline. This comparison will generate signals of disproportionate reporting.

The EMA and the NCA use statistical tolls that retrieve potential signal from the raw pharmacovigilance data and allow to draw conclusions on the statistical association between the use of the VMP and the occurrence of a given event or type of event.

The signal management process follows a specific methodology as mentioned before. The objective is to evaluate if there are new risks associated with that VMP or whether the risks have changed. This methodology is recommended for regulators, as well as MAH. Signal management is a process that occurs over time and evolves in several steps as described in the Figure 18.

Figure 18 – Signal management process (Adapted from EMA, 2015b)



Signal prioritization should verify strength, frequency and consistency of events. It should take into consideration the potential impact to humans exposed or affected (e.g. severity, reversibility, and clinical outcome), the clinical relevance (death or permanent disability), animal impact in general population or vulnerable population and the use of the product (off-label, misuse). Events that are already included as safety warning in the SPC are not considered as new signal but they still need to be assessed to confirm if there is an increased frequency, severity, change on the outcome and compare with the existing information (EMA, 2015b).

Signal validation is performed in order to confirm if there is a causal association and if it should proceed to the next step. It should consider: number of events, animal demographics, the VMP and the adverse event. It should also take into consideration the temporal association, clinical outcome in relation to VMP continuation or discontinuation and presence of alternative causes for the adverse event as well as concurrent medications, reporters MAH/NAC evaluation of causality

and plausibility of a biological and pharmacological relationship and possible VMP interactions and events occurring in specific populations (e.g. breeds) (EMA, 2015b).

Signal evaluation has the objective of drawing conclusions on the presence or absence of a suspected causal association between an adverse event and a VMP, in order to identify the need for additional data collection or risk minimization measures. This evaluation requires a thorough pharmacological and clinical assessment (EMA, 2015b).

Recommendation for action may be the result of the signal evaluation and comes as a logical conclusion after assessing the existing data. These recommendations include: continue monitoring (no change in the surveillance interval), intensive monitoring (change of surveillance interval), additional information from the MAH, targeted PSUR from MAH (targeted monitoring) or post authorisation safety study to investigate the potential safety issue.

When the MAH is requested to perform additional activities, it should be specified the timeframe. Temporary measures can be established until the activities are terminated or even the temporary suspension of the product.

The NAC or the EMA should inform the regulatory network using the existing tolls such as rapid alert and non-urgent information system. The determination of the post-authorisation surveillance interval will normally be of 6 months and then yearly (EMA, 2015b).

6 Comparison of the EMA and four member-states pharmacovigilance systems

Annual pharmacovigilance reports are available at the EMA and national agency's websites, in many cases. Despite having a common European legislation, each MS has their own pharmacovigilance system and local procedures. This diversity is illustrated in the following paragraphs, and some ideas and proposals will arise from this comparison.

6.1 Materials and methods

In this work, the EMA and four Member States' pharmacovigilance systems are compared, using the information made available by the competent authorities.

In the case of France and the UK the last published report reflects the year of 2016, while the EMA, Portugal and Spain already have the 2017 reports available. For the purpose of this analysis, it was decided to take into consideration the reports from 2016 from the five systems.

First, a description of the system, legal and well as some historical background is provided. Then the analysis will focus on the comparison of the total number of adverse event reports per year, the proportion of adverse events per target species and the total number of reports by therapeutic class/class of product.

Finally, a comparison is made; the number of reported adverse events reflect the efficacy of the system.

6.1.1 The EMA reporting system

MAHs and regulatory authorities in the EU have the obligation, for all authorized veterinary medicines, to electronically exchange adverse event reports (Grein, 2009). For the CPs this report has to be done in one single database system, EVVET. The system is operational since 2005 and there has been a yearly increase in reporting (Fig 19), mainly due to an increase in the implementation of the regulatory requirements as well as increased awareness of the value of pharmacovigilance reporting by veterinarians in the field. EVVET is therefore the common European pharmacovigilance database and allows the data-processing and evaluation of adverse event reports, and later the signal management process.

EVVET uses Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) terminology for the reporting of suspected adverse reactions in animals and humans (EMA, 2018c). EMA routinely publishes the lists of clinical terms to be used.

Users can report to EVVET by two different routes: via a Gateway or using the EudraVigilance Veterinary Web Reporting Module (EVWEB) (Grein, 2009). In the case the MAH has its own database (e.g. PVWorks) it will connect to EVVET and allow the automatic transmission on the safety information via the electronic Gateway. EVWEB is a web-based module that will allow the direct report of a case in the case the MAH does not have a Gateway.

In case of safety concerns, the EMA working together with the Rapporteurs responsible for that VMP will inform the CVMP/ PhVWP-V accordingly and decision will be made on possible actions to be taken after the assessment of the situation (European Commission, 2011).

6.1.2 Pharmacovigilance report

The EMA publishes a yearly report of the suspected adverse events that have been submitted in the previous year. The objective of the bulletin is to inform the veterinarians and the public of the main results of pharmacovigilance or post marketing activities for VMP. For that purpose, it contains information on recommendations to amend safety warnings, and some information on the continuous monitoring of CPs (EMA, 2017b).

Although there is a report available regarding 2017, it was decided to analyse the 2016 to be able to compare with the other countries, as some do not have the 2017 report available yet (France and United Kingdom).

The report, published in 2017 referring to 2016 (EMA, 2017b), it can be verified that 18.413 adverse event reports relating to exposure to CPs have been submitted. Of these, 17.859 adverse event reports were related to animals and 554 adverse event reports related to humans exposed to a VMP. In addition, it can be seen an evolution of the number of cases submitted from 2011 to 2016 (Figure 19).

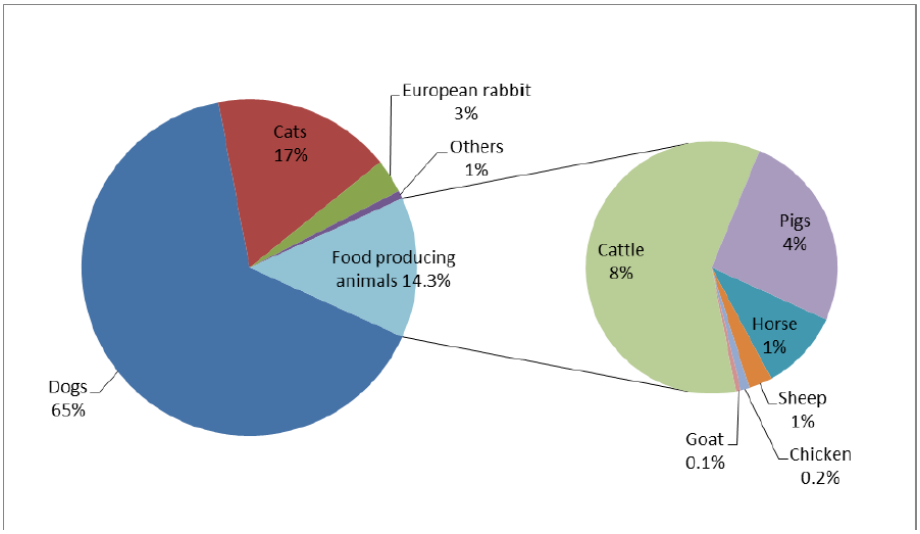
Figure 19: Total number of adverse events for CPs reported to EVVet from within and outside the EU/EEA between 2011 and 2016 (Adapted from EMA, 2017b)

The evolution and increase of the number of reported cases is due to the increase of number of VMP approved via the centralised procedure as well as the increase of awareness of the value of pharmacovigilance reporting from veterinarians. Another reason for this increase is the full implementation of the pharmacovigilance legal requirements by the veterinary pharmaceutical industry (EMA, 2017b).

This improvement is very positive and allows a more effective analysis of the safety information. Nevertheless, there is still concern about the underreporting, especially in the food producing species. The majority of the adverse event reports concern companion animals, with adverse event reports in dogs (11.657) and cats (3.072) representing approximately 80% of the cases.

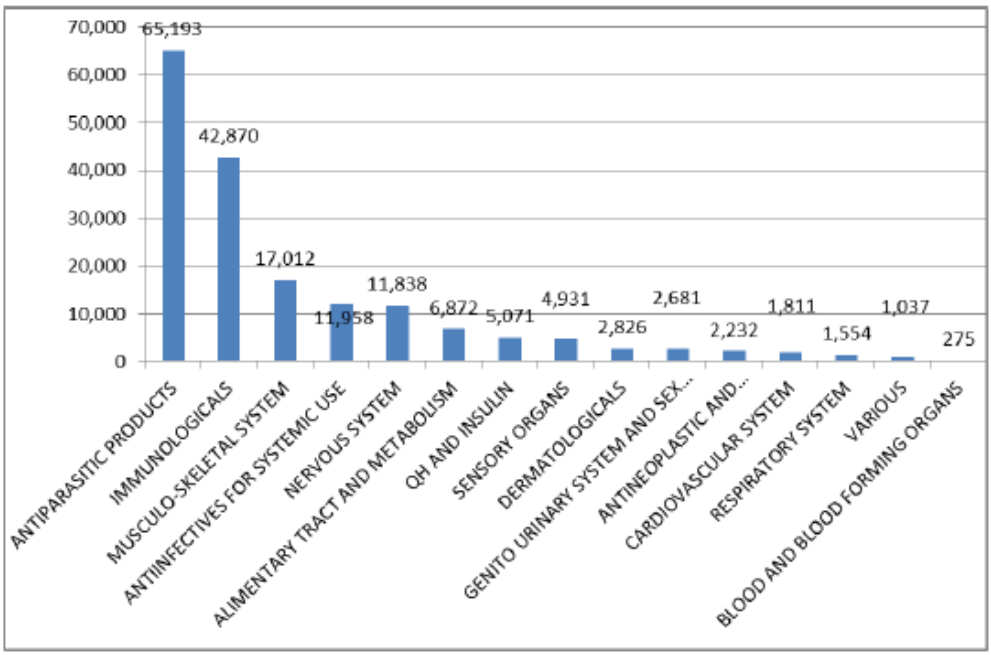
The underreporting from production animals can be verified in this graph (Figure 20) recovered from EMA bulletin. Food producing animal adverse events represent only 14,3% of the cases reported in 2016 (3.130).

Figure 20: Proportion of adverse event reports by species received during 2016 following the use of centrally authorised products (EMA, 2017b)



In addition, it can be seen the therapeutic classes of the products reported according to the ATCvet Code in Figure 21 (*ATCvet is a system for the classification of substances intended for therapeutic use in veterinary medicine, and can serve as a tool for the classification of medicinal products* [https://www.whocc.no/atcvet/atcvet_methodology/purpose_of_the_atcvet_system/]). The majority of the reported cases result from antiparasitic and insecticides, followed by immunologicals, and then musculoskeletal system.

Figure 21 - Total number of reports by ATCVet group in EVVet (1 January 2005-31 December 2016), (EMA, 2017b)



The continuous monitoring of signals and evaluation of PSURs there have been some recommendations related to centrally authorized VMP (EMA, 2017b).

In some cases, the PSUR assessment concluded that there was no concern and no need to amend the product information, but further monitoring is still recommended.

While in others resulted in regulatory measures and an amendment in the sections “Special precautions for use” and “Adverse reactions (frequency and seriousness)” to advert to some serious adverse events resulting from the use of the VMP.

Figure 22 shows some examples and conclusions of the assessment of pharmacovigilance data by the EMA and the concrete measures proposed for each product.

Figure 22: Examples of regulatory actions for CP (EMA, 2017b)

Activyl (indoxacarb)	It was noted the reiteration of neurological disorders (accompanied with deafness and blindness) allergic reactions, lethargy and anorexia in dogs and cats. During the assessment of the last period of surveillance it was concluded that there was no concern to be addressed via amendment of the product literature for the target species cat. However, section 4.6 of the SPC includes many more clinical signs for cats than for dogs; therefore, the MAH was requested to monitor the causal association of neurological signs, allergic reactions, lethargy and anorexia, due to the reiteration of these clinical signs in dogs.
Advocate (imidacloprid/ moxidectin)	Due to the high number of reports regarding "*convulsions*" the MAH was requested to monitor this signal for the next periodic safety updated report (PSUR) and consider updating the product literature, if necessary.
Apoquel (Oclatinib maleate)	The MAH was requested during 2016 to continue monitoring reports involving neoplasia and unexpected signs associated with hepato-biliary, renal and urinary and neurological disorders. It was concluded in October 2016 that no amendments to the product information were necessary as the potential for the occurrence of treatment related neoplasia is currently adequately reflected in section 4.5 of the SPC, and additionally it is noted that section 4.6 of the SPC lists some of the most frequently reported forms of neoplasia including histiocytoma, lipoma and papilloma. No new signals were confirmed relating to the unexpected signs associated with hepato-biliary, renal and urinary and neurological disorders.
Bravecto (Fluralaner)	The MAH was asked to provide a targeted PSUR that should include an extensive analysis and review of all serious reaction reports with neurological disorders, skin and appendages disorders, hypersensitivity/immune mediated reactions and hepatopathy, also with death and death by euthanasia. This targeted PSUR will be assessed by the CVMP and depending on the outcome additionally measures will be taken. In addition, during the last period of surveillance "*lethargy*" has been identified and the MAH was requested to update the SPC to include this term in the SPC.
Broadline (Fipronil, S-methoprene, epinomectin, praziquantel)	On the basis of a relative high number of neurological signs including death in cats, monitoring of these signs has been going on since 2014. The last PSUR included a recommendation for changing section 4.6 of the product literature as follows (changes highlighted in strikethrough and in

6.2 The UK pharmacovigilance system

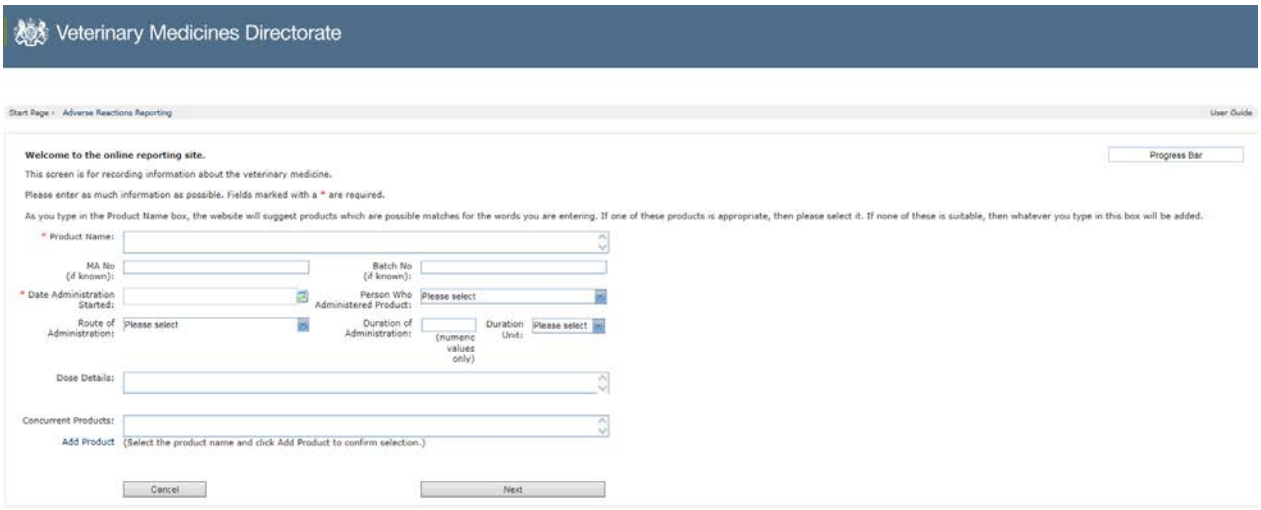
In the case of the UK, the origin of the pharmacovigilance system was the constitution of the Dunlop Committee, named after its Chairman Sir Derek Dunlop. Although this committee worked on a voluntary basis, it started to control the medicines, including the VMP in the UK. Later, legislative measures were established, which resulted in the Medicines Act 1968 (Woodward, 2009). Currently it is the Veterinary Medicines Directorate (VMD) that has the responsibility to deal with the applications for VMP.

The UK pharmacovigilance scheme is called Suspected Adverse Reaction Surveillance Scheme (SARSS) (Woodward, 2009). The SARSS has been operating in its modern computerised form since 1986 (Woodward, 2009) and serves as a good example for the purpose of this work.

6.2.1 The yellow form system

The spontaneous events reporting can be done using the “yellow form” that is made available at the VMD website (VMD, 2018a). Currently the reporting can be done online (Figure 23) and the adverse event case is submitted directly to the VMD.

Figure 23 – Online reporting at the VMD website (VMD, 2018c)



Alternatively, in case the reporters do not have online access, they can report using the VMD “yellow form”, which is a paper formulary.

The form (Figure 24) should be filled in with information on the VMP, as for example the commercial name, batch number, date of administration, amount administered and site and route of administration.

The person reporting the adverse event should also provide contact detail name, address, email address, telephone number. This is very important, as it may be necessary to contact the reporter

to obtain more information or to clarify any questions that may arise during the assessment of the event. The form also has a field to identify the attending veterinarian.

The details of the adverse event should be entered: number of treated animals, number of affected animals, number of deaths (if applicable), and number of animals that recovered, and also information about who administered the product (the pet owner, the veterinarian, other).

There is also a field for stating if the VMP had been administered previously, if there was a reaction in the previous administration.

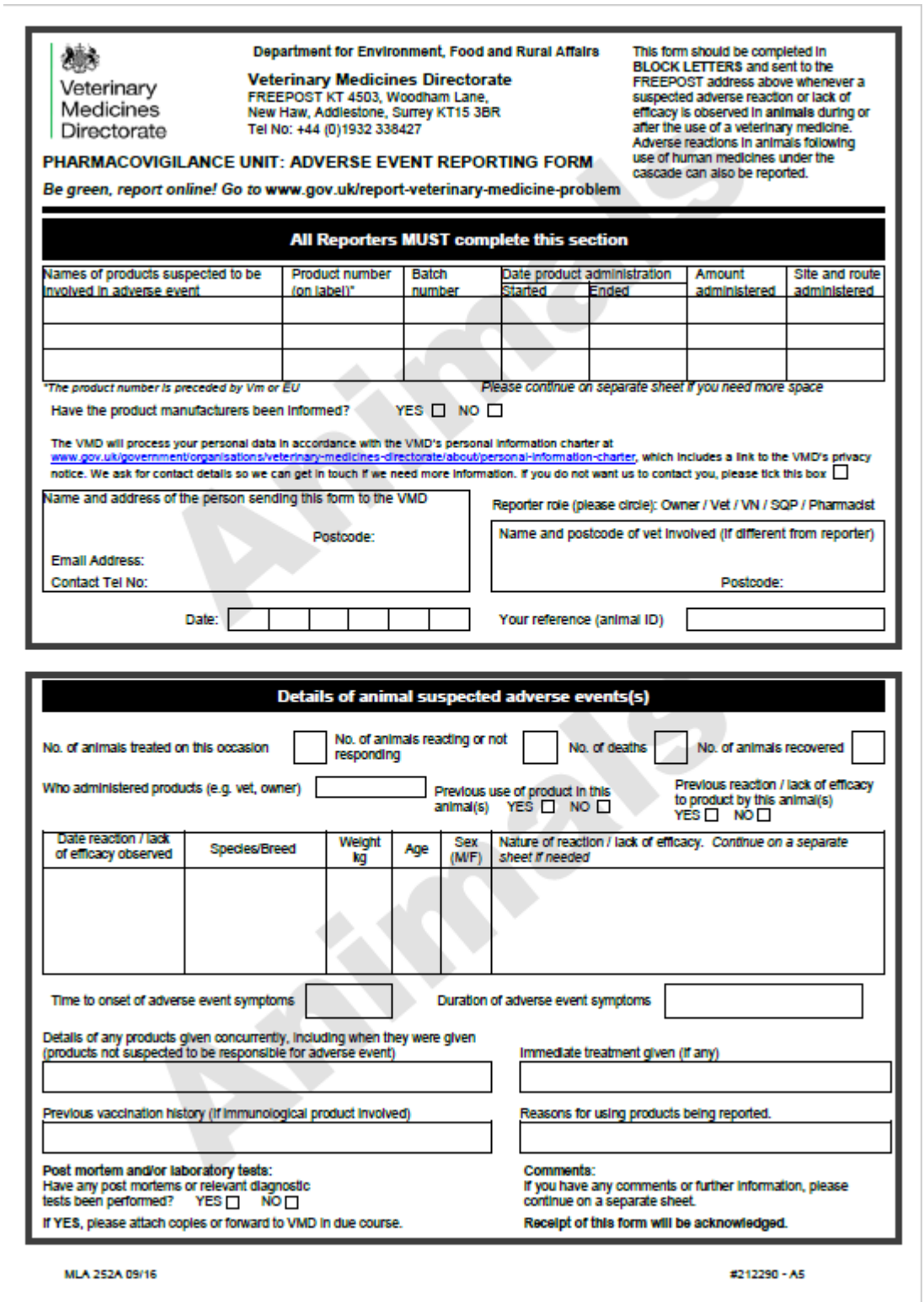
The animal details should also be provided: date of reaction, species/breed, age, weight and nature of the reaction or lack of efficacy. Information on the time of onset of symptoms and duration of the adverse events symptoms should also be provided and are of importance for the assessment of the case.

Information of any products given concurrently, if the symptoms were treated, reasons for using the products being reported and previous vaccination history are also valuable information.

Finally if there is more clinical information available as laboratory exams (blood or histopathologic analysis) or post mortem test, they should also be provided.

The more detailed and precise is the report, the better analysis can be performed from the pharmacovigilance perspective.

Figure 24: The yellow form to report adverse events to the VMD, UK (VMD, 2018a)



Department for Environment, Food and Rural Affairs

Veterinary Medicines Directorate

Veterinary Medicines Directorate
FREEPOST KT 4503, Woodham Lane,
New Haw, Addlestone, Surrey KT15 3BR
Tel No: +44 (0)1932 338427

This form should be completed in BLOCK LETTERS and sent to the FREEPOST address above whenever a suspected adverse reaction or lack of efficacy is observed in animals during or after the use of a veterinary medicine. Adverse reactions in animals following use of human medicines under the cascade can also be reported.

PHARMACOVIGILANCE UNIT: ADVERSE EVENT REPORTING FORM

***Be green, report online! Go to* www.gov.uk/report-veterinary-medicine-problem**

All Reporters MUST complete this section

Names of products suspected to be involved in adverse event	Product number (on label)*	Batch number	Date product administration Started	Ended	Amount administered	Site and route administered

**The product number is preceded by Vm or EU*

Please continue on separate sheet if you need more space

Have the product manufacturers been informed? YES ☐ NO ☐

The VMD will process your personal data in accordance with the VMD's personal information charter at www.gov.uk/government/organisations/veterinary-medicines-directorate/about/personal-information-charter, which includes a link to the VMD's privacy notice. We ask for contact details so we can get in touch if we need more information. If you do not want us to contact you, please tick this box ☐

Name and address of the person sending this form to the VMD

Postcode:

Email Address:

Contact Tel No:

Reporter role (please circle): Owner / Vet / VN / SQP / Pharmacist

Name and postcode of vet involved (if different from reporter)

Postcode:

Date:

Your reference (animal ID)

Details of animal suspected adverse events(s)

No. of animals treated on this occasion

No. of animals reacting or not responding

No. of deaths

No. of animals recovered

Who administered products (e.g. vet, owner)

Previous use of product in this animal(s) YES ☐ NO ☐

Previous reaction / lack of efficacy to product by this animal(s) YES ☐ NO ☐

Date reaction / lack of efficacy observed	Species/Breed	Weight kg	Age	Sex (M/F)	Nature of reaction / lack of efficacy. *Continue on a separate sheet if needed*

Time to onset of adverse event symptoms

Duration of adverse event symptoms

Details of any products given concurrently, including when they were given (products not suspected to be responsible for adverse event)

Immediate treatment given (if any)

Previous vaccination history (if immunological product involved)

Reasons for using products being reported.

Post mortem and/or laboratory tests:
Have any post mortems or relevant diagnostic tests been performed? YES ☐ NO ☐

If YES, please attach copies or forward to VMD in due course.

Comments:
If you have any comments or further information, please continue on a separate sheet.

Receipt of this form will be acknowledged.

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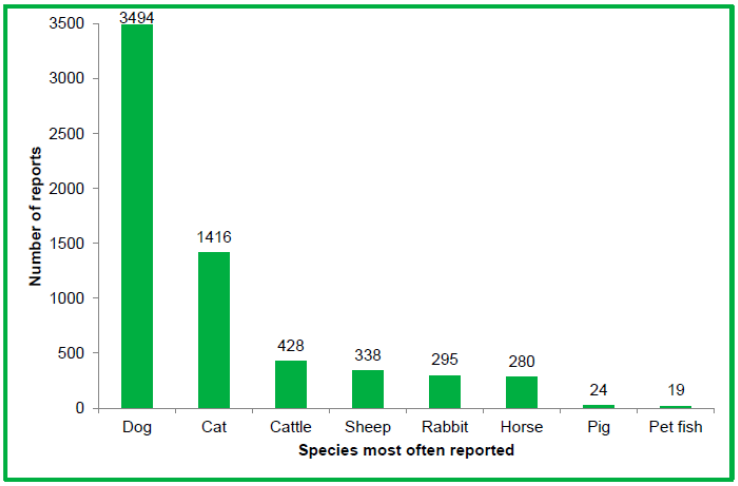
The online reporting has the advantage to be connected to the VMPs database and allows the correct identification of the product, by the use of a drop-down list.

6.2.2 Pharmacovigilance report

The VMD publishes an annual report with a comprehensive overview of the adverse events that took place in the UK (VMD, 2018b). The last report available was published in 2018 and relates to the events that took place in 2016. From this report, we can conclude that the VMD received and processed 6559 adverse event reports (Figure 25). This is an increase of 15% compared to the previous year (VMD, 2018b).

Regarding the spontaneous reports in 2016, the VMD received 6342 animal reports (Figure 25). The majority were from pets: dogs (3494), cats (1416) and horses (280) being the rest distributed between other species as rabbit, canary, donkey, etc. Regarding food producing species, the majority of reports concern cattle (428) and sheep (338).

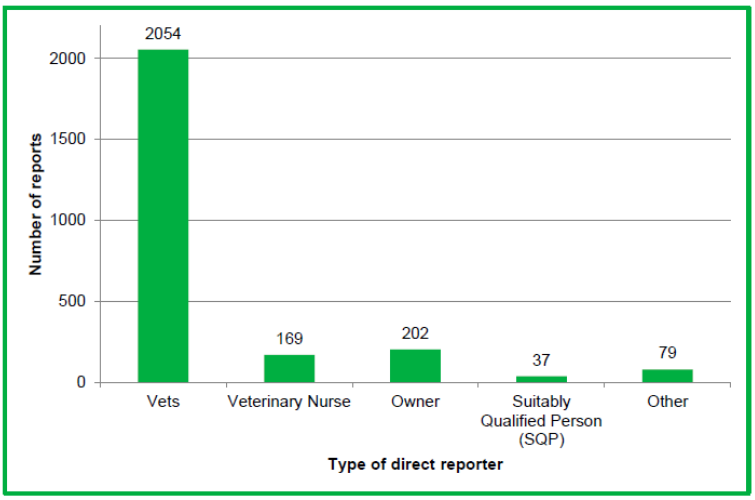
Figure 25 - Number of reports received for the most commonly reported species (VMD, 2018b)



Although there is no legal obligation to report adverse events from the veterinary profession in the UK, there is an existing Code of Professional Conduct that states the veterinarians should report the adverse events either to the MAH or directly to the VMD (Royal College of Veterinary Surgeons, 2016).

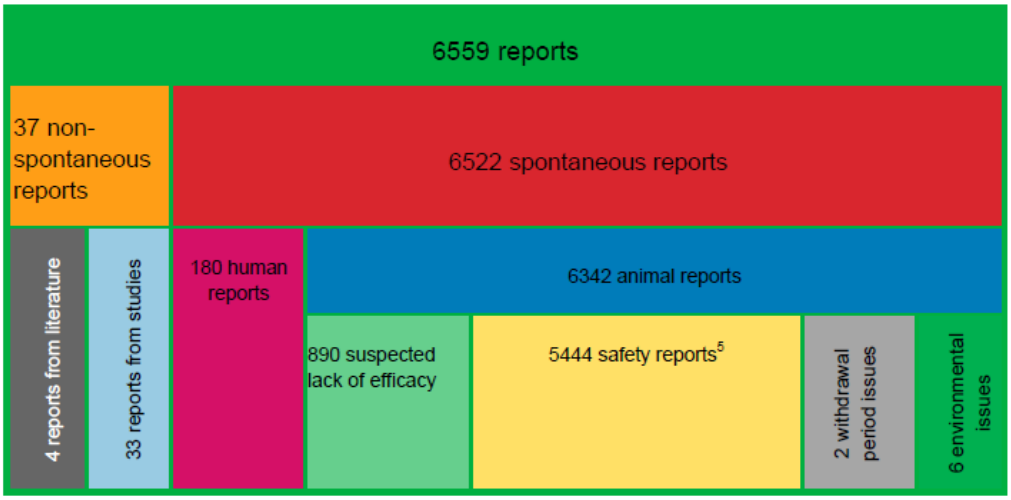
The majority of the cases are reported to the VMD by the MAH (61% in 2016); the remaining 39% come directly from the reporter (VMD, 2018b). The different types of reporters include veterinarians, veterinary nurses, owners, others (Figure 26).

Figure 26 – Number of reports from different types of direct reporters (VMD, 2018b).



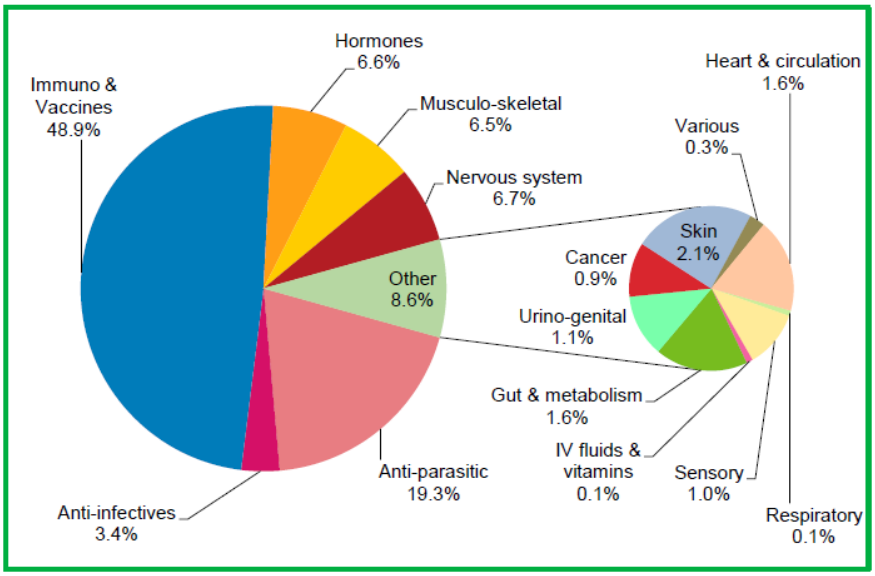
The different types of reports are also analysed (Figure 27): from 6559 reports, 37 are non-spontaneous (4 reports from literature review, 33 reports from studies) and 6522 are spontaneous reports. From the spontaneous, 6342 are animal reports (890 lack of efficacy, 5444 safety reports, 2 withdrawal period issues and 6 environmental issues) and 180 are human reports.

Figure 27 – Different types of adverse event report received (VMD, 2018b)



The reports of authorised VMP are the vast majority (96,6%) and there are VMP that have more adverse events than others. The majority of the adverse events (48,9%) originate from immunologic and vaccines, followed by anti-parasitic (19,3%) and being other type of products the third (8,6%), followed by nervous system (6,7%), musculo-skeletal (6,5%) and hormones (6,6%) (Figure 28).

Figure 28 - Types of authorised VMPs mentioned in spontaneous animal adverse event reports (VMD, 2018b)



It is interesting to verify that the VMD report also has a didactic purpose. There is advice about specific product safety concerns (e.g. advice to seek medical treatment in the case of mineral oil accidental auto-injection, advice of social media information not being reliable, veterinary doctors should check the VMD database to get updated product information, etc.).

6.3 The French pharmacovigilance system

The legal basis from the French pharmacovigilance system was established in 1992 and the system has been operational since 2002. The first Symposium on Veterinary Pharmacovigilance was held at the veterinary School of Lyon, on April 24-25, 1990, organized by the CNITV (Centre National d'Informations Toxicologiques Vétérinaires), under the auspices of French Ministry of Agriculture and the Ministry of Health and Welfare (Keck, 1992).

The French system is based on the existence of pharmacovigilance centres, the anti-poison centres, a pharmacovigilance committee and the L'Agence Nationale du Médicament Vétérinaire part of the Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES-ANMV), which is the French authority for veterinary medicines. The system is an adaptation of the European legislation together with the human French system with the existence of 30 regional centres located at teaching hospitals, with a pharmacovigilance committee. There were two centres located at the veterinary schools of Lyon and Nantes in 2009 (Keck and Pineau, 2009).

6.3.1 The French reporting system

Currently the Centre de Pharmacovigilance Vétérinaire de Lyon (CPVL) is the responsible for receiving the direct reports from the veterinary professionals (ANSES-ANMV, 2017a). The French veterinarians can contact this centre and report the adverse events, usually by telephone. The description of the case is provided and there is an immediate feedback and answers to questions from the reporter and further actions to be taken. The information resulting from these reports is assessed by the pharmacovigilance committee that can recommend the authorities on possible actions to be taken in regard to the VMP. The French legislation obliges the health professionals (veterinarians and pharmacists included) to report serious adverse events (ANSES, ANMV, 2017b). The non-serious events should also be reported, although it is not considered mandatory, it is recommended.

This center collects and evaluates all notifications, except from pharmaceutical companies, and is supported by the CNITV, which ensures a permanently 24 hours per day and 7 days per week of operation, through a common telephone access (Keck & Ibrahim, 2001). All reports can be submitted by the health professionals either directly to the authorities, i.e. ANSES-ANMV and the Veterinary Pharmacovigilance Centre in Lyon, or by MA holders electronically to ANSES-ANMV.

All reports transmitted either to the CPVL or directly to ANSES-ANMV are registered in the national database. Regarding the reports sent to the MA holders, there is a regulatory requirement to transmit reports of all serious cases occurring in France to ANSES-ANMV, by electronic means, within 15 days, as defined in the European legislation (European Parliament and Council, 2001, European Parliament and Council, 2004). However, at present, this requirement to transmit reports as they come does not apply to non-serious cases. Although these are also saved and analysed by the MA holders, they are only brought to the attention of ANSES-ANMV when the MA holders submit their PSURs. These PSURs provide a summary of the cases (serious and non-serious cases collected and analysed by the MA holder) and are transmitted according to a schedule defined by the regulations, as already mentioned in previous chapters. Thus, non-serious cases may only be brought to the attention of ANSES-ANMV as much as three years after they occur. For the purpose of this document, for reports transmitted by MA holders, only those transmitted electronically have been considered.

In France, the reporting model is determined by a decision of the Director General of ANSES. In summary, there are currently several systems available for reporters to transmit these reports to the authorities (Figure 29).

Figure 29 –Various means for reporting an adverse event in France (Adapted from ANSES-ANMV, 2017b)

Printing out and posting the reporting forms that are available on the websites of both ANSES and the CPVL

Telephoning the CPVL, open 24h a day. Following this telephone call, the CPVL sends the reporter a pre-filled report form that should be completed and returned to the CPVL.

Electronic submission via the ANSES website

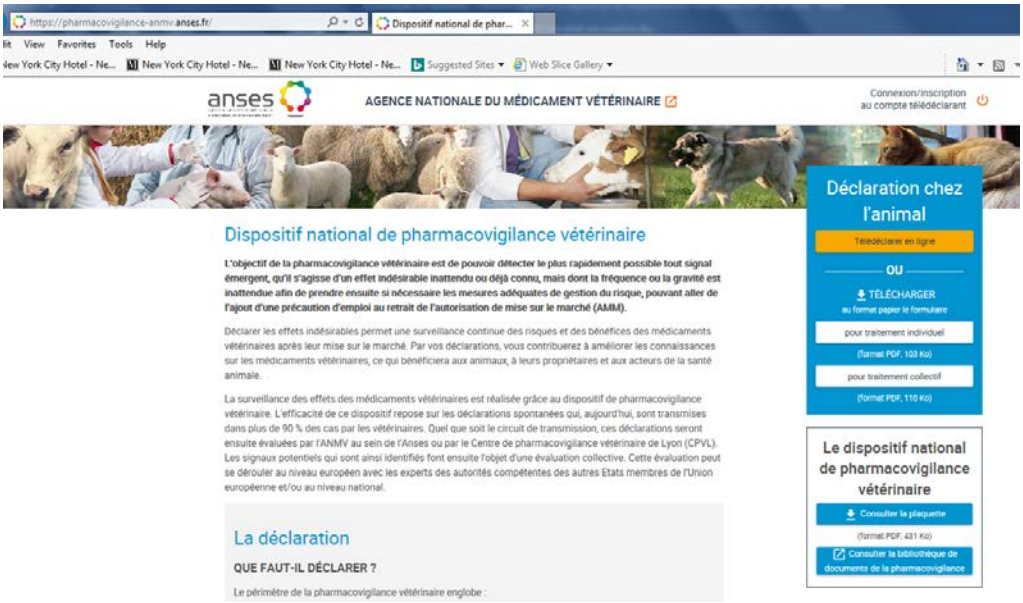
Report to the MAH

6.3.2 Pharmacovigilance report

From the total number of cases in France in 2016 (4113), 987 were submitted directly to ANSES-ANMV, 801 via the web portal.

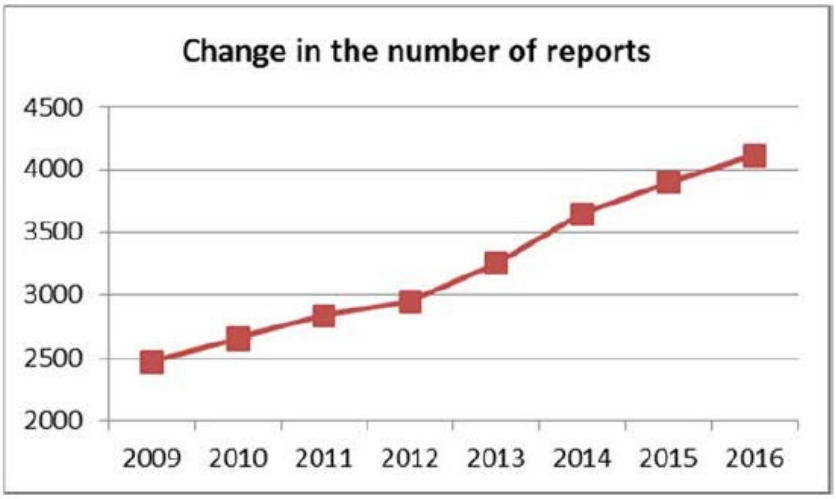
The system allows an *online* report for the veterinarians and it is shown in Figure 30.

Figure 30 - On-line reporting at the ANSES-ANMV website (ANSES-ANMV, 2018)



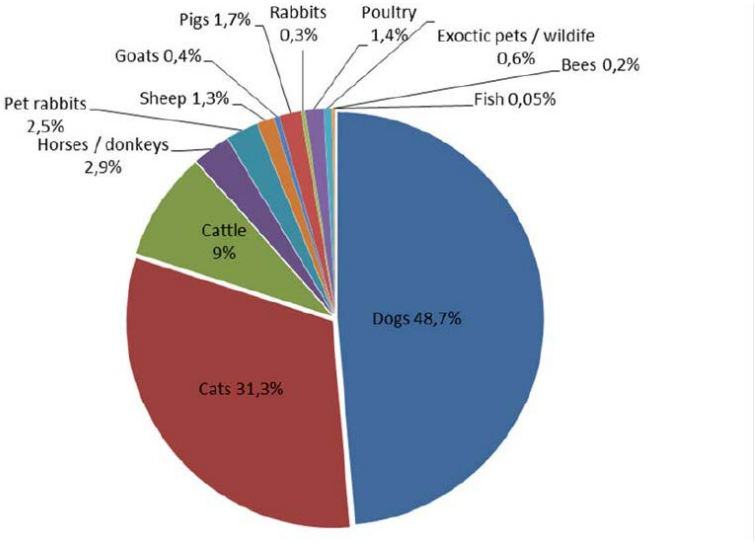
The reports can be sent directly to CPVL, to the MAH and directly to the ANSES-ANMV. These reporting channels represent 40%, 35% and 24%, respectively (ANSES-ANMV, 2017a).
From the ANSES-ANMV report published in 2017, relating to 2016, it can be seen an increase on the cases reported. In 2016 there were 4113 cases received, which mean an increase of 5% when compared to 2015 and 46% increase when compared with 2011 (ANSES-ANMV, 2017a).
The system has allowed a continuous increase in the case reporting, that can be seen in Figure 31.

Figure 31 – Evolution of the number of reports from 2009 to 2016 (ANSES-ANMV, 2017a)



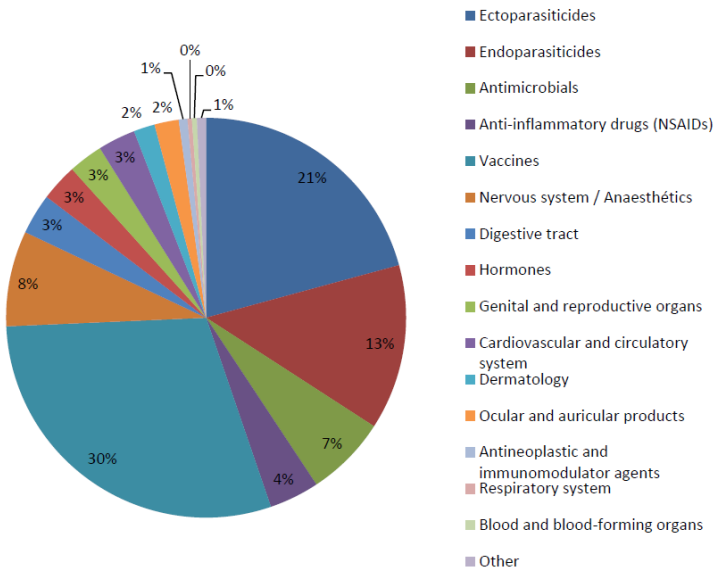
In addition, it can be seen a breakdown of the cases per target species (Fig. 32). Also in France it can be seen a majority of the cases from dog (48,7%), followed by cats (31,3%) and then cattle (9%), see Figure 32.

Figure 32 – Breakdown of reports from 2016 by species (ANSES-ANMV, 2017a)



The French report also reflects the adverse events per therapeutic class where vaccines represent 30% of the cases, ectoparasiticides 21%, endoparasiticides 13% and nervous system/anaesthetics 8% (Figure 33).

Figure 33 – Breakdown of reports from 2016 by therapeutic category (ANSES-ANMV, 2017a)



The report also shows a list of all regulatory measures taken because of pharmacovigilance reasons. Figure 34 shows a few examples of regulatory actions, i.e. SPC modifications that resulted from pharmacovigilance activities.

Figure 34 – Extract of the list of regulatory actions in 2016 (ANSES-ANMV, 2017a)

Name of medicinal product	MA holder	Section modified	Wording of the modified section
ADVOCATE (6 medicinal products)	BAYER HEALTHCARE	*Contra-indications*	Addition of the contra-indication: **Do not use on canaries**
		Special precautions for use in animals	Addition of the precaution: **Imidacloprid is toxic for birds, especially canaries.**
KEXXTONE 32.4 G CONTINUOUS-RELEASE INTRARUMINAL DEVICE FOR CATTLE	ELI LILLY AND COMPANY	*Special precautions for use*	**Ingestion or oral exposure to monensin can be fatal in dogs, horses, other equines or guinea fowl.** Do not allow dogs, horses, other equines or guinea fowl access to formulations containing monensin. **Due to the risk of bolus regurgitation, do not allow these species access to areas where treated cattle have been kept.**
		Adverse reactions	**In rare cases, digestive signs (e.g. diarrhoea, ruminant stomach disorder) have been observed.** **In very rare cases, oesophagus obstruction has been observed.**
FRADEXAM OINTMENT	LABORATOIRE TVM	*Adverse reactions*	~~Unknown.~~ **In very rare cases, local allergic reactions, such as redness, swelling of the eyelids and pain have been observed.**

By chance, one of them is an Elanco product. In this particular case the modification aims the strengthening of an existing safety warning for the protection of accidental ingestion by dogs, horses and guinea fowls, which is a species particular sensible to monensin. This regulatory action is the result of a PSUR evaluation that originated the submission of a variation for the modification of the approved product texts (EMA, 2018b). There is also a modification on the adverse events, an addition of warnings in the target species.

There is also a suspension of a MA described. It concerns VELACTIS (cabergoline) marketed by CEVA Santé Animale to help with dry-off, as part of the management programme for dairy herds. It has a centralised authorisation since March 2016. Serious adverse events, sometimes resulting in the death of dairy cows, have been observed following the use of this product in some countries (mainly Denmark). It was decided to suspend the MA and later recall the product because adverse events continued to be reported.

The 2017 program from the VMD includes a few measures to allow an increase of reporting such as: improvement of the electronic submission website (e.g. creation of a user account, drop down lists explanatory notes), variable reporting data, selecting authorised VMP and associated data (MAH, MA numbers) via interfacing with the VMP database, option of attaching documents.

6.4 The Portuguese pharmacovigilance system

The Portuguese pharmacovigilance system has been established in 1994 with the Portaria nº 487/94, of 4 of July 1994 (Ministério da Agricultura, 1994) and it was initially nominated as "Sistema Nacional de Farmacovigilância e Toxicologia Veterinária" (Batalha, 1993).

This system allowed the direct notification of the adverse events and not necessarily to the MAH. The adverse events submitted were assessed and if necessary preventive measures could be applied. Also the system had an interaction with several institutions as the National Committee for Veterinary Products, the anti-poison centre (Centro de Informação Anti-Venenos), the European Groups, the WHO, OIE (Office International des Épizooties), FDA, etc.

The adverse events were reported using a paper form (Annex I) and sent via regular mail, using the included pre-paid envelop.

Currently the Sistema Nacional de Farmacovigilância Veterinária is regulated by Decree Law nº 148/2008 of 29 July, modified by Decree Law nº 314/2009, of 28 October, which is a transposition of Directive 2004/28/CE, of the European Parliament and Council. The national legislation adds some national specificities regarding pharmacovigilance e.g. the Veterinary Qualified Person responsible for the Pharmacovigilance at a local level. This Qualified Person is responsible for establishing and managing the pharmacovigilance system that allows the retrieval of all the adverse events communicated to the company, their assessment and storage and the submission of serious adverse event reports or events in humans to the national competent authority, Direção Geral de Alimentação Veterinária (DGAV). Providing training to the company's employees about technical information on the marketed products as well as pharmacovigilance are also responsibilities of this qualified person.

Based on the information provided by the reporter or MAH the causality assessment is performed by DGAV. In the case it is necessary, regulatory actions can be initiated as for example: addition of warnings, contra-indications, change in the administration route, product recall, suspension or revocation of the MA of the VMP.

There is published information on the DGAV website, including pharmacovigilance bulletins but recent information is missing. It was decided to conduct an interview with H. Costa, responsible for pharmacovigilance at the Portuguese authority, DGAV (personal interview on 6 September 2018). The pharmacovigilance data originates from this interview.

6.4.1 The Portuguese reporting system

The reports of adverse events can be sent to DGAV by the veterinarians using the paper form and sending it via regular mail or filling in the PDF form provided online and submitting it via email.

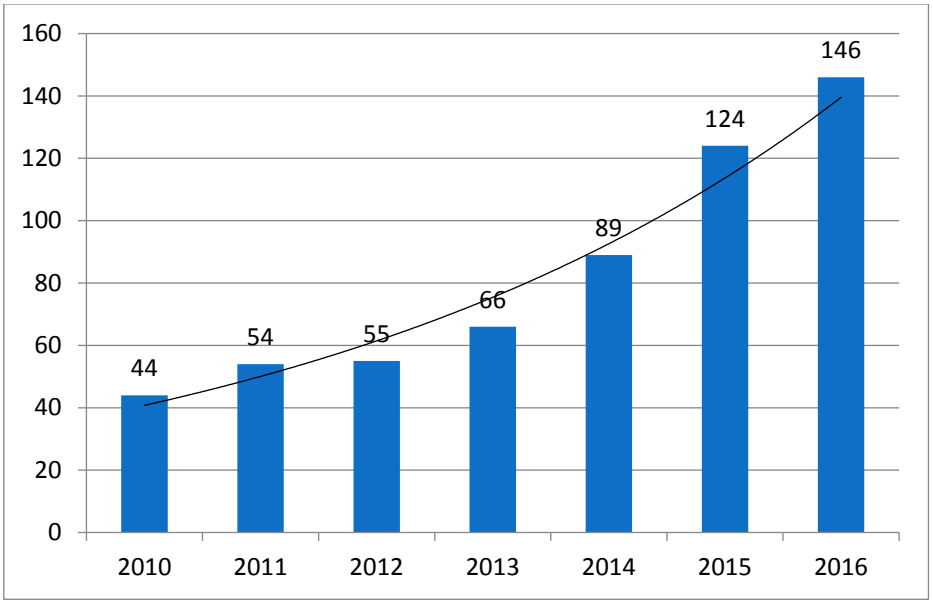
The veterinarians, health care professionals or pet owners can also report to the MAH, which will then report via the electronic platforms (e.g. Eudravigilance).

6.4.2 Pharmacovigilance report

The number of cases reported has been growing since 2010 to 2017 (Costa, 2018). In 2016, 146 cases have been reported.

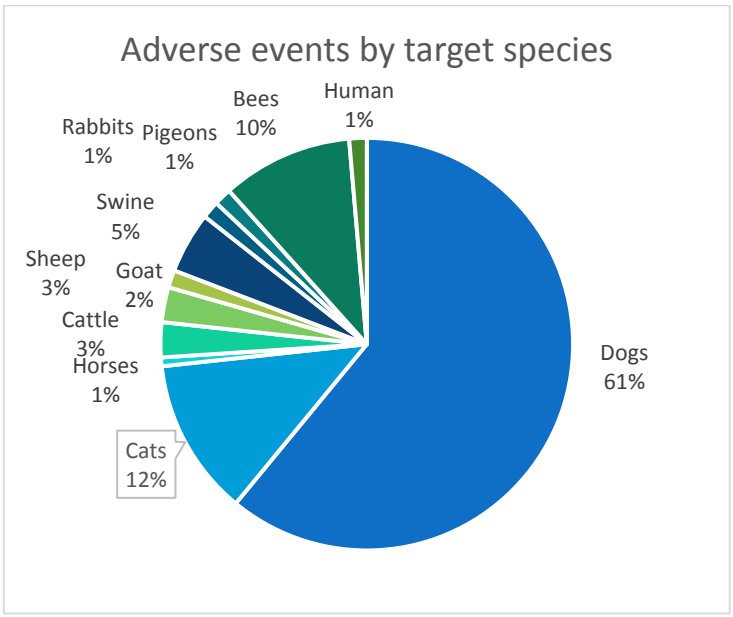
There is stabilization on the number of reports for the last two years (Figure 35).

Figure 35 - Number of reported adverse events reported from 2010 to 2016 (Adapted from Costa, 2018)



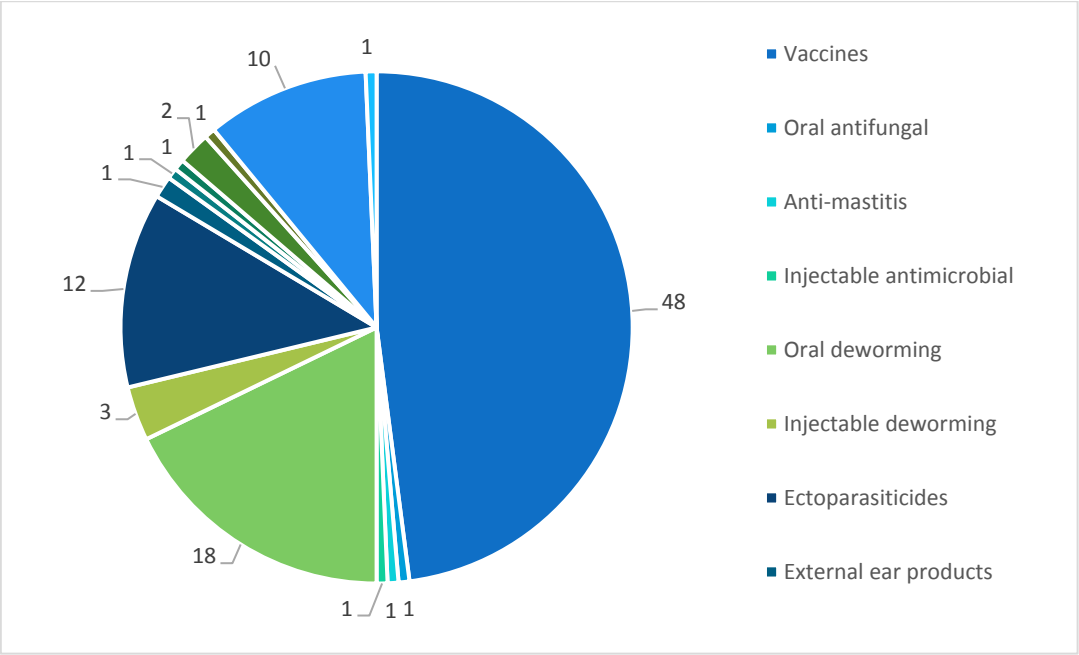
In addition, it can be seen a breakdown of the cases per target species (Fig. 36). Also in Portugal it can be seen a majority of the cases from dog (61%), followed by cats (12% of the cases), bees (10% of the cases), followed by swine (5% of the cases), cattle (3% of the cases), sheep (3% of the cases), goat (2% of the cases), horses (1% of the cases), rabbit (1% of the cases), pigeon (1% of the cases), and human (1% of the cases), as detailed in Figure 36.

Figure 36 – Relative frequency (percentage) of adverse events by target species in 2016 (Adapted from Costa, 2018)



It is also interesting to analyse the report of adverse events per category of product (Figure 37). The graphic below shows the adverse events per therapeutic area. It shows that the majority of the events result from vaccines (48%), followed by oral deworming products (18%) and then ectoparasiticides (12%).

Figure 37 – Relative frequency (percentage) of adverse events by category of product in 2016 (Adapted from Costa, 2018)



Common to other European countries, there are examples of regulatory actions from previous years. The injectable ivermectin in dogs, where a warning has been added for the breeds Collies and Border Collies or crossed breeds, in 2001. There has also been a change in the SPC for enrofloxacin in cats, were a warning for retinotoxic effects including blindness in the case of overdosing, in 2002. Another change in the SPC was the warning about auto-injection with mineral oil products, as vaccines, due to cases of necrosis in case of accidental injections, in 2002.

6.5 The Spanish pharmacovigilance system

The Spanish pharmacovigilance system was established with the publication of Real Decreto 1275/2011, of 16 September, that also established the Governmental Spanish Medicines and Sanitary Products Agency (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS). The formulary for the notification of adverse events by veterinary professionals is made available in the AEMPS website as well as in paper with an enclosed enveloped prepaid by the Agency. This form is known as the green card. There is a form in Spanish available for the MAH to report as well.

Spain has a national pharmacovigilance database called VIGIAVET. This database is connected to the European database, Eudravigilance. VIGIAVET has been one of the first European databases allowing electronic notification of adverse events, with access to MAH and veterinarians (AEMPS, 2018b).

6.5.1 The Spanish reporting system

Reports are received at AEMPS via paper, VIGIAVET or Eudravigilance.

VIGIAVET is an online reporting system but only available upon registration (Figure 38). MAH and veterinarians can report via this system and the adverse event is automatically included in the Spanish database.

Figure 38 - Online access to the Spanish pharmacovigilance database (AEMPS, 2018b)

The Veterinary Medicines Safety Committee (Comite de Seguridad de Medicamentos Veterinarios) has been established to provide technical and scientific support to the AEMPS in all pharmacovigilance matters.

There is also a Spanish VMP Pharmacovigilance System Technical Committee (Comité Técnico del Sistema Español de Farmacovigilancia de Medicamentos Veterinarios). This Committee is responsible for harmonizing criteria and assessing signals in VMP detected by the Spanish pharmacovigilance system. The committee has the participation of the autonomous communities and the Autonomous Cities of Ceuta and Lelilla.

6.5.2 Pharmacovigilance report

The number of reported adverse events in 2016 was 1538 (Figure 39), showing an increase of 14,69% compared to the previous year (AEMPS, 2017). Figure 39 shows the evolution of the number of cases since 2001 to 2016. The increase in 2002 and 2003 was due to a specific problem with some policlostridial vaccines and in 2009 and 2010 to cases due to the vaccination against Blue Tongue disease, which provoked a distortion in the two periods (AEMPS, 2017).

Figure 39 – Evolution of the cases reported in Spain from 2001 to 2016 (Adapted from AEMPS, 2017)

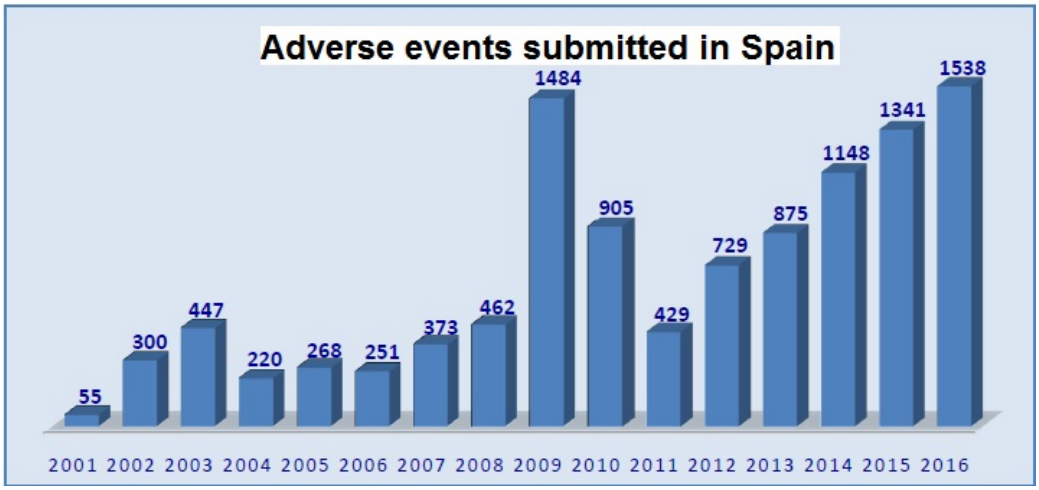
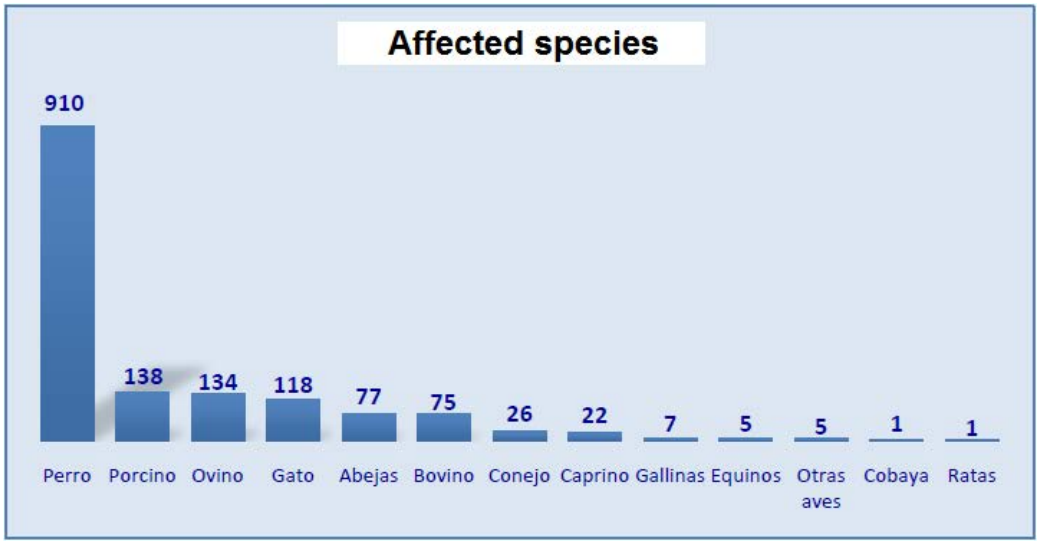


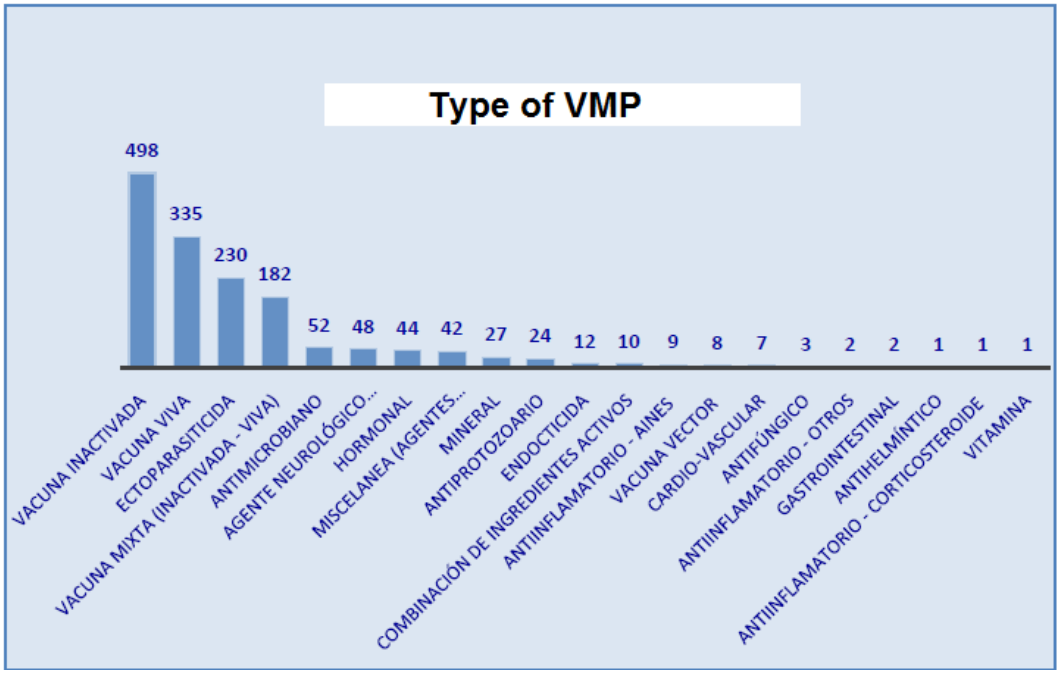
Figure 40 shows the number of adverse events distributed by target species. It can be verified that the most reported species is the dog (910 cases), followed by pig (138 cases), sheep (134 cases) and cat (118 cases). There were also cases reported from bees (77 cases), bovine (75 cases), rabbit (26 cases), goat (22 cases), chicken (7 cases), horses (5 cases), other birds (5 cases), guinea pigs (1 case) and rats (1 case).

Figure 40 – Distribution of adverse events by target species (Adapted from AEMPS, 2017)
Legend: Dogs, swine, sheep, cat, bees, cattle, rabbit, goat, chicken, horses, other birds, guinea pigs and rats.



Similar to the other MS and the EMA, in Spain it can be verified a dominance of adverse events notified from vaccines (1023 cases), followed by ectoparasiticides (230 cases). The distribution of the cases by therapeutic class is shown in the Figure 41.

Figure 41- Distribution of adverse events for type of VMP (Adapted from AEMPS, 2017)
Legend: Inactivated vaccine, live vaccine, ectoparasiticide, mixed vaccine (inactivated and live), antimicrobial, neurological agent, hormonal, miscellaneous, mineral, antiprotozoal, endectocide, combination of active ingredients, non-steroidal anti-inflammatory, vector vaccine, cardio-vascular, antifungal, anti-inflammatory (others), gastrointestinal, anti-helminthic, anti-inflammatory corticosteroids, vitamins.



6.6 Comparison of the EMA system and four European systems

In order to compare the maturity and efficacy of the systems, it was decided to make some data analysis and comparison in Table 3. As previously mentioned, the data originates from the annual pharmacovigilance bulletins from 2016, available in the agency's websites (except for Portugal, which are not available online). Although there was information already available from 2017 in the case of EMA, Portugal and Spain, it the case of France and the UK the reports available were from 2016; the 2017 reports were not yet available for consultation at the moment the websites were last consulted (December 2018).

Table 3 – Comparison of the number of cases reported to the EMA, France, Portugal, Spain and the UK in 2016

	EMA /EU	France	Portugal	Spain	UK
Number of reported AE	18.413	4.113	146	1.538	6.559
Population	512.059.044	67.105.513	10.300.300	46.593.171	65.997.509
Number of reports/ resident population (per 1M inhabitants)	51,9	61,3	14,2	33,0	99,4

The number of reported adverse events reported to the EMA, corresponding to centralized products (corresponding to the EU in a broad sense, but in fact only covers CP) is 18.413, in France is 4.113, in Portugal is 146, in Spain is 1.538 and in the UK is 6.559. There is a distortion regarding the EMA cases: they include third country reporting so in fact they do not correspond to the adverse events that happened only in the EU. Nevertheless, it has been decided to keep the EMA in the comparison of the pharmacovigilance system as it provides an idea of the magnitude of the adverse event reporting.

In human pharmacovigilance, the comparison is made between the number of cases *versus* the country's population, which is the target species in which the medicines are used. In the case of the veterinary situation, this was considered but it was not pursued for two reasons: there is no official data on the animal population in the various countries and because the comparison would have to be made for each target species experiencing the adverse event *versus* the population.

So, it was decided to compare the number of reports per 1 M inhabitants to be able to make a more meaningful comparison between countries that have such a different population (for example, France has 67.105.513 inhabitants while Portugal has 10.300.300). For this purpose, the resident population for each region is provided in the table (PORDATA, 2018).

In the case of the EMA there are 51,9 reports per 1 M inhabitants, France has 61,3 reports per 1 M inhabitants, Portugal has 14,2 reports per 1 M inhabitants, Spain has 33,0 reports per 1 M inhabitants and the UK has 99,4 reports per 1 M inhabitants. Therefore, it can be verified that France and the UK have a reasonable mature and efficacious pharmacovigilance system as the reports are even in greater number than the EMA reports, that include third country reporting, as already mentioned. On the other hand, there is room of improvement for both Portugal and Spain for the increase of the notification.

Another interesting comparison is to consider that regarding human medicine, the OMS has the target of 200 adverse event notifications /1 million inhabitants per year (WHO, 2004). Therefore, it can be concluded that the UK has the most mature pharmacovigilance system, reaching almost 50% of this target and France 30,6%, while the other member states (Portugal 7,2% and Spain 14,5% and the EMA 26%) have a much lower performance, when comparing the number of reports.

Regarding the species reported; the dog is always the most reported species, followed closely by the cat. Cattle is the third species reported. UK has a very important sheep population and farming, that explains the fact that it is the fourth species reported there, while the other MS the pig holds the fourth place. See Table 4 for more detailed information.

Table 4 – Proportion of adverse event reports by species received during 2016 in EMA, France, Portugal, Spain and the UK

	EMA	France	Portugal	Spain	UK
Species	%	%	%	% (calculated)	% (calculated)
Dog	65,0	48,7	61,0	59,2	53,3
Cat	17,0	31,3	12,3	7,7	21,6
Cattle	8,0	9,0	2,7	4,9	6,5
Sheep	1,0	1,3	2,7	8,7	5,2
Pig	4,0	1,7	4,8	9,0	0,4
Chicken	0,2	1,4	0,0	0,5	0,0
Goat	0,1	0,4	1,4	1,4	0,0
Horses	1,0	2,9	0,7	0,3	4,3
Rabbit	3,0	0,3	1,4	1,7	4,5
Pet rabbit	_	2,5	_	_	_
Pet fish	_	0,9		_	0,3
Bees	_	_	10,3	5,0	_
Others	1,0	_	2,7	1,7	_

Regarding the therapeutic classes (Table 5), the presentation of the results is not fully harmonized; some MSs present the results by ATCvet code (e.g. EMA, UK) while others use other classifications (France, Spain and Portugal). Nevertheless, it is still possible to make some analysis. There is a common situation to all the systems analysed: the majority of the adverse events originate from vaccines, followed by ectoparasiticides. NSAIDs and antibiotics vary, as also the presentation of the results from the various sources is not done in a harmonized manner.

Table 5 - Breakdown of reports by therapeutic category in France, Portugal, Spain and the UK during 2016

	France	Portugal	Spain	UK
Vaccines	30	48	67	48,9
Ectoparasiticides (UK antiparasitic, EMA Antiparasitic and insecticides)	21	12	15	19,3
NSAIDs	4	0	1	_
AB	7	1	3	3,4
Endoparasiticides	13	18	1	_
Musculo-skeletal	_	_	0	6,5
Nervous system/Anesthetics	8	2	3	6,7
Hormonal	3	_	3	6,6
Other	14	19	8	8

The EMA results are not compared in this table as the graph in the EMA bulletin presents the results in absolute number and accumulated until 2016. Nevertheless, it can be verified as per Figure 21 that the vast majority of cases arise from parasiticides and insecticides, followed by immunological products, and musculo-skeletal system.

6.7 Discussion

The pharmacovigilance systems from the EMA and the four MS have been compared concerning the way they are organized, and an analysis is performed regarding the number of adverse events reported per year, affected target species and therapeutic class of the products involved in the adverse events.

The English and the French systems seem to be the most mature systems that already incorporate new technologies as online reporting possibility, for the veterinarians and general public. The UK has the highest number of adverse events reported, but the French system was found to be a more complete system, with the involvement of the Academia and the students, the anti-poison centres that ensure a 24h response to the veterinarian need for support. In addition, the system allows an interactive reporting where the veterinarian can not only notify the adverse event but also get advice on the clinical case. There is also a response to the adverse event report, with the written information on the case and the causality assessment.

The Spanish system already has online reporting possibility (for registered users) but still has a low number of adverse events reported. The Portuguese system still relies on paper/email reporting systems (for the general public) and has a very low number of cases. There are no recent pharmacovigilance bulletins made available in the competent authority website.

7 How to improve notification/report of adverse events

7.1 The role of the Veterinarian in the safety of the VMP

VMPs are widely used in the animals treated in the EU. In a small number of cases an adverse event might occur during or a period after the use of the medicine. Veterinary professionals (as well as animal owners, farmers, pharmacists) can and should report the event either to the competent authority or to the company that markets the product.

The European Legislation encourages Member States to enforce the obligation for the veterinarians to report adverse events: “The Member States may impose specific requirements on veterinary practitioners and other health care professionals in respect of the reporting of suspected serious or unexpected adverse reactions and human adverse reactions…” (European Parliament and Council, 2001). However, there are different approaches in the various member states. In the UK, for example, there is recommendation about reporting adverse events from the professional organizations as the Code of Professional Conduct (Royal College Veterinary Surgeons, 2016) while other Member States have decided to enforce it by legislation, as it is the case of France were it is a legal obligation to report suspected serious and/or unexpected adverse reactions in animals and human adverse reactions (ANSES, 2017b).

The veterinary practitioner plays a key role in the pharmacovigilance system. He/she is the person that has more information about the animals, adverse events and the conditions of use. It is of outmost importance that the veterinarians understand the pharmacovigilance system as a way to make the VMP the safest possible for the animals at their care. The reporting of the adverse events (or lack of efficacy) helps to build knowledge about the VMPs and leads to its better and safer use.

The adverse event may result from the prescription, the administration or the clinical act. Regarding prescription, veterinarians should ensure that they have the current product information by checking the EMA or national databases where the most updated SPCs and product information are available. In addition, they should ensure that the necessary information is provided to the animal owner as for example the correct posology, mode of administration, contraindications, and special precautions. Concerning the administration, also special precautions for administration need to be understood, for example in the case of mineral oil adjuvated vaccines were medical treatment should be sought immediately, in case of accidental injection. In the case of the clinical act, care must be taken, especially in the case of injectable products, where appropriate administration route, amounts to be administered, hygiene and asepsis at the point of injection.

7.2 Under-reporting of spontaneous adverse events

Veterinarians should report the adverse events, as they are made aware. As referred in the previous point, it is either a legal requirement or a recommendation from the professional code of conduct.

However, it is well known that there is underreporting of adverse events in VMPs, especially on the animal farm area, and this fact constitutes the major problem in the pharmacovigilance system as it relies greatly in the spontaneous adverse events reporting.

The underreporting can mean that a given adverse event is not reported and for that reason, it will not be assessed. In addition, even if the events are reported, the real incidence of the events might not correspond to the real situation.

There is a need for the system to be populated with data and this means that there should be involvement of the veterinary profession as well as the academia, NCAs, professional organizations, etc.

7.2.1 Under-reporting in Human Medicine

There are several published references about underreporting from human medicines (Rawlins, 1988, Alvarez-Requejo, Carvajal, Bégaud, Moride, Veja & Martín Arias, 1998, Hazell & Shakir, 2016). It has been considered to be of relevance its inclusion in this work as it provides a quantification of the extent of the under-reporting and can give an idea of the situation in VMPs.

A study has been conducted in Spain (Alvarez-Requejo, 1998) with general practitioners from a specific region (Castilla and León). A random sample of general practitioners established a “sentinel network” that had to report all the adverse events from three non-consecutive days. These results were then compared with the spontaneous adverse event reporting from general practitioners in the same region, during the period of 12 months. Approximately only 0,08 per cent

of the cases were reported from the total observed adverse events: “one out of 1114 observed adverse events” (Alvarez-Requejo, 1998). Although there is a variety of estimations of rates of under-reporting, all authors agree that the rate is enormous and that there is a positive selection, remaining unreported the less serious and better known (Alvarez-Requejo, 1998).

There are other published references that estimate doctors report approximately only 10 to 15 per cent of the observed adverse events (Rawlins, 1988).

The reasons for the lack of reporting from medical doctors include lack of time, different care priorities, and uncertainty about the drug causing the adverse event, difficulty in accessing forms, lack of awareness of the requirements of reporting and lack of understanding of the purpose of spontaneous reporting systems. Well-known and non-serious adverse events are less likely to be reported (Hazell, 2006).

7.2.2 Under-reporting in veterinary medicine

As mentioned previously, spontaneous adverse event reports are a very important source of safety information on VMPs. However, as already mentioned, the underreporting constitutes the major drawback in this system.

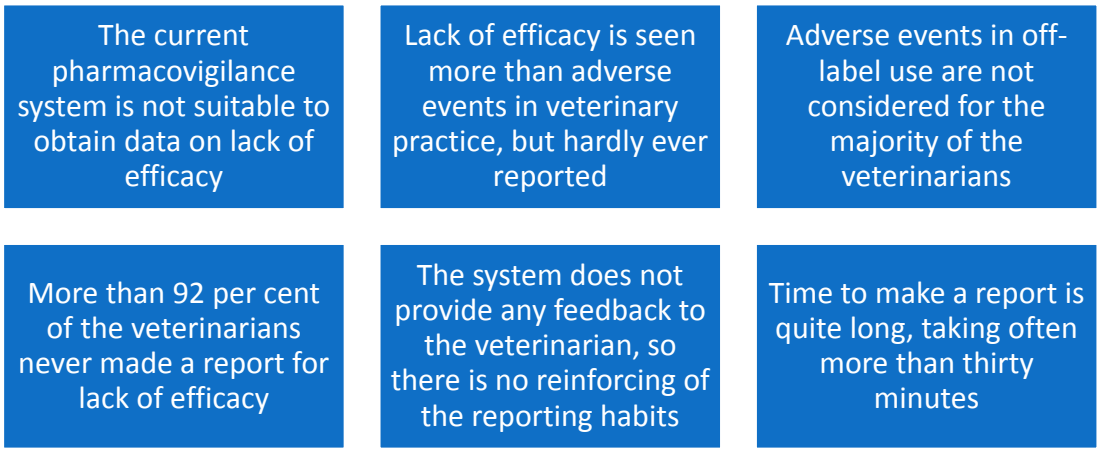
Pharmacovigilance is of vital importance to ensure safe and effective treatments in practice.

The Federation of Veterinarians of Europe (FVE) and the EMA decided to conduct a survey in 2015 “to gain a better insight into the adverse event reporting habits of veterinary practitioners and the level of information on reported adverse events that flows back to them” (Briyne, Gopal, Diesel, Iatridou & O’Rourke, 2017).

The participants were veterinarians from 57 countries, including EU and European Free Trade Association (EFTA) with a target audience of approximately 108 000 practicing veterinarians, from which a total of 3545 veterinarians responded (approximately 3,1 per cent).

There are a number of facts around the reporting of adverse events in the veterinary profession, that raised from this survey and which are reflected in Figure 42.

Figure 42 – Fact around under-reporting (Adapted from Briyne et al., 2017)



There is a need for improvement in the under-reporting in veterinary medicine and some of the possible actions could be: create motivation for the veterinarians to report by understanding that the information is useful and enables the improvement of the VMPs; make reporting more quick and easy (e.g. via mobile applications, via practice management system, via social media), improve practitioner awareness of the importance and the value of adverse event reporting; greatly improve the feedback, need for structural relationships between competent authorities for pharmacovigilance and veterinary organizations, and for new products or products with concerns, the MAHs should be encouraged to do pro-active searching (signal detection) (Briyne et al., 2017).

8 Future developments in pharmacovigilance Legislation

The EU pharmacovigilance system has the objective of ensuring the continuous assessment of the risk-benefit balance of the VMP.

A revision of the European Legislation of VMP is currently undergoing. The current Directive and Regulation referred in the chapter “Legal Basis and Regulations”, with be replace by one unique Regulation. It is estimated that the new Regulation will be published in early 2019 and have a transition period for implementation of three years (European Commission, 2018).

The future pharmacovigilance system will eliminate some administrative burdens as the five-year renewal (the administrative act in which the MAH had to submit a renewal of the VMP after five years of the granting of the initial MA) and the PSUR submission and rely more in the signal detection system in order to ensure a continuous assessment of the benefit-risk balance.

The EMA will establish and maintain a pharmacovigilance database that will enable the inclusion of not only the adverse event cases but also the results and outcomes of signal management process and other pharmacovigilance relevant information. There will also be a product database for the EU with information on all the authorized VMP and the two databases will be interconnected.

The MAH will establish a pharmacovigilance system master file that provides a detailed description on the pharmacovigilance system for its authorized VMPs. The MAH also shall carry out signal management process for its VMPs, considering the sales data and other relevant pharmacovigilance data. This data may include scientific information resulting from scientific literature reviews.

9 Conclusions

VMPs are highly regulated in Europe and Pharmacovigilance has increased its importance in the Regulatory area.

Pharmacovigilance is one of the legal requirements for the MAH and in some European countries there is even a legal obligation for the veterinarians to report adverse events. There is a need to submit a dossier that includes the DDPS in order to gain a marketing authorisation and be able to place the VMP in the European market. The MAH has to continuously monitor the VMPs that are placed in the market and perform a benefit-risk assessment throughout the product's life. The MAH needs to have a QPPV in Europe at his service to make sure that a pharmacovigilance system is in place and all adverse events that are reported to all personnel are handled and reported to the competent authorities.

Information on the product safety can be obtained from spontaneous reports that are compiled in the PSUR and from continuous monitoring by signal detection. Pharmacovigilance has developed greatly in the recent years, especially due to the existence of large databases that allow the use of statistical tools to perform signal detection to have a good surveillance system.

The PSUR assessment as well as some serious event reporting lead to updates in the product information as well as specific measures: continuous monitoring or investigation of a specific signal, elaboration on a targeted PSUR or even amendment of the product literature.

The pharmacovigilance systems from the EMA and four MS are described and there is an analysis performed regarding the number of adverse events reported, target species and therapeutic class. Namely, the French and the UK pharmacovigilance system are explained and analysed as a good example of mature systems that already incorporate new technologies as online reporting possibility. Although the UK has the highest number of adverse events reported, the French system was found to be a more complete system, with the involvement of the Academia and the students, the anti-poison centres that ensure a 24h response to the veterinarian need for support. In addition, the system allows an interactive system where the veterinarian can not only notify the adverse event but also get advice on the clinical case. There is also a response to the adverse event report, with the written information on the case and the causality assessment.

Underreporting constitutes a challenge for the pharmacovigilance system, as the reported events do not correspond to the reality of the use of the product. For that reason it is important to rely on a good signal detection system while in parallel reporting of adverse events should be encouraged. Some initiatives could improve the reporting of adverse events (or lack of efficacy) for example: facilitate the reporting by building online reporting or electronic tools; providing education to undergraduates; encourage veterinarians to report by sharing the importance and value of pharmacovigilance; improve feedback when people report adverse events and sharing relevant information on a regular basis by publishing periodic bulletins/newsletters.

The future pharmaceutical regulation will bring some changes to the existing system, namely the disappearance of the mandatory PSUR submission therefore eliminating some administrative burdens for the MAH. In addition, the creation of a European database and the connection to the pharmacovigilance database to which both NCA and MAH will gain access, will allow the strengthening of the signal management process as a pillar of the pharmacovigilance system.

The veterinarian is of outmost importance for the pharmacovigilance science. Both on the field by ensuring the good use of the VMP and by reporting the adverse events as well as in the pharmaceutical companies by working in the pharmacovigilance department or as qualified person for pharmacovigilance.

Because finally the main objective of pharmacovigilance is to ensure the protection of our patients and food safety.

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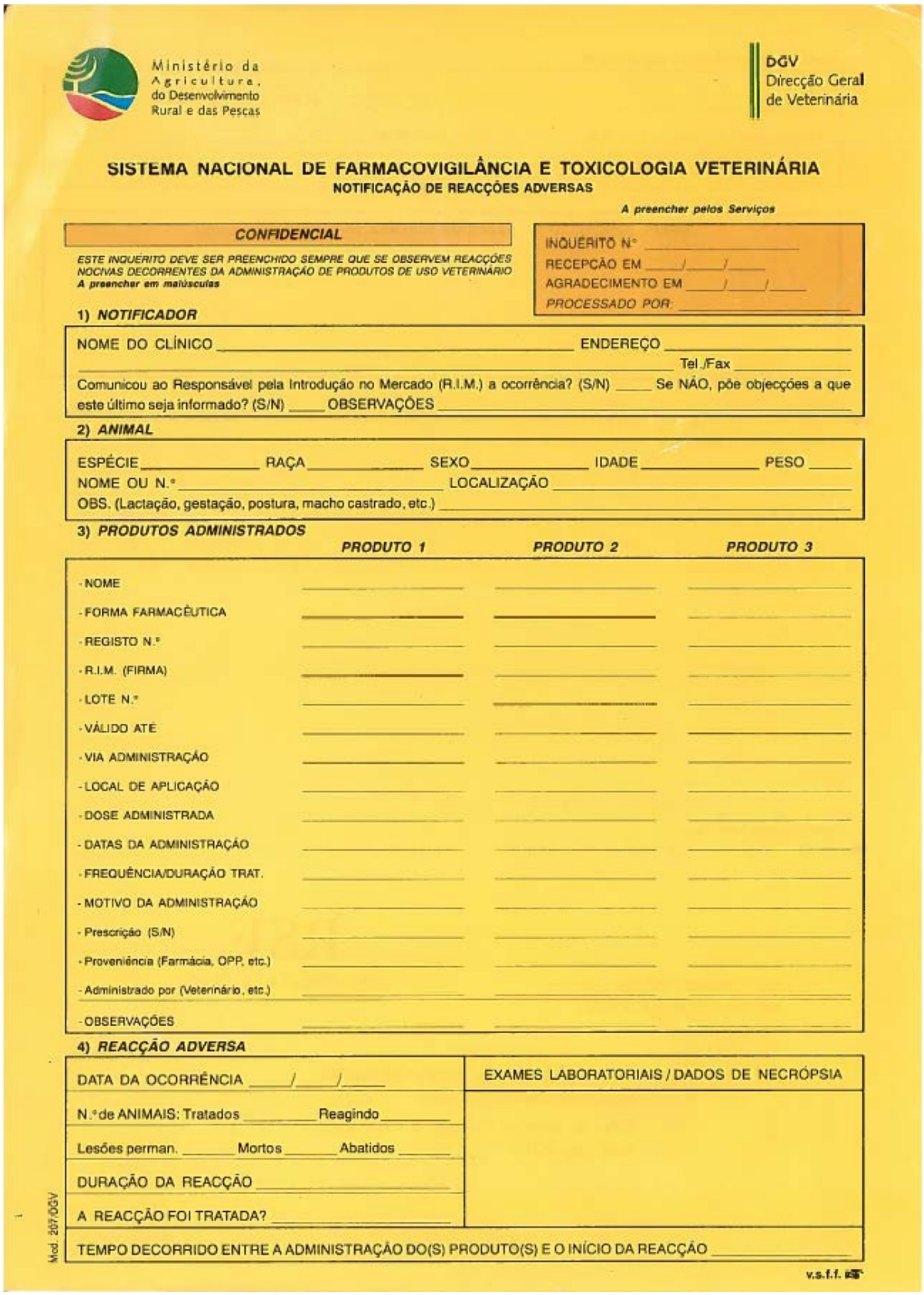
Annex I – The first Portuguese official formulary for reporting adverse events and the pre-paid envelope for regular mail (Costa, 2018)



Ministério da Agricultura, do Desenvolvimento Rural e das Pescas

DGV Direcção Geral de Veterinária

SISTEMA NACIONAL DE FARMACOVIGILÂNCIA E TOXICOLOGIA VETERINÁRIA

NOTIFICAÇÃO DE REACÇÕES ADVERSAS

A preencher pelos Serviços

CONFIDENCIAL

ESTE INQUERITO DEVE SER PREENCHIDO SEMPRE QUE SE OBSERVEM REACÇÕES NOCIVAS DECORRENTES DA ADMINISTRAÇÃO DE PRODUTOS DE USO VETERINÁRIO
A preencher em maiúsculas

INQUÉRITO N.º _____
RECEPÇÃO EM ____/____/____
AGRADECIMENTO EM ____/____/____
PROCESSADO POR: _____

1) *NOTIFICADOR*

NOME DO CLÍNICO _____ ENDEREÇO _____
_____ Tel./Fax _____
Comunicou ao Responsável pela Introdução no Mercado (R.I.M.) a ocorrência? (S/N) ____ Se NÃO, põe objecções a que este último seja informado? (S/N) ____ OBSERVAÇÕES _____

2) *ANIMAL*

ESPÉCIE _____ RAÇA _____ SEXO _____ IDADE _____ PESO _____
NOME OU N.º _____ LOCALIZAÇÃO _____
OBS. (Lactação, gestação, postura, macho castrado, etc.) _____

3) *PRODUTOS ADMINISTRADOS*

	PRODUTO 1	***PRODUTO 2***	***PRODUTO 3***
- NOME			
- FORMA FARMACÊUTICA			
- REGISTO N.º			
- R.I.M. (FIRMA)			
- LOTE N.º			
- VÁLIDO ATÉ			
- VIA ADMINISTRAÇÃO			
- LOCAL DE APLICAÇÃO			
- DOSE ADMINISTRADA			
- DATAS DA ADMINISTRAÇÃO			
- FREQUÊNCIA/DURAÇÃO TRAT.			
- MOTIVO DA ADMINISTRAÇÃO			
- Prescrição (S/N)			
- Proveniência (Farmácia, OPP, etc.)			
- Administrado por (Veterinário, etc.)			
- OBSERVAÇÕES			

4) *REACÇÃO ADVERSA*

DATA DA OCORRÊNCIA ____/____/____ | EXAMES LABORATORIAIS / DADOS DE NECRÓPSIA

N.º de ANIMAIS: Tratados _____ Reagindo _____

Lesões perman. _____ Mortos _____ Abatidos _____

DURAÇÃO DA REACÇÃO _____

A REACÇÃO FOI TRATADA? _____

TEMPO DECORRIDO ENTRE A ADMINISTRAÇÃO DO(S) PRODUTO(S) E O INÍCIO DA REACÇÃO _____

Mod. 207/DGV

v.s.f.f.

Annex I (continuation)

REACÇÃO OCORRIDA NO HOMEM

NOME _____ SEXO _____ IDADE _____

NATUREZA DA EXPOSIÇÃO (Picada, contacto com a pele, ingestão, etc.) _____

RECEBEU ASSISTÊNCIA MÉDICA? _____

BREVE DESCRIÇÃO DA REACÇÃO ADVERSA (SINTOMAS, lesões, etc.)

LOCAL _____, *em* ____/____/____ *ASSINATURA* _____

DOBRE POR AQUI, PRIMEIRO

DEPOIS, DOBRE POR AQUI

RSF

NÃO PRECISA DE SELO

AUTORIZADO PELOS CTT
NO SERVIÇO NACIONAL

DIRECÇÃO GERAL DE VETERINÁRIA
NÚCLEO DE FARMACOVIGILÂNCIA
Largo da Academia Nacional de Belas Artes, 2
1249-105 LISBOA

Annex II - La tarjeta verde (AEMPS, 2018a)

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS VETERINARIOS

Fax: 91 822 54 43 Tel: 91 822 54 01 E-mail: fv_vet@aemps.es Página Web: www.aemps.gob.es

CONFIDENCIAL
Para uso exclusivo de la AEMPS
Número de Referencia.

IDENTIFICACIÓN	**NOMBRE Y DIRECCIÓN DEL NOTIFICADOR**	**NOMBRE Y DIRECCIÓN/ REF. DE LA EXPLOTACIÓN / DEL PACIENTE**
Problemas de Seguridad: en animales ☐ en personas ☐ **Presunta falta de eficacia** ☐ **Probl. de tiempos de espera** ☐ **Problema medioambiental** ☐	Veterinario ☐ Farmacéutico ☐ Otros ☐ Nombre : Dirección : Teléfono: Fax :	

PACIENTE(S) *Animal(es)* ☐ *Persona (s)* ☐ *(en personas rellenar sólo la edad y el sexo)*

Especies	Raza	Sexo	Estado	Edad	Peso	Razón del tratamiento
		Hembra ☐ Macho ☐	Castrado ☐ Preñada ☐			

MEDICAMENTO VETERINARIO ADMINISTRADO ANTES DE LA APARICIÓN DE LA SUPUESTA REACCIÓN ADVERSA

(si se administraron más de tres medicamentos simultáneamente, por favor duplique este formulario)

	1	**2**	**3**
Nombre del medicamento veterinario			
Forma farmacéutica y concentración (pe: comprimidos de 100 mg)			
Número de registro			
Número de lote			
Vía y lugar de administración			
Dosis / Frecuencia (posológica)			
Duración del tratamiento /Exposición Día de inicio: Día final:			
¿Quién administró el medicamento? (veterinario, propietario, otro)			
¿Cree que la reacción se debe al medicamento?	Si ☐ / No ☐	Si ☐ / No ☐	Si ☐ / No ☐
¿Ha sido informado el Laboratorio?	Si ☐ / No ☐	Si ☐ / No ☐	Si ☐ / No ☐

Annex II (continuation)

FECHA DE LA SUPUESTA REACCIÓN ADVERSA __/__/__	**Tiempo transcurrido entre la administración del medicamento y la reacción** en minutos, horas o días	Nº animales tratados ____ Nº animales con signos ____ Nº animales muertos ____	Duración de la reacción adversa en minutos, horas o días

DESCRIPCIÓN DE LA REACCIÓN *(Problemas de seguridad en animales o en personas / Presunta falta de la eficacia esperada / Problemas con el tiempo de espera / Problemas medioambientales) – Por favor, describalos. Indicar también si la reacción ha sido tratada. ¿Cómo y con qué y cuál fue el resultado?*

OTRA INFORMACIÓN RELEVANTE (adjuntar la documentación oportuna, pe. estudios realizados o en marcha, informes médicos, informes de necropsias).

REACCIONES EN PERSONAS (Si el caso se refiere a personas, por favor complete los datos que figuran más abajo).

- Contacto con el animal tratado ☐
- Ingestión oral ☐
- Exposición tópica ☐
- Exposición ocular ☐
- Exposición por inyección ☐ dedo ☐ mano ☐ articulación ☐ otro ☐
- Otro (deliberado …) ☐

Dosis recibida:

Si no desea que su nombre y dirección se envíe al laboratorio para recabar más información, por favor indíquelo en este cuadro ☐

Fecha: **Lugar:** **Nombre y firma del notificador:**

Punto de contacto (teléfono) (si difiere del número indicado en la primera página)

Annex III – Current Formulary for the notification of adverse events in Portugal (DGAV, 2018)

Formulário comunitário veterinário para notificação de suspeita de reação adversa destinado a veterinários e profissionais de saúde

Formulário a ser enviado à **Direção Geral de Alimentação e Veterinária** **Campo Grande, 50.** **1700-093 LISBOA** **Faxe 217 808 251** **Telefone 217 808 221** **farmacovigilancia.vet@dgav.pt** **Endereço Web dgv.min-agricultura.pt**	**CONFIDENCIAL** *Somente para uso oficial* **Número de Referência**

IDENTIFICAÇÃO	**NOME E ENDEREÇO DO NOTIFICANTE**	**NOME E ENDEREÇO/ REF. DO PACIENTE** *(de acordo com a lei nacional)*
Problema de Segurança em animais ☐ em humanos ☐ **Falha na eficácia prevista** ☐ **Problemas de Intervalo de Segurança** ☐ **Problemas ambientais** ☐	Veterinário ☐ Farmacêutico ☐ Outro ☐ N.º de telefone: N.º de faxe:	

PACIENTE(S) *Animal(ais)* ☐ *Humanos* ☐ *(para humanos, preencha, abaixo, apenas a idade e o sexo)*

Espécie	Raça	Sexo	Estado	Idade	Peso	Razões para o tratamento
		Fêmea ☐ Macho ☐	Esterilizado ☐ Gestante ☐			

MEDICAMENTO(S) VETERINÁRIO(S) ADMINISTRADO(S) ANTES DA SUSPEITA DE REAÇÃO ADVERSA

(se foram administrados mais medicamentos que as colunas disponíveis, por favor, copie este formulário)

	1	2	3
Nome do medicamento veterinário administrado			
Forma farmacêutica e dosagem (ex.: comprimidos de 100 mg)			
Número de AIM			
Número de lote e validade			
Via/local de administração			
Dose/Frequência			
Duração do tratamento/ Exposição Data do início Data do fim			
Quem administrou o medicamento veterinário? (veterinário, proprietário, outro)			
Pensa que a reação é devida a este produto?	Sim ☐ / Não ☐	Sim ☐ / Não ☐	Sim ☐ / Não ☐
O titular da AIM foi informado?	Sim ☐ / Não ☐	Sim ☐ / Não ☐	Sim ☐ / Não ☐

Annex III (continuation)

DATA DA SUSPEITA DE REAÇÃO ADVERSA ……/……/……	Tempo entre a administração e a reação em minutos, horas ou dias ……	Número de tratados ____ Número reagindo ____ Número de mortos ____	Duração da reação adversa em minutos, horas e dias ……

DESCRIÇÃO DO EVENTO (*Problema de segurança em animais ou Problema de segurança em humanos/Falha na eficácia prevista/Problemas de intervalo de segurança/Problemas ambientais – Por favor, descreva:*

Indique, também, se a reação foi tratada, como, com o quê e qual foi o resultado.

OUTROS DADOS RELEVANTES (ANEXE FOLHAS ADICIONAIS SE FOR NECESSÁRIO p. ex.: investigações realizadas ou a decorrer, uma cópia do relatório médico para os casos em humanos)

CASO HUMANO
Se o caso notificado se refere a um ser humano, por favor, complete os detalhes da exposição a seguir

- Contacto com animal tratado ☐
- Ingestão oral ☐
- Exposição tópica ☐
- Exposição Ocular ☐
- Exposição a injeção ☐ dedo ☐ mão ☐ articulação ☐ outro ☐
- Outro (deliberado….) ☐

Dose de exposição:

Se não concorda que o seu nome completo e endereço sejam enviados ao titular da AIM, se for pedida mais informação, p. f., assinale com uma cruz ☐

Data: **Local:** **Nome e assinatura do notificante:**

Ponto de Contacto (telefone) (se diferente do número na página 1)