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Committee for Medicinal Products for Veterinary Use

Veterinary pharmacovigilance 2016

Public bulletin

1. Executive Summary

This public bulletin is aimed at informing veterinarians and the public of the main outcome of post-marketing surveillance activities for veterinary medicinal products (VMPs) during 2016 at the level of the European Medicines Agency (EMA). The bulletin summarises recommendations to amend the safety warnings and highlights ongoing monitoring of several centrally authorised products (CAPs[1]). A summary of the discussions and agreements at European level by the Pharmacovigilance[2] Working Party (PhVWP-V) regarding pharmacovigilance issues concerning nationally authorised veterinary medicinal products is also included.

The post marketing surveillance of CAPs has been further strengthened through the overall increased reporting and the availability of all adverse event reports in a central database (in total approximately 205,000 reports involving more than 100 million animals affected[3]. One report can contain more than one animal affected, especially in food producing animals).

It is essential to emphasize the importance of the contributions made by the veterinarians in the field through their reporting of adverse events. By EU legislation, the adverse event reports that are initially reported to either the marketing authorisation holder (MAH) or the regulatory authority are collected in the European central database together with events from outside the European Union (EU) on the same or similar products that are reported by the MAHs. The availability of these reports sent by veterinarians, animal owners, farmers and others, remains the pre-dominant route for regulators to follow-up on the safety and efficacy of VMPs once these are marketed. Veterinarians are encouraged to continue reporting directly to the local regulatory authority[4] or to the MAH.

[1] These are veterinary medicinal products that are authorised through the centralised marketing authorisation procedure operated by the European Medicines Agency.

[2] Pharmacovigilance relates to any adverse events potentially linked to the use of a VMP, including possible lack of efficacy, environmental problems and investigations of the validity of the withdrawal periods.

[3] See graph 3 in the annex for further detail on the number of animals affected by species and humans.

[4] In some Member States reporting to the regulatory authority is mandatory for veterinarians.

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2. Introduction

This is the 14th public bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2016. The aim of this bulletin is to contribute to the public communication on veterinary medicinal products, particularly on the surveillance of adverse events and safety issues of veterinary medicines in the EU.

All adverse event reports occurring in the EU related to the use of authorised veterinary medicinal products are collected and evaluated both by the MAH, who places the product on the market, and by the national competent authorities or the EMA. These reports may include events such as death, life-threatening reactions or permanent lesions and reactions in humans handling the veterinary medicinal product or the treated animal(s). The MAH is, in addition, obliged to report serious and unexpected adverse event reports occurring outside the EU, when the product concerned is also authorised in the EU.

Electronic reporting became mandatory in November 2005 for serious reports only which are collated in a single EU database: EudraVigilance Veterinary (EVVet). EVVet now contains 205,540 reports of adverse events, approximately 119,317 of which occurred within the EU/EEA and 85,428 outside the EU/EEA.

The overall surveillance of the adverse events is carried out predominantly using two processes. The periodic safety update reports (PSURs), which are a review of all adverse event reports having occurred in a set period, are compiled by the MAH and submitted to the responsible authority for review at defined time points. At the same time continuous monitoring of all pharmacovigilance data available is carried out via signal detection by national competent authorities and EMA.

The responsibility for the surveillance and assessment of reports depends on which authority is responsible for the authorisation of the specific veterinary medicinal product. Under current European legislation, the EMA, the Committee for Medicinal Products for Veterinary Use (CVMP) and its Pharmacovigilance Working Party (PhVWP-V) are responsible for the pharmacovigilance of centrally authorised veterinary medicinal products, i.e. the products that have been granted an EU-wide marketing authorisation, whereas the surveillance of non-centrally authorised veterinary medicinal products are carried out by the competent authorities at Member State level.

On May 2016, a workshop on surveillance of veterinary medicinal products was hosted at the EMA in order to exchange views on the current status of pharmacovigilance activities within the network and to explore new approaches for potential improvement of collaboration and simplification of surveillance.

This document gives an overview of the outcome of the pharmacovigilance issues, which have been considered by the CVMP and the PhVWP-V during 2016.

3. Adverse events in animals and humans involving centrally authorised products

There are now 174 veterinary medicinal products that have been authorised via the centralised procedure since 1995 through the EMA and which have marketing authorisations valid across the entire EU. An overview of the products and detailed information on each product, including the summary of product characteristics, is accessible on the EMA website (http://www.ema.europa.eu/ema/).

A total of 18,413 adverse event reports relating to exposure to centrally authorised products were received in 2016, concerning 17,859 adverse events in animals and 554 adverse events in humans concerning a veterinary medicinal product.

Graph 1. Total number of adverse event reports for centrally authorised products reported per year to the central EU database from within and from outside the European Economic Area (EEA)

A long-term trend towards increased reporting (Graph 1) can be observed and is mainly attributed to the increased awareness of the value of pharmacovigilance reporting by veterinarians as well as the increased control by the regulators of the implementation of the pharmacovigilance legislative requirements by the veterinary pharmaceutical industry. While there is still concern regarding underreporting for several major food-producing animals, the availability of an increased dataset is a very positive development that increases the ability to analyse the data effectively. A dedicated focus group on the topic of underreporting related to food producing animals (cattle, sheep, goat, horse, fish and poultry) took place in November 2016 with participants from authorities, industry as well as, for the first time, with practice veterinarians specialised in the main food producing species.

The majority of reports concern companion animals, with adverse event reports in dogs and cats accounting for 82% of the cases. Further descriptive statistics regarding the reports received in 2016 can be found in Annex 1.

The EMA's CVMP and its PhVWP-V reviewed during 2016 in total 150 periodic safety update reports provided by the MAHs.

The continued monitoring of centrally authorised veterinary medicinal products through signal detection resulted in 2016 in 538 surveillance reports based on potential signals of safety or lack of efficacy concerns. These signals are further analysed and have led for some products to the recommendation to e.g. add additional warnings to the product literature or to request the MAH for a targeted PSUR (see table below). For some signals the assessment concluded that the observed signs were either not likely to be linked to the use of the product or it was considered that the observed signs fall within the norm and/or the warning statements already included on the product literature. A small number of analyses include signals of potential safety or lack of efficacy concerns for which a potential causal relationship with the product administered could not yet be excluded. These issues remain under investigation in 2017 (see also table below). In general however, most of the signals identified are inconclusive because of insufficient data or lack of detailed information.

4. Findings and recommendations related to centrally authorised veterinary medicinal products

During 2016, the continued monitoring of signals and evaluation of PSURs resulted in the following findings and recommendations related to centrally authorised veterinary medicinal products.

4.1. Companion animals

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

	bold); *"A temporary clumping or spiking of the hair ~~may be seen at the application site after treatment~~.* ***and ~~M~~m****ild, transient skin reactions at the application site (itching, hair loss) ~~may occur~~* ***have been commonly observed at the application site after treatment in clinical studies.*** *If the cat ~~licks~~* ***licked*** *the application site after treatment,* ***common*** *temporary excessive salivation ~~can be~~* ***was*** *observed in clinical trials. ~~Oral ingestation of the veterinary medicinal product may also result in vomiting and/or in transient neurological signs such as ataxia, disorientation, apathy, and pupil dilation.~~* ***Oral ingestion of the product may result in digestive tract and/or in neurological disorders (see section 4.5).*** ***Symptomatic treatment can be required if the ~~All these~~*** *signs* ***do not*** *resolve spontaneously within 24 hours. Correct application will minimise the occurrence of such events (see section 4.9).* ***The frequency of adverse reactions is defined using the following convention:*** ***- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)*** ***- common (more than 1 but less than 10 animals in 100 animals)*** ***- uncommon (more than 1 but less than 10 animals in 1,000 animals)*** ***- rare (more than 1 but less than 10 animals in 10,000 animals)*** ***- very rare (less than 1 animal in 10,000 animals, including isolated reports)."*** However, the casual relationship between the product, neurological signs and possible death in cats had been considered still unclear. Therefore, these signals along with lack of expected efficacy will continue to be monitored.
Comfortis (Spinosad)	On the basis of a relative high number of cases of blindness in dogs and cats it had been considered necessary to continue specific monitoring for this event during 2016. Finally, it has been demonstrated to be due to a drug interaction between spinosad and ivermectin at the blood-brain-barrier and that increased levels of ivermectin in the brain are responsible for the observed ophthalmologic toxicity. Dose-dependency is a strong indicator for substance-mediated toxicity and has been shown for ivermectin neurotoxicity in dogs. It was concluded that the benefit risk profile for Comfortis remains positive.

Canigen L4, Nobivac L4 & Versican Plus DHPPi/L4, Plus DHPPi/L4R, Plus L4, Plus Pi/L4, Plus Pi L4R (vaccine to prevent leptospira infections in dogs)	A high number of reports for painful local reactions and systemic reactions were reported with different multivalent Leptospira vaccines. Further investigations on the underlying cause e.g. role of the additional antigenic load, is required.
Osurnia (Terbinafine, florfenicol, betamethasone acetate)	On the basis of the reports received involving deafness in dogs, the MAH was recommended to amend the section 4.6 of the SPC as follows (changes highlighted in strikethrough and in bold); ~~*No adverse reactions that could be related to the veterinary medicinal product were observed in dogs with otitis externa under field conditions when administered as indicated in section 4.9.*~~ ***Post authorisation experience indicates that very rare cases of deafness or impaired hearing, usually temporary, in dogs have been reported after use, mainly in elderly animals.*** Considering the numerous cases of lack of expected efficacy received, the MAH was also recommended to amend section 4.4 of the SPC as follows: *4.4. Special warnings for each target species* *Clean the ears before the initial treatment is applied. Ear cleaning should not be repeated until 21 days after the second administration. In clinical trials, saline only was used for ear cleaning.* *Transient wetness of the inner and outer pinna can be observed. This observation is attributed to presence of product and is not of clinical concern.* ***In animals with a history of chronic or recurrent otitis externa, efficacy of the product may be affected if the underlying causes of the condition such as allergy or anatomical conformation of the ear are not addressed.*** *Bacterial and fungal otitis is often secondary to other conditions. Appropriate diagnosis should be used and therapy of causative conditions should be investigated before antimicrobial treatment is considered.* Reports involving auricular signs other than deafness (otorrhoea, internal ear disorders…), systemic signs (lethargy, anorexia, vomiting) and signs of hypersensitivity/intolerance (application site inflammation, ulceration, pruritus) were analysed and discussed by the MAH in the PSUR due in September 2016 but did not lead to SPC amendment at this stage.
Suprelorin (deslorelin acetate)	Further investigation is required on the mechanism(s) underlying testosterone modulation of seizure susceptibility in dogs. Further considerations as the need of amending the SPC reflecting "uncommon occurrence" of lack of expected efficacy are ongoing.

Trifexis (Spinosad/ Milbemycin oxime)	It was noted the high number of reports involving abnormal vision (impaired vision), neurological disorders, abnormal posture and star-gazing, therefore, the company proposed to continue monitoring them during 2017.
Vectra 3D (dinotefuran, pyriproxyfen and permethrin)	Due to the relatively high number of reports in cats following use of Vectra 3D it was suggested that there may be potential confusion amongst product users between Vectra 3D (authorised for dogs) and Vectra Felis, which may lead to accidental exposure in cats, hence, the MAH was requested to investigate on the issue. CVMP concluded that the warning together with a visual symbol on the packaging and on the spot-on applicator and the explanation on the toxicity of permethrin in cats given in the SPC was sufficient.

4.2. Food producing animals

Draxxin (tulathromycin)	A new potential signal was identified in 2014 for convulsions in cattle, along with persistence of signals related to lack of efficacy. Continued monitoring has not yet resulted in sufficient information that would allow concluding on the potential signals.
Improvac (synthetic peptide analogue of gonadotropin-releasing factor conjugated to dipthheria toxoid)	Reports involving anaphylaxis reactions in pigs are being monitored in order to decide if the frequency has been increased compared to the existing product literature text as follows: *"Transient erythema, pruritus or other signs of discomfort at the application site have been reported rarely and usually disappear spontaneously, within 24 hours following administration of the product.* *In rare cases, behavioural disorder signs such as hyperactivity, vocalisation or anxiety, systemic signs such as lethargy or anorexia, and neurological signs such as muscle tremor have been reported.* *Gastrointestinal signs such as vomiting or diarrhoea have also been reported very rarely.* *Transient cosmetic effects (wet appearance, spiking of hair coat and deposits) at the application site have been reported very rarely, however these effects are usually not noticeable after 48 hours."*
Velactis (cabergoline)	Ceva informed the EMA on 8 June 2016 of a pharmacovigilance signal: recumbency in cows, some of which resulted in death. The majority of those reports had occurred in Denmark. A preliminary analysis of the pharmacovigilance data available, conducted by the CVMP, indicated that there were serious animal health concerns related to the use of Velactis due to the number of reports and severity of the adverse events occurring in a short time period. The CVMP considered that the potential risk of serious unexpected adverse events such as recumbency, some of which were fatal, following recommended use of Velactis, to healthy cows, was unacceptable and that the risks outweigh the benefits of the product. Consequently, the CVMP concluded that the benefit-risk balance of the product was considered unfavourable, at present, under the authorised

	conditions of use. Therefore, the CVMP recommended the suspension of the marketing authorisation for Velactis on the basis of the benefit-risk evaluation. In view of the estimated amount of product available within the distribution chain and the severity and frequency of the observed adverse events, as a precautionary measure to prevent further exposure, the CVMP recommended that the product should be recalled at all levels of the distribution chain - wholesaler, retail and user (veterinarians/farmers) - to ensure timely removal of product so it does not get used. On 22 August 2016, the European Commission adopted the opinion of the CVMP on suspending the marketing authorisation under Article 45 of Regulation (EC) No 726/2004 of the European Parliament and of the Council. http://ec.europa.eu/health/documents/community-register/2016/20160822135656/dec_135656_en.pdf For the suspension to be lifted the MAH shall provide scientific evidence on the following conditions to the CVMP: • elucidate the underlying cause of the adverse events and potential contributing factors, which may include but should not be limited to hypocalcaemia; • demonstrate that the administration of the product to cattle does not lead to an unacceptable risk of serious adverse events, including recumbency and death and if necessary, to propose management measures to mitigate this risk to be included in the product information; and • demonstrate a favourable benefit-risk balance for the product.
Zolvix (Monepantel)	In light of reports of resistance the CVMP concluded on the need of additions of the wording in section 4.4. of the SPC (changes highlighted in strikethrough and in bold); ***"It is recommended that product is used not more than twice in one year"*** ***"In order to help delay the development of resistance, users are advised to check the success of the treatment (e.g. clinical appearance, faecal egg counts). Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. Faecal Egg Count Reduction Tests) in discussion with their animal health advisor"*** ***"Increasing refugia (i.e. a source of parasites which have not been exposed to the anthelmintic) has been demonstrated to delay the development of resistance. However, this should be considered only after advice has been taken from an animal health advisor."*** And section 5.1.; ***"Isolated cases of resistance against monepantel have been identified***

	within the European Union"

4.3. Humans

Activyl (indoxacarb)	Adverse event reactions were reported in humans involving application site pruritus, eye irritation and erythema which will continue to be monitored.
Equisolon (prednisolone)	Reports concerning human exposure were received and considerations on the need to add a specific warning to the SPC on the safe handling of the product are ongoing.
Osurnia (Terbinafine, florfenicol, betamethasone acetate)	A single case of corneal ulceration in a human following exposure to Osurnia was investigated but amendments to the SPC were not considered necessary.

5. Findings and recommendations related to non-centrally authorised veterinary medicinal products

While pharmacovigilance of non-centrally authorised products fall fully under the responsibility of each Member State there are regulatory tools within the EU that are established to allow early communication of safety concerns and rapid exchange of pharmacovigilance information between national competent authorities and the EMA, such as rapid alert (RA) and non-urgent information (NUI).

The following products were discussed during 2016 at EU level:

Advantix (imidaclopride and permethrin)

In 2014, 17 cases of permethrin intoxication in cats were reported to the Belgian regulatory authority following unauthorised use of the product in cats. One case concerned a French product. In all other cases, the product Advantix was used. In 2015, 9 intoxication cases were reported for Advantix and one case of Defendog. For Advantix, authorised products, which do not have the flea allergy dermatitis claim, can be delivered freely (over the counter). The Belgian competent authority is considering potential inclusions of warnings in the relevant product information; regular communication to veterinarians and general public; and the prescription status in relation to other products authorised in the European Union (EU).

Genta 100 mg/ml (nationally authorised)

In January in Germany two batches were recalled by the MAH following receipt of adverse event reports concerning horses which presented anaphylactoid reactions like urticaria, increased breathing frequency, colic-like signs, trembling and sweating. All occurred shortly after a new batch was placed on the market. The active pharmaceutical ingredient and the finished products produced with the concerned batches were re-tested by both MAH and manufacturing company but no root cause could be determined.

Following to this, a Rapid alert was circulated by the UK in December concerning a product authorised via decentralised/mutual recognised procedure containing gentamicin for horses, regarding also anaphylactoid signs including increased respiratory rate, sweating, weakness, recumbency, shaking and colic.

UK started a recall for the specific batch but since reports were still being received involving a second batch, the MAH was asked to further investigate on this.

Finally, the German National Authority sent a request for information on observed similar symptoms in horses after using different gentamicin containing products from the same active substance manufacturer and proposed to review these events on a substance related level and not per product. The investigations are still on going.

Slice 2 mg/ml premix for medicated feeding stuff

The company submitted an environmental report to the UK National Competent Authority (VMD) in September 2015 stating that they had been made aware of a draft publication suggesting that emamectin benzoate use was correlated with the reductions in richness and abundance of the benthic crustacea community surrounding fish farms in Scotland. Further data also submitted by the MAH indicated that some farms in Scotland use the product at higher doses than recommended.

The MAH has been requested to submit a revised environmental risk assessment based on current in-field use and using appropriate predicted environmental concentrations and predicated no effect concentrations based on currently available evidence.

6. Overall conclusions

The trend of increased reporting of adverse event reports has also continued for 2016. The overall pool of 205,540 reports within the EU central database and the improvement of the analysing tools and expertise allows for a better follow-up of the post-marketing pharmacovigilance data. The EU experts concluded on several improvements to the product literature for centrally authorised veterinary medicinal products as a follow-up to the available pharmacovigilance data. For the majority of the centrally authorised veterinary medicinal products the available reports were considered in line with the approved product literature and the benefit-risk balance was considered unchanged. For a small number of products, investigations are continuing to further validate and corroborate the potential observed signals with future data.

There has been a slight increase on reports related to veterinary medicinal products used in food producing animals compared to 2015 even though underreporting continues being an issue. The dedicated focus group on the topic of underreporting related to food producing animals created the first instance at EU level where regulators exchanged and discussed directly with veterinarians in practice on the topic of pharmacovigilance. It is anticipated that similar future initiatives will become instrumental in exploring specific actions towards effective monitoring of products for food producing animals.

It is recognised that increased transparency and feedback are important factors for encouraging veterinarians to report and it is hoped that this report provides information of value to the practitioner. Establishing an increased active interaction between veterinarians, who have the expertise on the actual use of veterinary medicinal products, and the regulators is essential to improve animal and public health. Therefore, all veterinarians in the EU are encouraged to report any adverse events, including potential lack of efficacy to the national competent authority in their country or to the relevant marketing authorisation holder of the product involved[5]. Several authorities have online templates available to facilitate reporting. The continued increase of the number of reports in the central EU database allows for better monitoring and allows the authorities to provide better feedback to the veterinarians on the safe and effective use of veterinary medicinal products in the EU.

[5] Certain Member States require veterinarians to report directly to the national competent authority only.

ANNEX 1: Descriptive analysis of adverse event reports received in EudraVigilance Veterinary

A total of 18,413 reports relating to exposure to centrally authorised veterinary medicinal products (CAPs) were received in 2016, concerning 17,859 adverse events in animals and 554 adverse events in humans.

The adverse event reports received concerned 142 products, which is approximately 80% of the total of centrally authorised products with a valid marketing authorisation granted by the end of 2016.

Of 17,859 reports in animals, 14,729 reports concerned companion animals, most frequently dogs (11,657) and cats (3,072), and 3,130 reports concerned food-producing animals.

The most common adverse events reported concern systemic disorders (29.6%) following by digestive tract disorders (12.2%) and neurological disorders (11.7%).

Of the reports received for CAPs in 2016 8,992 occurred in EU/EEA countries. Most of the 9,417 were from the United States (77%) and Canada (9%), with the remainder being, listed by number of reports received, from Australia, Brazil, Japan, South Africa, New Zealand, Colombia, Switzerland, Mexico, Israel, Taiwan, China, Korea (South), Serbia, Argentina, Ecuador, Russia, Ukraine, Puerto Rico, Thailand, Honduras, Mozambique, Zimbabwe, Chile, Costa Rica, Egypt, Philippines, Singapore, Tunisia, Turkey, Belarus, Bolivia, India, Malaysia and Venezuela.

Table 1 and related charts show the numbers of reports by target animal species (and human beings). A single report may relate to one or more animals or individuals (especially for treatment concerning livestock) and to one or more products, which may have been used concurrently.

The table gives raw figures of reports received, irrespective of whether or not the reaction can be definitely attributed to administration of the product.

Summary statistics on reports for centrally authorised products by target species, including reports in humans (Reports received between 1 January 2016 and 31 December 2016.) are presented in the table below.

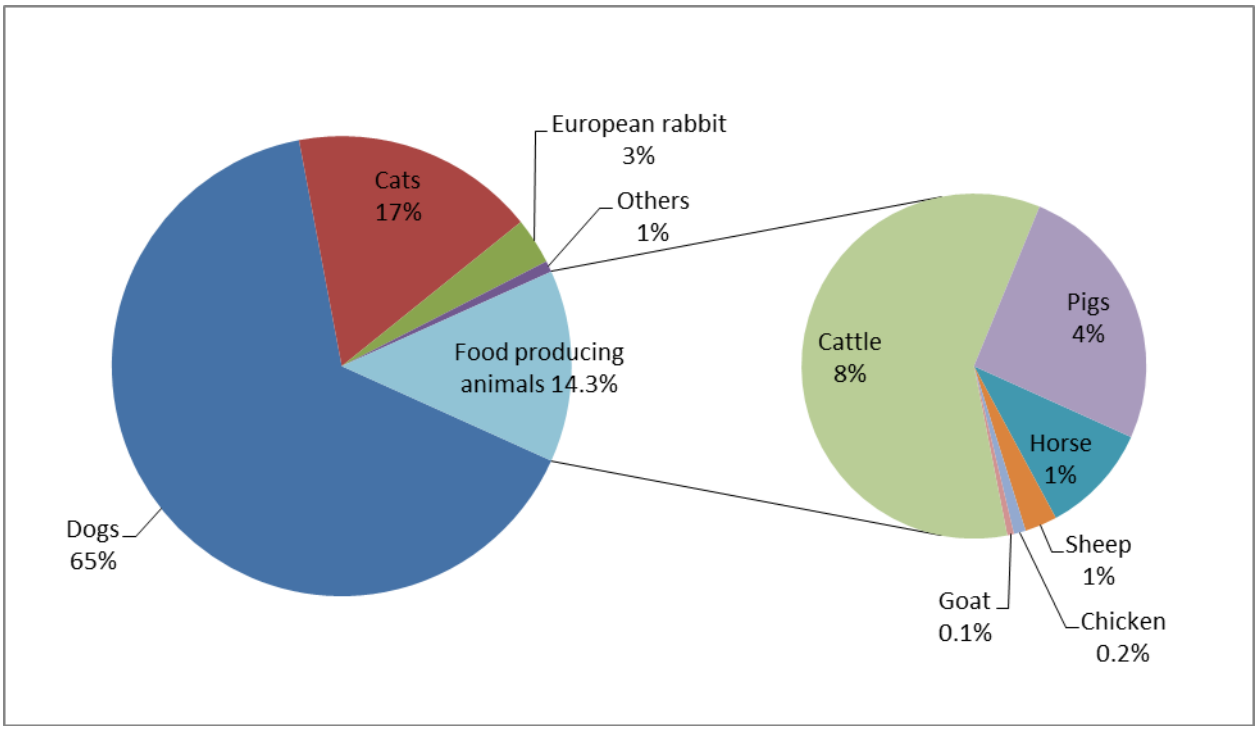
Table 1. 2016 data:

Human or Animal Report	Species	Number of Safety Reports	Number of animals affected
Animal	Dogs	11,657	12,312
	Cats	3,072	3,499
	Cattle	1,429	52,926
	Pigs	615	320,550
	Rabbit	582	6,025
	Horse	250	399
	Others*	139	148,161
	Sheep	73	875
	Chicken	27	927,766
	Goat	15	2,072
Total animal		**17, 859**	**1,474,585**
Human	Human	554	554
Grand Total		**18,413**	**1,475,139**

* “Other” species include mainly duck, ferret and guinea pig amongst others.

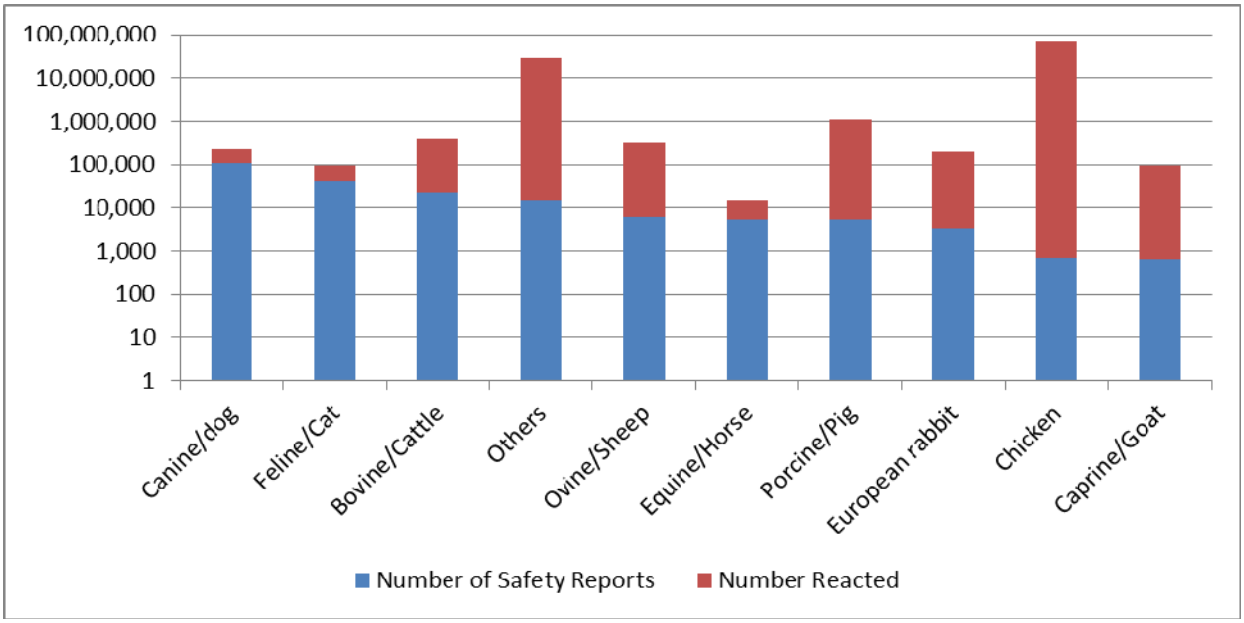
The percentage of adverse event reports by species for reports received during 2016 related to the use of centrally authorised products is presented in the graph below.

Graph 2. 2016 data:



Total number of animals reacting and safety reports within the EU central database by species until 2016, the logarithmic scale on the y-axis allows including the total number of affected animals which in particular for food producing animals is multitude of the actual number of reports, is presented in the graph below.

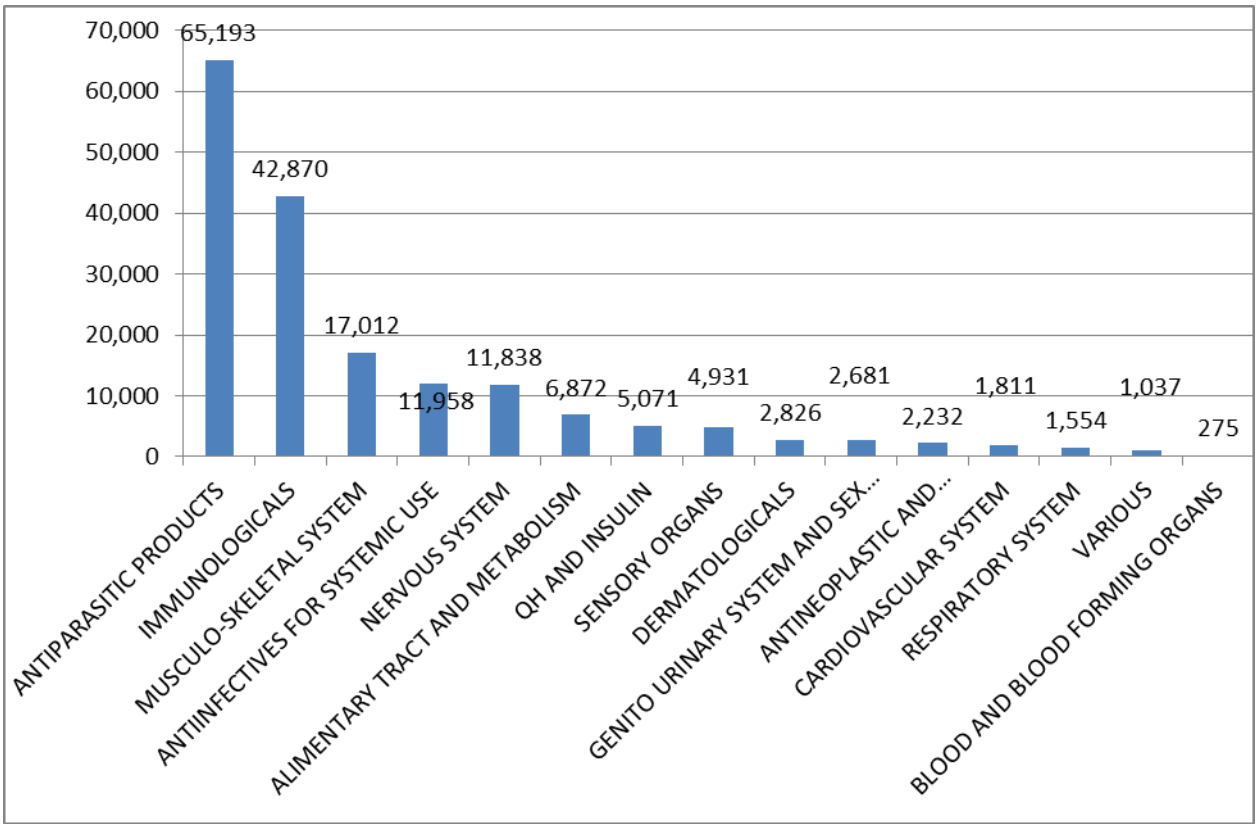
Graph 3. Total data in EVVET (2005-31 Dec 2016):



In the following charts (graphs 4 & 5), the reports of adverse events in various animal species and in human beings for all products have been grouped according to the anatomical therapeutical chemical coding system (ATCvet; see http://www.whocc.no/atcvet/ for further explanations).

The number of adverse event reports classified by ATC coded type of product until 2016 is presented in the graph below.

Graph 4. Total data in EVVET (2005-31 Dec 2016):



The number of AER classified by ATC coded type of product until 2016 per percentage is presented in the graph below.

Graph 5. Total data in EVVET (2005-31 Dec 2016):