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Committee for Medicinal Products for Veterinary Use (CVMP)

Veterinary pharmacovigilance 2015

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 2015 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 170,000 reports involving a multitude of affected animals[3]). The analysing tools that are made available to all national competent authorities have also been further improved in 2015.

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 all 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 to the MAH or directly to the local regulatory authority[4] in particular for events occurring in food-producing animals for which considerable under-reporting of adverse events is suspected.

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

2. Introduction

This is the 13th public bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2015. 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 serious 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, reactions in humans handling the veterinary medicinal product or the treated animal(s), or less serious events. The MAH is, in addition, obliged to report serious adverse event reports occurring outside the EU, when the product concerned is also authorised in the EU.

All these adverse event reports are collated in a single database: EudraVigilance Veterinary (EVVet). Electronic reporting became mandatory in November 2005, and EVVet now contains approximately 170,000 reports of adverse events, approximately 101,000 of which occurred within the EU and 69,000 outside the EU.

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 is 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. The scientific bodies responsible for pharmacovigilance of veterinary medicinal products at EU level are EMA's Committee for Medicinal Products for Veterinary Use (CVMP) and its PhVWP-V.

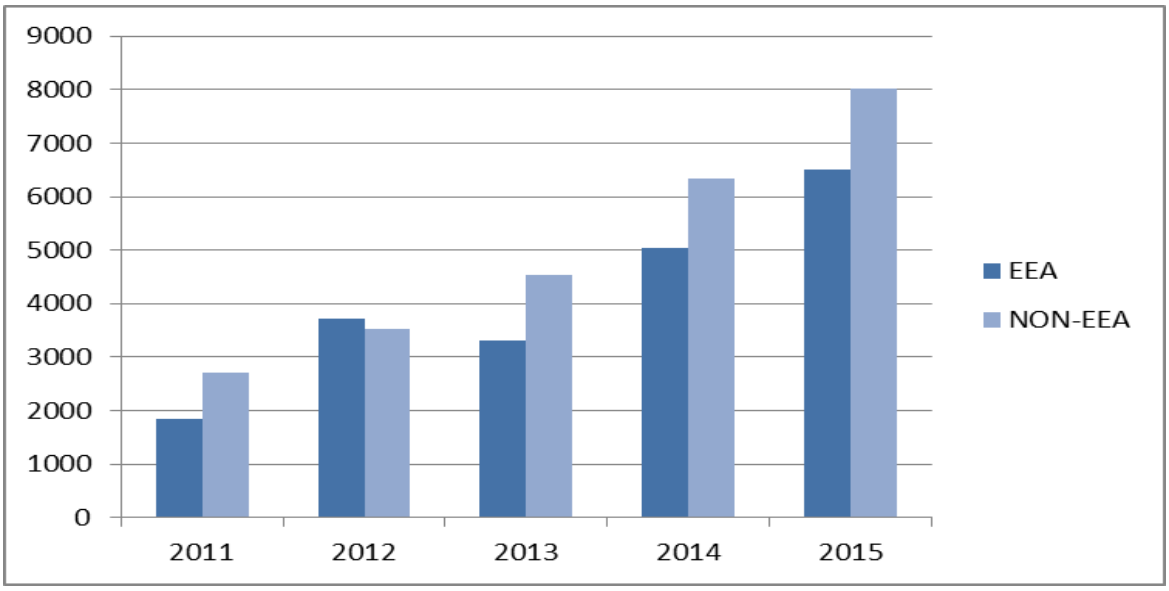
This document gives an overview of the outcome of the pharmacovigilance issues, which have been considered by the CVMP and the PhVWP-V during 2015.

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

There are now 170 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/), which is searchable to e.g. show only the products for a certain species of interest.

A total of 14,387 adverse event reports relating to exposure to centrally authorised products were received in 2015, concerning 13,847 adverse events in animals and 540 adverse events in humans.

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 overall increase of data 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 is foreseen for 2016.

The majority of reports concern companion animals, with adverse event reports in dogs and cats accounting for 90% of the cases. Further descriptive statistics regarding the reports received in 2015 can be found in Annex 1.

The EMA's CVMP and its PhVWP-V reviewed during 2015 in total 157 periodic safety update reports provided by the MAHs.

With the increased amount of electronic data available in the central European database, signal detection is carried out at predefined intervals. The monitoring of centrally authorised veterinary medicinal products resulted in 2015 in 383 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 2016 (see also table below). In general however, most of the signals identified are inconclusive because of insufficient data or lack of detailed information.

During 2015, the continued monitoring of signals and evaluation of PSURs resulted in the following findings and recommendations related to centrally authorised veterinary medicinal products:

Table 1: Findings and recommendations related to centrally authorised veterinary medicinal products

Product name *(active ingredient)*	***Findings and recommendations***
Activyl (indoxacarb)	Monitoring was on-going for neurological signs in cats since 2013 (e.g. ataxia, convulsion). Subsequently in April 2015, the MAH was recommended to amend the product literature and to add the following warnings in order to ensure that the indications and risks of the product are fully understood; "*Include a pictogram in section 4.9 Amounts to be administered and administration route to clarify the recommended location for administration"* and also add: *"In rare cases in cats, neurological signs (e.g. incoordination, tremor, ataxia, convulsions, mydriasis and impaired vision) have been observed. Other signs observed in rare or very rare cases in cats included emesis, anorexia, lethargy, hyperactivity and vocalisation. All signs are generally reversible following supportive treatment."*
Advocate (imidacloprid, moxidectin)	Adverse event reports that included death in ornamental birds (canaries) were the reason in June 2015 for asking the MAH for a targeted PSUR focusing on these and similar reports. Based on the targeted PSUR this, in December 2015 it was recommended to add a warning to the product literature: *"Do not use on canaries"* and also: *"Imidacloprid is toxic for birds, especially canaries."*
Apoquel (oclatinib maleate)	Potential signals that include hepato-biliary disorders, renal and urinary disorders were identified during 2015 and requested to be addressed by the MAH in the PSUR. It was concluded in October 2015 that no amendments to the product information were necessary. The SPC already highlights that continued veterinary monitoring is recommended following treatment considering that the active modulates the immune system. The MAH is requested to continue monitoring reports involving neoplasia and unexpected signs associated with Hepato-biliary, renal and urinary and neurological disorders.
Bravecto (fluralaner)	Monitoring is on-going since 2014 because of a relative high number of reports for this relatively new product. "*Lethargy*" has been identified as a potential additional term to be included in the product literature however the analysis has not been concluded.

	Further analysis of the reports is expected with the next PSUR due in February 2016
Broadline (fipronil, S-methoprene, epinomectin, praziquantel)	On the basis of a relative high number of neurological signs including death in cats it was considered necessary in 2014 to continue specific monitoring for these events. The MAH was requested to evaluate in the next PSUR, all adverse events with neurological signs including reports with death since the product has been placed in the market (March 2014). The next PSUR is due in December 2015
Cimalgex (cimicoxib)	In March 2015, it was recommended to amend the product literature and to add the following warnings to address the reporting of a relatively high number of reports that include renal disorders and renal failure: "*In very rare cases, increases in renal biochemistry parameters were noted. Furthermore, in very rare cases, renal failure has been reported. As for any long term NSAID treatment, renal function should be monitored*".
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.
Eurican Herpes 205 (vaccine against herpes virus in dogs (f205 strain))	Monitoring was ongoing since 2013 related to adverse event reports that include abortion, still birth, premature parturition and vulvovaginitis in dogs. Subsequently in March 2015, it was recommended to amend the product literature and to add the following warnings in order to ensure that the indications and risks of the product are fully understood; *"Active immunisation of bitches to prevent mortality, clinical signs and lesions in puppies resulting from canine herpes virus infections acquired in the first few days of life through passive immunity."* and also: *"Abortion and premature parturition can occur as a result of CHV infection in bitches, the protection of the bitch against infection has not been studied for this vaccine. In order for immunity to be conferred to the puppies, sufficient intake of colostrum is required."*

NexGard (afoxolaner)	Monitoring started in 2014 with the identification of adverse event reports that involved emesis, convulsion, lethargy, abnormal test result, anorexia and diarrhoea. Subsequently in March 2015, the MAH was recommended to amend the product literature and to add the following warnings: "*Mild gastrointestinal effects (vomiting, diarrhoea), pruritus, lethargy, or anorexia may be observed on very rare occasions. These occurrences are generally self-limiting and of short duration*."
Nobivac L4 (vaccine to prevent leptospira infections in dogs)	On the basis of a relatively high number of reports that included several signals relating to anaphylaxis and various immune-mediated conditions such as anaemia, thrombocytopenia and arthritis, MAH was advised for the upcoming PSUR to compare the incidence of these adverse events with its other Leptospira product, which contains only two serovars. Subsequently in July 2015, the MAH was recommended to amend the product literature and to add the following warnings in order to ensure that the indications and risks of the product are fully understood; "*In very rare cases clinical signs of immune-mediated haemolytic anaemia, immune-mediated thrombocytopenia, or immune-mediated polyarthritis have been observed*".
Nobivac Myxo-RHD (vaccine to prevent myxoma infections in rabbits)	The MAH was requested to collect pharmacovigilance data from pet animals (including dwarfs) via a post-authorisation safety study to evaluate safety information for this category of the target species and to undertake an additional benefit-risk evaluation for the use of the product in this sub-group. The study was carried out during 2014 and the assessment finalised in October 2015 with no need of actions to be taken.
Parvoduk (vaccine against parvovirus in ducks)	A post authorisation safety study was requested after authorisation of the product in order to clarify some risks towards safety. One of those risks was a remaining immunosuppressive feature inherent to parvoviruses which may be expressed in specific epidemiological conditions, namely one-day old ducklings without maternal antibody protection. The assessment of the study was finalised in September 2015 with a recommendation to add the following warning to the SPC: *"A small occasional impact on growth cannot be excluded upon vaccination of day-old ducklings free of maternally derived antibodies*".
Pexion (imepitoin)	Monitoring started in 2014 with the identification of high of number of reports of lack of efficacy found in dogs. The United Kingdom, German, French and Belgian authorities published specific information regarding the events and providing further advice to the use of the product in particular to advice on careful consideration before deciding to switch a stabilized dog onto imepitoin from a different treatment.

	In January 2015, the MAH was recommended to amend the product literature with the following text: "*The pharmacological response to imepitoin may vary and efficacy may not be complete. On treatment, some dogs will be free of seizures, in other dogs a reduction of the number of seizures will be observed, whilst others will be non-responders. For this reason, careful consideration should be given before deciding to switch a stabilized dog onto imepitoin from a different treatment. In non-responders, an increase in seizure frequency may be observed. Should seizures not be adequately controlled, further diagnostic measures and other antiepileptic treatment should be considered. When transition between different antiepileptic therapies is medically required, this should be done gradually and with appropriate clinical supervision.* *The benefit/risk assessment for the individual dog should take into account the details in the product literature.* *The efficacy of the veterinary medicinal product in dogs with status epilepticus and cluster seizures has not been investigated. Therefore, imepitoin should not be used as primary treatment in dogs with cluster seizures and status epilepticus.* *No loss of anticonvulsant efficacy (tolerance development) during continuous treatment of 4 weeks was observed in experimental studies lasting 4 weeks.*" A further amendment of the warnings included the following change: *"The following mild and generally transient adverse reactions have been observed in pre-clinical and clinical studies ~~(~~in order of decreasing frequency~~)~~: ~~In rare cases~~ polyphagia ~~was reported~~ at the beginning of the treatment **(very common)**, ~~also~~ hyperactivity, polyuria, polydypsia, somnolence, hypersalivation, emesis, ataxia, apathy, diarrhoea, prolapsed nictitating membrane, decreased sight and sensitivity to sound."* In July 2015, on the basis of a confirmed signal involving reports on aggressive behaviour in treated dogs it was recommended to amend the product literature to add the following warning: "*In the field, aggression has been uncommonly reported. This aggression is potentially treatment related. Aggression may also be present during the postictal period or as a behaviour change which occurs as part of disease itself*."
Rabigen SAG2 (rabies vaccine for oral administration to red foxes)	On the basis an increased number of reports received in the non-target species dogs due to ingestion of the bait, in April 2015 it was recommended to amend the product literature to add the following warning: "*Vomiting due to gastric intolerance (potentially due to the aluminium/PVC sachet as part of the bait vaccine), in dogs which have accidentally ingested the bait, has been reported."*

Slentrol (dirlotapide)	Monitoring on the adverse events of hepatopathy and pancreatic or eye disorders took place since 2013. Slentrol was withdrawn from the market by the MAH on 15 January 2015.
Suprelorin (deslorelin acetate)	Monitoring of epileptic seizure findings in dogs during 2015 is on-going and to be investigated further with regard to time-laps (time from implant till seizures first observed).
Vectra 3D (dinotefuran, pyriproxyfen and permethrin)	"Muscle tremor" was identified as a potential signal in 2015, often accompanied by allergic conditions (from application site pruritus to anaphylaxis). Muscle hyperexcitability coincides with the toxicological profile of pyrethroids. De-contamination (by e.g. simple bath) seems effective with quick recovery however extended recovery time up to 9 days was also observed. As outcome of the PSUR assessment, it was recommended the following amendments of the product literature: *"Transient erythema, pruritus, or other signs of discomfort at the application site have been reported ~~very~~ 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."*
Zolvix (monepantel)	Reports on potential lack of expected efficacy (LEE) were identified during 2014 and 2015. The MAH was requested to provide a targeted PSUR focusing on LEE which is expected to be finalised by early 2016.
Zuprevo (tildipirosin)	On the basis of a relative high number of reports, in 2014 it was decided to further monitor for cases of lack of efficacy and respiratory signs in cattle. Further monitoring did not allow confirming whether reports that include respiratory tract disorders may be related to potential lack of efficacy.

4. Rapid alerts and non-urgent information

The rapid alert (RA) and non-urgent information (NUI) systems have been established to allow early communication of safety concerns and rapid exchange of pharmacovigilance information between national competent authorities and the EMA. These procedures are not restricted to centrally authorised products, but are applicable to all veterinary medicinal products authorised within the EU/EEA.

There was one rapid alert raised in 2015:

Closamectin pour-on solution for cattle (ivermectin 5 mg/ml, closantel (as closantel sodium) 200 mg/ml).

A community procedure was initiated in June 2015 on the basis of pharmacovigilance data in France, notably potential closantel overdose toxicity related adverse events including neurological signs and gastrointestinal disorder some of which had a fatal outcome. The products had been recalled in France at veterinary clinic and wholesale level.

The Article 78 procedure was concluded by the CVMP in October 2015 which included a complete review of the available scientific data available pre-marketing as well as post-marketing of the relevant products available on the EU market. It was considered that risk factors may exist in the field, leading to either overexposure of some animals to closantel or enhanced intrinsic sensitivity of these animals to the toxic effects of closantel. Vitamin A, E and selenium deficiencies and poor nutritional status in general were considered potential factors associated with the adverse events observed following treatment and considered possible explanations for the higher frequency of reported adverse events in France. Further investigations were considered necessary to confirm or refute nutritional status and specific micro-nutrient deficiencies as risk factors for the adverse events. It was concluded to improve to product information of the products in the EU with the following text:

> *"Care should be taken when treating animals which may be of low nutritional status as this may increase susceptibility of adverse events occurring.*
>
> *In very rare cases (less than 1 animal in 10,000 animals, including isolated reports), neurological signs such as blindness, ataxia, and recumbency may occur after administration of the product. These cases may also be associated with gastrointestinal signs such as anorexia, diarrhoea and in extreme cases signs may persist and may result in death of the animal.*
>
> *Even though the overall incidence of adverse events is very rare, it has been noted that, when there is an adverse event in a herd, several animals may be affected. Therefore, should neurological signs be observed in one animal, it is recommended to reinforce surveillance, at the herd level, of all treated animals."*

Additionally the MAH proposed to implement a risk management plan comprising submission of annual 'combined' PSUR reports for the products concerning Closamectin Pour-On Solution and associated names, detailed investigation of future pharmacovigilance reports which should include data collection from treated un-affected animals within the same herd (including farm history and herd health status, assessment of animal health and nutritional status involving biochemistry and micronutrient analysis; investigation of potential closantel toxicity (via blood plasma sampling and post-mortem examinations); and 'education, training and guidance' for end-users to ensure that the risks of the products and the precautions for use are fully understood. These measures were considered to be appropriate to mitigate the risks observed following treatment.

Although the underlying mechanism for the adverse events has not yet been determined, the benefit-risk balance of Closamectin Pour-On Solution and associated names was considered favourable subject to amendments to product information and implementation of additional risk mitigation and surveillance measures as described above.

The following **non-urgent information requests**, with potential relevance to veterinarians in practice, were discussed during 2015:

Somulose Solution for Injection (cinchocaine Hydrochloride).

The VMD (UK) reported on several cases related to potential lack of efficacy to Somulose Solution for Injection (UK-VMD-0033/15). In these cases, horses had to be administered with an overdose or the time taken for the horse to die was longer than expected. The last PSUR (2013) had estimated the incidence of lack of efficacy to be 0.05%.

Kexxtone (monensin)

In the period 30/4/2015-21/7/2015 the VMD received four spontaneous reports of accidental exposure to Kexxtone Boluses in dogs. All reports were associated with exposure to Kexxtone boluses regurgitated by treated cattle with the most common presenting signs being neurological (e.g. collapse and convulsions). One animal died, two were euthanized and one recovered. A PSUR covering the period 01/08/2014 to 31/1/2015. During this PSUR there were two reports in dogs, both following accidental exposure. The first report involved paralysis, cardiovascular failure and death. The second report involved hypersalivation, mydriasis, hypertension, haemorrhagic diarrhoea and death by euthanasia. The findings will be further addressed in the next PSUR assessment which is expected to be finalised by early 2016.

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, the company has introduced products authorized via informed consent, that do not have the flea allergy dermatitis claim and which can be delivered freely (over the counter). For safety reasons in the non-target species cat, a Prescription Only Medicine-status for permethrin containing products is under investigation in Belgium.

5. Overall conclusions

The trend of increased reporting of adverse event reports has also continued for 2015. The overall pool of 170,000 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.

The data however also show very few adverse event reports related to veterinary medicinal products used in food producing animals which is most likely explained by underreporting. A focus group on the topic of underreporting related to food producing animals has been planned for 2016. The focus group aims to discuss with all stakeholders and in particular with veterinary specialists for the different food producing species.

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 14,387 reports relating to exposure to centrally authorised veterinary medicinal products (CAPs) were received in 2015, concerning 13,847 adverse events in animals and 540 adverse events in humans.

The adverse event reports received concerned 132 products, which is approximately 78% of the 170 centrally authorised products with a valid marketing authorisation granted by the end of 2014.

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.

Of the 13,847 reports in animals, 12,429 reports concerned companion animals, most frequently dogs (9,515) and cats (2,914), and 1,357 reports concerned food-producing animals.

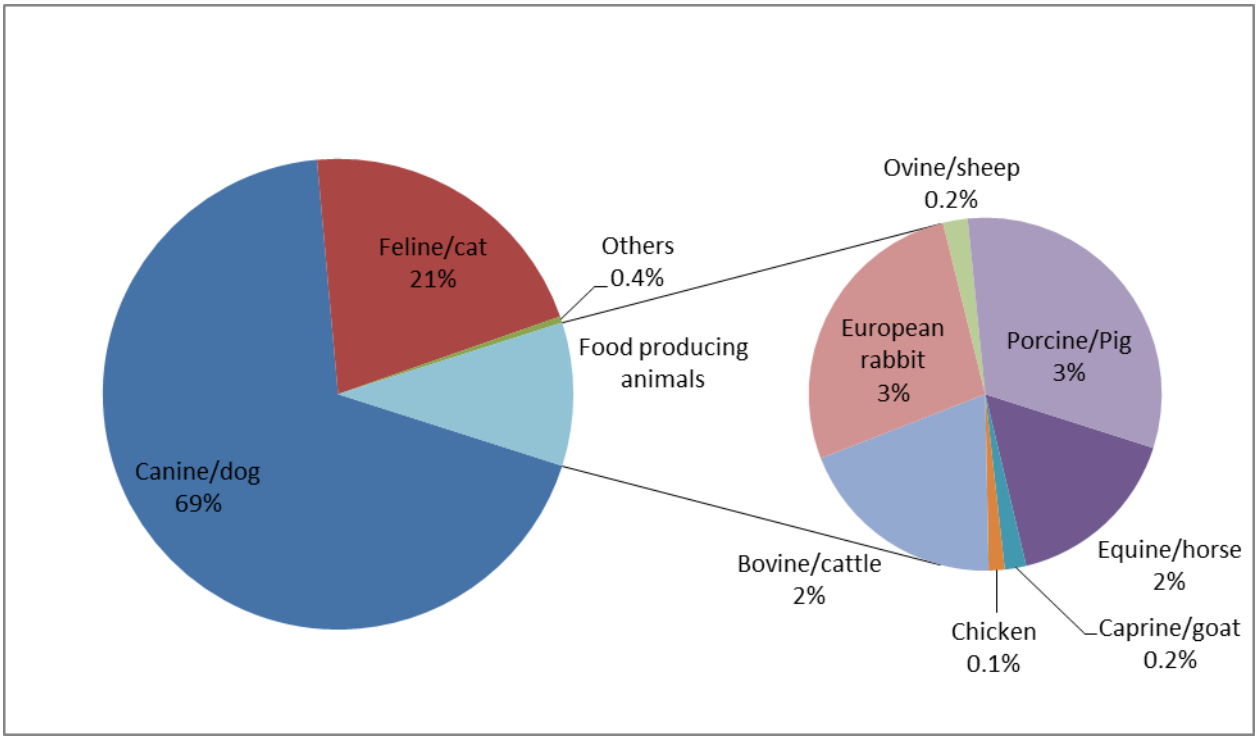
Of the reports received for CAPs in 2015 6,433 occurred in EU/EEA countries, of which 6,327 concerned animal adverse events and 106 concerned human adverse events. Most of the 7,947 reports received from third countries (7,513 concerning animals and 434 concerning humans) were from the United States (82%) and Canada (6%), with the remainder being, listed by numbers of reports received, from Australia, Brazil, Japan, Colombia, New Zealand, South Africa, Switzerland, Korea (South), Israel, Mexico, Taiwan, Argentina, Puerto Rico, Turkey, China, Russia, Costa Rica, Ecuador, Ukraine, Chile, Grenada, Guatemala, Kuwait, Macedonia, Philippines, Serbia and United Arab Emirates.

Table 1. Centrally authorised products: summary statistics on reports by target species, including reports in humans (Reports received between 1 January 2015 and 31 December 2015.)

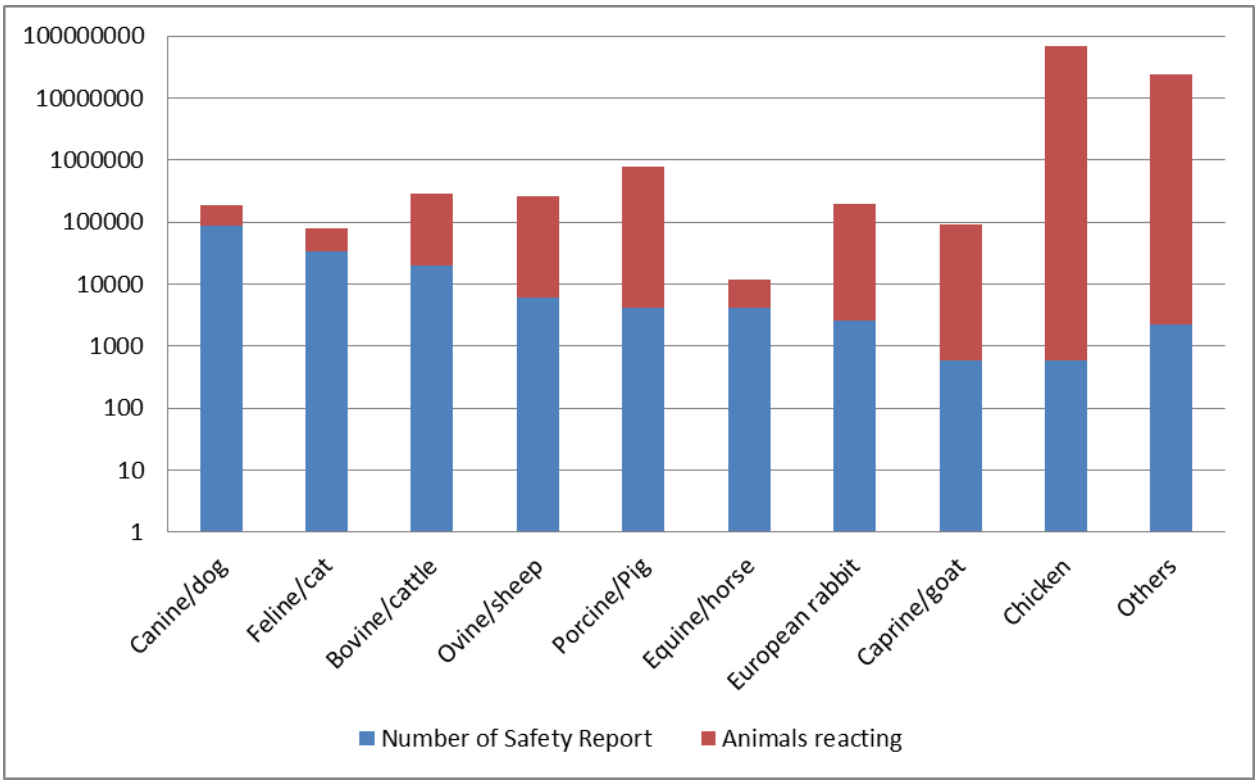
Species	Species	Number of Safety Report ID	Total reacting animals included in the reports
Companion animals	Canine/dog	9515	10,041
	Feline/cat	2914	3,490
Food producing animals	Bovine/cattle	261	3,322
	Caprine/goat	27	4,072
	Chicken	19	286,073
	Equine/horse	222	461
	European rabbit	366	3,016
	Ovine/sheep	31	958
	Porcine/Pig	431	278,363
Others	Others	61	65,261
Human	Human	540	NA

There are 50 products out of the 170 CAPs involved in the adverse event reports in humans. More than 70% of the reports concern antiparasitic products. Approximately 27% of the reactions are skin reactions, followed by sensory abnormalities (22%), injection site reactions (19%), eye reactions (13%) general symptoms (10%) and allergic conditions (7%).

Graph 2. % of adverse event reports by species for reports received during 2015 related to the use of centrally authorised products

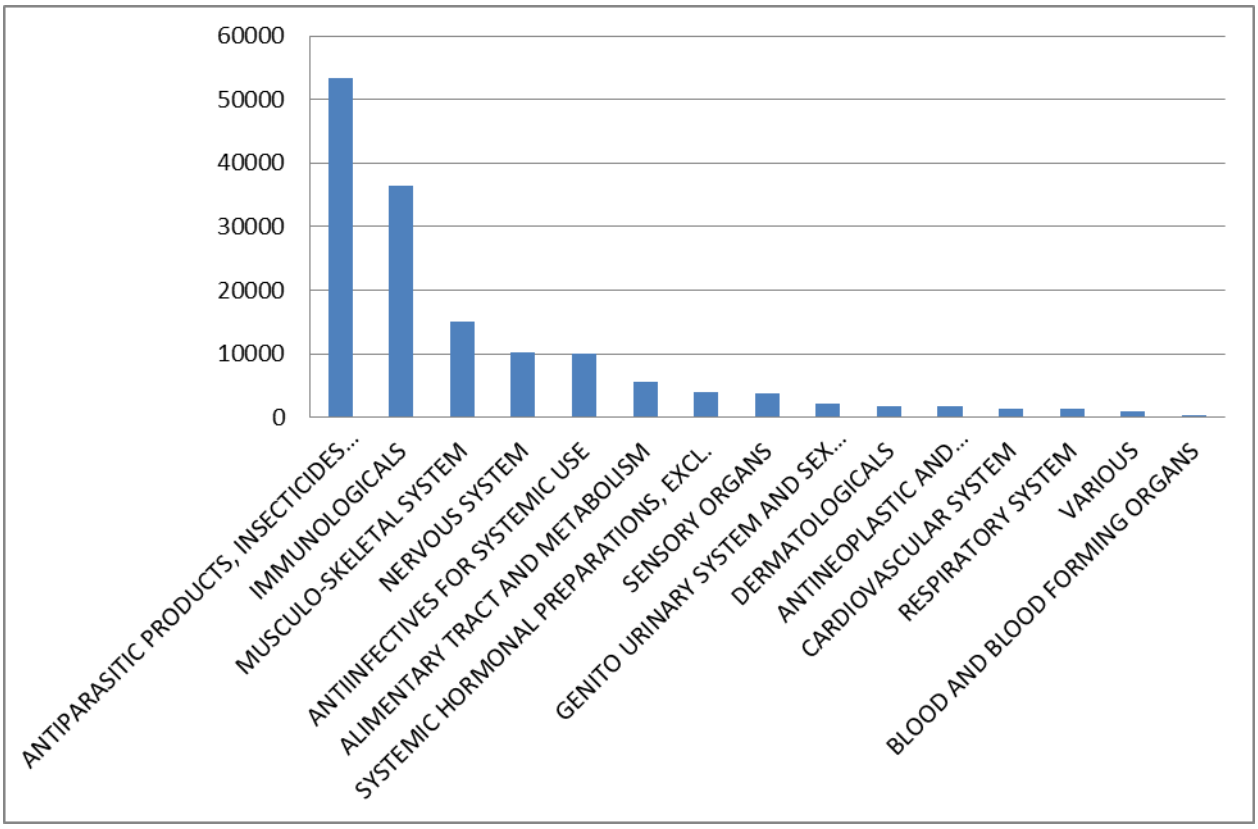


Graph 3: Total number of animals reacting and safety reports within the EU central database by species until 2015, the logarithmic scale on the y-axis allows including the total number of affected animals which in particular for food producing animals is multitude of the actual number of reports.



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

Graph 4: Number of adverse event reports classified by ATC coded type of product until 2015.



Graph 5: % of total adverse event reports classified by ATC coded type of product for a subset of 132947 reports in the database that contain the ATC product classification..