EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use (CVMP)

Veterinary pharmacovigilance 2014

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 2014 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 Working Party (PhVWP-V) regarding pharmacovigilance[2] 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 140,000). The analysing tools that are made available to all national competent authorities have also been further improved in 2014.

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 EU on the same or similar products that are reported by the MAHs. The availability of these reports sent by veterinarians 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 marketing authorisation holder or directly to the local regulatory authority[3] 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] In some Member States reporting to the regulatory authority is mandatory for veterinarians.

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2. Introduction

This is the 12th public bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2014. 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 European Union (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 marketing authorisation holder, 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 marketing authorisation holder is, in addition, obliged to provide adverse event reports having occurred 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 139,200 reports of adverse events, approximately 84,600 of which occurred within the EU and 54,600 outside the EU.

The overall surveillance of the adverse events is carried out using two processes –which are in part carried out in parallel. Pharmacovigilance involves signal detection as well as the evaluation of periodic safety update reports (PSURs), which are a review of all adverse event reports having occurred in a set period. A PSUR is compiled by the marketing authorisation holder 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. In addition, procedures are also in place within the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) and its PhVWP-V for the assessment of adverse events relating to national products, where appropriate.

This document gives an overview of the outcome of the pharmacovigilance issues, which have been considered by the CVMP and the PhVWP-V during 2014.

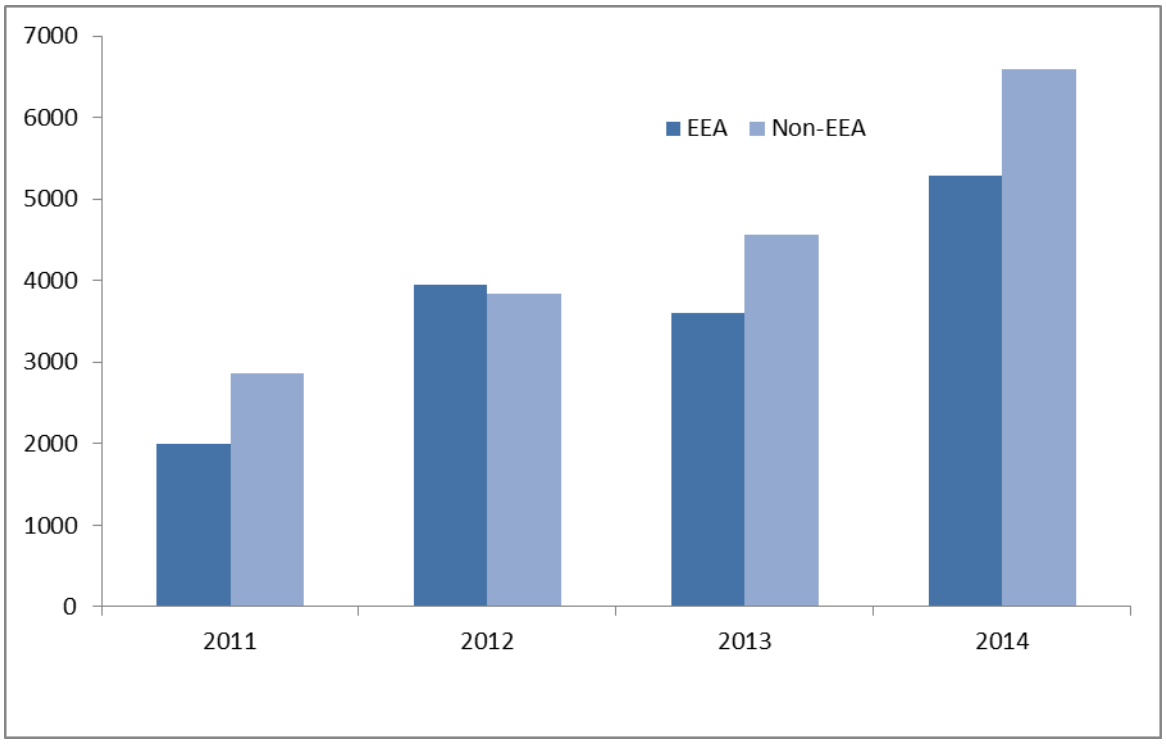
3. Adverse events in animals and humans involving centrally authorised products

There are now 159 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 11,878 adverse event reports relating to exposure to centrally authorised products were received in 2014, concerning 11,274 adverse events in animals and 604 adverse events in humans.

This is a 60% increase of reports concerning adverse events in humans and a 45% increase in animals compared to 2013.

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



The increase that is observed is not attributed to e.g. the availability of more centrally authorised products but instead coincides with the long-term trend (Graph 1) that is attributed to the increased awareness of the value of pharmacovigilance reporting by veterinarians as well as the increased control of the regulators to 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. This increased commitment to reporting from the veterinarians allows the regulator to further control and ensure the safety and efficacy of the centrally authorised products on the market.

The majority of reports concern companion animals, with adverse event reports in dogs and cats accounting for 84% received compared to 11% for cattle, pigs, rabbits, sheep, chickens and goats combined. Further descriptive statistics regarding the reports received in 2014 can be found in Annex 1.

The EMA's CVMP and its PhVWP-V reviewed during 2014 in total 154 periodic safety update reports provided by the marketing authorisation holders.

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 2014 in 357 surveillance reports. During 2014, and as a result from the continuous surveillance of adverse events and the evaluation of PSURs, the following regulatory actions were taken, which involved in particular changes to the product literature to include additional warnings:

Table 1. Regulatory actions taken during 2014 on the basis of pharmacovigilance data for centrally authorised products.

Product name (active ingredient)	**Findings and recommendation to the marketing authorisation holder**	**Date issued**
Activyl Tick Plus (indoxacarb)	On the basis of a relatively high number of reports that include neurological signs it was recommended to amend and add the following warning to the product literature: "In very rare cases, gastrointestinal signs (e.g. emesis, diarrhoea or anorexia), reversible neurological signs (e.g. tremor or ataxia) or lethargy have been observed. These signs are usually transient and generally resolve within 24-48 hours."	09/2014
Comfortis (spinosad)	On the basis of a relatively high number of reports that include eye disorders it was recommended to amend and add the following warning to the product literature: "In very rare cases, blindness, impaired vision and other eye disorders were observed". From the findings of a targeted PSUR, the MAH also proposed to include the term "muscle tremor" in the product literature.	04/2014
Nobivac Myxo RHD (live myxoma vectored rhd virus strain 009)	On the basis of reported events of RHD occurring after vaccination it was recommended to limit the indication to the classic strains rather than to indicate potential cross-protection against variant RHD virus strains. A changed text to the indication section for the product literature was recommended as follows: "For active immunisation of rabbits from 5 weeks of age onwards to reduce mortality and clinical signs of myxomatosis and to prevent mortality due to rabbit haemorrhagic disease caused by classical RHD virus strains."	10/2014
Pexion (imepitoin)	Following a relatively high number of reports in relation to non-responders it was recommended to amend the special warning section in the product literature to: "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	10/2014

	therapies is medically required, this should be done gradually and with appropriate clinical supervision."	
Recuvyra (fentanil, fentanyl)	Following a relatively high number of reports related to urinary retention and dysphoria it was recommended to add the following text in the special precaution section: Additional class effects that may be observed following administration of Recuvyra include dysphoria and urinary retention, therefore appropriate precautionary measures should be in place. And to add the following text to the adverse reaction section of the product literature: In rare cases, dysphoria and urinary retention have also been observed. In field trials, 2 % of dogs treated with the veterinary medicinal product required reversal of adverse opiate effects with naloxone. See section 4.10 The frequency of adverse reactions is defined using the following convention: • very common (more than 1 in 10 animals displaying adverse reaction(s) 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.	10/2014
SUPRELORIN (deslorelin, deslorelin acetate)	Following reports of prolonged or irreversible infertility it was recommended to include the following special warnings section of the product literature: in the SPC section 4.4 special warnings: "In very rare cases (< 0.01 %) the infertility may last more than 18 months."	02/2014

From the continued monitoring (signal detection) a small number of analyses include signals of potential safety or lack of efficacy concerns for which no causal relationship has been established yet. However, subsequent surveillance analysis will focus on potentially more findings that may (or may not) confirm the initially observed signal. In other cases of the surveillance activities it was 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.

However, most of the continuous surveillance of adverse events is inconclusive because of lack of data or lack of detailed information.

The following findings were identified in 2013 from continued monitoring and were further investigated during 2014. The last column contains the outcome of the subsequent analysis of new data in 2014.

Table 2. Issues identified during 2013 that were further monitored during 2014:

	Status of monitoring during 2013 (see also 2013 Public Bulletin)	**Follow-up outcome and conclusions in 2014**
Activyl (indoxacarb)	Monitoring is on-going for neurological signs (e.g. ataxia, convulsion) in dogs. There are no conclusions yet related to potential causal relationship and regulatory action has not been considered necessary at this stage.	The investigation of the neurological signs is still ongoing as part of the PSUR assessment.
Aivlosin (tylvalosin)	Respiratory tract irritation in humans was reported in several reports. Two reports also involved skin irritation in human. Regulatory action has not been considered necessary at this stage.	This issue is closed. More recent surveillance has shown that these were isolated incidents that do not require regulatory action.
Comfortis (spinosad)	Specific monitoring for neurological events and eye disorders including blindness is on-going and a targeted periodic safety update report has been requested from the marketing authorisation holder. There are no conclusions yet related to potential causal relationship and regulatory action has not been considered necessary at this stage.	From the analysis of the PSUR it was recommended to continue the monitoring of eye disorders, neurological disorders and potential adverse effects in the progeny of treated bitches and queens.
Dexdomitor (dexmedetomidine)	Monitoring is on-going concerning cardio-vascular events, including cardiac arrest in dogs. There are no conclusions yet related to potential causal relationship and regulatory action has not been considered necessary at this stage.	This issue is closed. More recent surveillance has shown that these were isolated incidents with unclear causal relationship that do not require regulatory action.
Eurican Herpes 205 (canine herpes virus (f205 strain) antigens)	Monitoring is on-going related to abortion, still birth, premature parturition and vulvovaginitis in dogs, however there are yet no conclusions in relation to potential causal relationship and regulatory action has not been	The MAH has been requested to investigate further. The outcome is expected following the conclusion of the next periodic assessment report in 2015.

	considered necessary at this stage.	
Onsior (robenacoxib)	Monitoring is on-going for renal disorders in cats. The product literature already includes a warning. No additional regulatory action is considered necessary at this stage.	This issue is closed. More recent surveillance has shown that these were isolated incidents with unclear causal relationship that do not require regulatory action.
Slentrol (dirlotapide)	Monitoring is on-going for: • hepatopathy, • pancreatic or eye disorders There are no conclusions yet in relation to potential causal relationship and regulatory action has not been considered necessary at this stage.	Monitoring is still on-going.
Stronghold (selamectin)	Monitoring of reports that include potential lack of efficacy is on-going. No regulatory action is considered necessary at this stage.	This issue is closed. More recent surveillance showed that this signal was not confirmed.
Trocoxil (mavacoxib)	Monitoring is on-going in relation to systemic disorders, including deaths involving bleedings (haemorrhagic diarrhoea) and small intestine ulcers. There are no conclusions yet related to potential causal relationship and regulatory action has not been considered necessary at this stage.	This issue is closed. More recent surveillance showed that these findings were not unexpected for the type of product.

Table 3. Findings identified during 2014 for specific continued monitoring:

	Findings identified in monitoring during 2014
Zuprevo (tildipirosin)	On the basis of a relative high number of reports it was decided to further monitor for cases of lack of efficacy and respiratory signs in cattle. There are no conclusions yet related to potential causal relationship and regulatory action has not been considered necessary at this stage.
Nobivac L4 (vaccine to prevent Leptospira infections in dogs)	Several signals were identified, mainly relating to anaphylaxis and various immune-mediated conditions such as anaemia, thrombocytopenia and arthritis. The 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. There are no conclusions yet related to potential causal relationship and regulatory action has not been considered necessary at this stage.
Pexion (imepitoin)	An unusual high number of non-responders including safety signals were found in dogs. The MAH was recommended to update the product literature (see previously p. 5). 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. Specific monitoring will be continued to follow-on these and future adverse events for this product.
Draxxin (tulathromycin)	A new potential signal was identified for convulsions in cattle, along with persistence of signals related to lack of efficacy. There will be continued monitoring to assess the potential causal relationship with the use of the product.
Bravecto (Fluralaner)	A relative high number of reports are the reason for continued monitoring for this relatively new product.
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 to continue monitoring for these events. There are no conclusions yet related to potential causal relationship and regulatory action has not been considered necessary at this stage.
NexGard (Afoxolaner)	A relative high number of reports involved emesis, convulsion, lethargy, abnormal test result, anorexia and diarrhoea. There will be continued monitoring to assess on the potential causal relationship with the use of the product.

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 were no rapid alerts raised in 2014.

The following non-urgent information, with potential relevance to veterinarians in practice, were discussed during 2014:

Breed-related sensitivity to vaccinations (German and miniature pinscher).

There is information that breed-related sensitivity to vaccinations occurs in German pinschers and to some extent also in miniature pinschers. The reactions occur mainly when the dogs are vaccinated for the first time at the age of twelve weeks and when the vaccine contains a distemper component. The reactions are usually not seen until about 9-12 days after the vaccinations and are characterized primarily by neurological symptoms, such as ataxia and seizures. Most dogs recover, although the symptoms sometimes are severe. The mechanism is probably a vaccine related encephalitis and may be related to an immunological characteristic in the relatively small pinscher-populations.

These reactions have been described in an article in of the Finnish drug information in 2005 (Tabu 2005) as well as in an article in "Svensk Veterinärtidning 2006". Following the publication Swedish veterinarians have become aware of this problem and several reports on adverse reactions following vaccination in pinschers have been sent to the Swedish Medical Products Agency. Based on a report of the typical pinscher reactions received in Germany, a discussion on this issue was re-initiated, though without adding new information to the subject.

Praziquantel, safety in pregnant bitches.

Dog breeders had raised an issue due to some Member States requiring/recommending regular treatment of dogs with praziquantel. The conclusion, supported by the responses from Member States, was that there is no reason to believe that praziquantel poses a safety risk to pregnant bitches.

Porcilis PRRS, live attenuated PRRS virus.

The issue came up after an adverse event report on a herd experiencing problems with increasing mortality rate. The herd had problems with PRRS and carried out a vaccination programme against PRRS. The veterinarian associated with the farm had the virus sequenced before vaccination and when the mortality rate increased over the next year, he once again examined the virus strain in the herd. This time the virus strain showed a 99% homology to Porcilis PRRS as opposed to 85% before vaccination. It was noted that the vaccine strain persists (for at least 1½ year) but otherwise no conclusion could be drawn.

Ovilis Enzovac and Cevac Chlamydia, live vaccine based on attenuated temperature-sensitive mutant of Chlamydophila abortus 1B strain.

The issue was first raised in 2010 and brought up for follow up in 2014. Researchers from the Moredun Research Institute of Edinburgh identified vaccine strains (strain 1B) of Chlamydophila abortus bacterium in abortion material from vaccinated ewes[4]. Gene sequencing techniques showed that some

[4] Evidence of Chlamydophila abortus vaccine strain 1B as a possible cause of ovine enzootic abortion, Vaccine 2010, Wheelhouse N. et al

of the samples submitted contained DNA only present in the vaccine strain and the publication by Wheelhouse et al. reads that the bacteria were present in numbers large enough to be the probable cause of abortion. It was agreed that the obligations on the MAHs for these vaccines to carry out investigations of the strains in aborted foetuses and to submit yearly safety update reports to the national competent authorities should be lifted. The MAHs were requested to carry on investigations of the strains involved in abortions on a voluntary basis.

Domosedan Gel, application site reactions.

Based on the severity of 2 adverse event reports on application site reactions in horses in the oral cavity (oedema, necrosis), a request to do a targeted periodic safety update report was submitted to the MAH. In parallel all Member States were requested to give feedback on the topic to make sure that no similar reports were overlooked. The NUI is ongoing.

5. Overall conclusions

The periodical surveillance of centrally authorised products by signal detection using the increased pool of data and the analysis tools are now well established. The overall number of regulatory actions required for CAPs was in line with experience from previous years and in general the large majority of PSURs were concluded on no change to the benefit/risk balance for a product. Also most of the signals identified during signal detection activities were considered inconclusive. This may signify that the conditions of use of veterinary medicinal products as authorised and published on the product information is in general sufficiently accurate and in line with day to day practice.

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. It is recognised that increased transparency and feedback is a prerequisite for 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 own 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 quality data 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 for centrally authorised veterinary medicinal products during 2014

A total of 11,878 reports relating to exposure to centrally authorised veterinary medicinal products were received in 2014, concerning 11,274 adverse events in animals and 604 adverse events in humans.

The adverse event reports received concerned 114 products, which is approximately 72% of the 159 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.

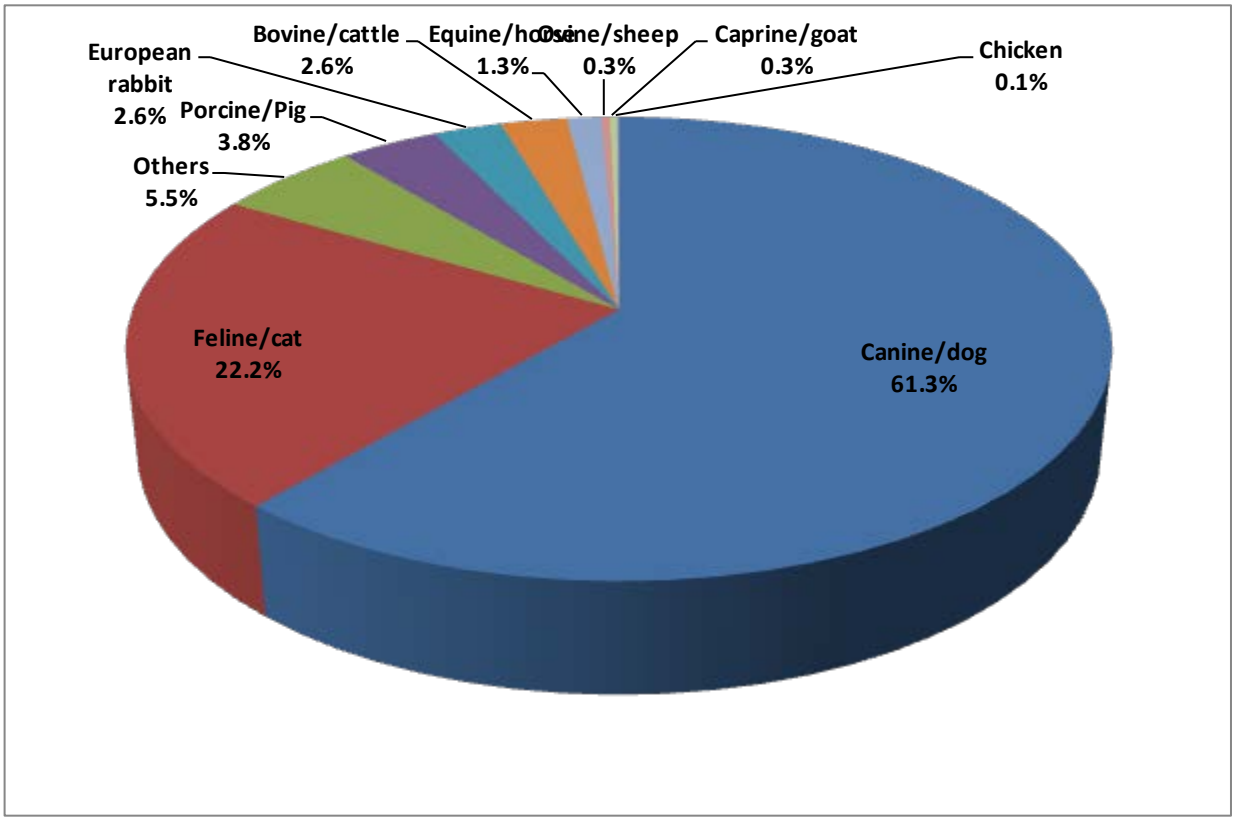
Of the 11,274 reports in animals, 9,905 reports concerned companion animals, most frequently dogs (7,269) and cats (2,636), and 1,304 reports concerned food-producing animals.

Of all the reports received in 2014 5,284 occurred in EU/EEA countries, of which 5,191 concerned animal adverse events and 93 concerned human adverse events. Most of the 6,594 reports received from third countries (6,083 concerning animals and 511 concerning humans) were from the United States (83%) and Canada (6%), with the remainder being, listed by numbers of reports received, from Australia, Switzerland, Brazil, Japan, South Africa, Colombia New Zealand, Argentina, Mexico, Thailand Russia, China, Costa Rica, Philippines, Taiwan, Ecuador, Guatemala, Ukraine, Bahamas, Bolivia, Honduras, Puerto Rico, Singapore, Uruguay and Vietnam.

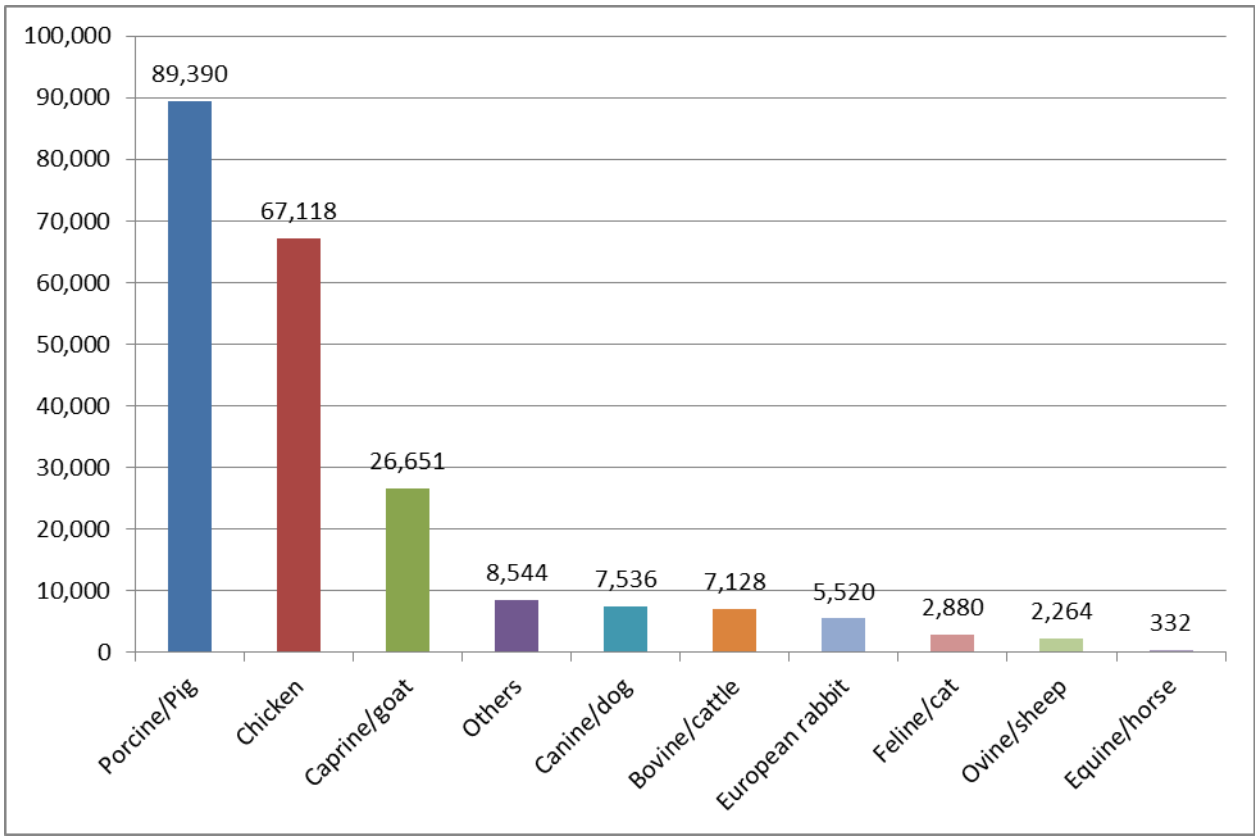
Table 4. Centrally authorised products: summary statistics on reports by target species, including reports in humans (Reports received between 1 January 2014 and 31 December 2014.)

Species	Total reports (n)	Total reacting animals included in the reports (n)
Food producing animals		
Porcine/Pig	448	89,390
European rabbit	313	5,520
Bovine/cattle	305	7,128
Equine/horse	157	332
Ovine/sheep	40	2,264
Caprine/goat	32	26,651
Chicken	9	67,118
Companion animals		
Canine/dog	7,269	7,536
Feline/cat	2,636	2,880
Others	656	8,544
Human beings	604	N/A

Graph 2. % of total adverse event reports within the EU central database by species.



Graph 3: Total number of animals reacting within the EU central database by species



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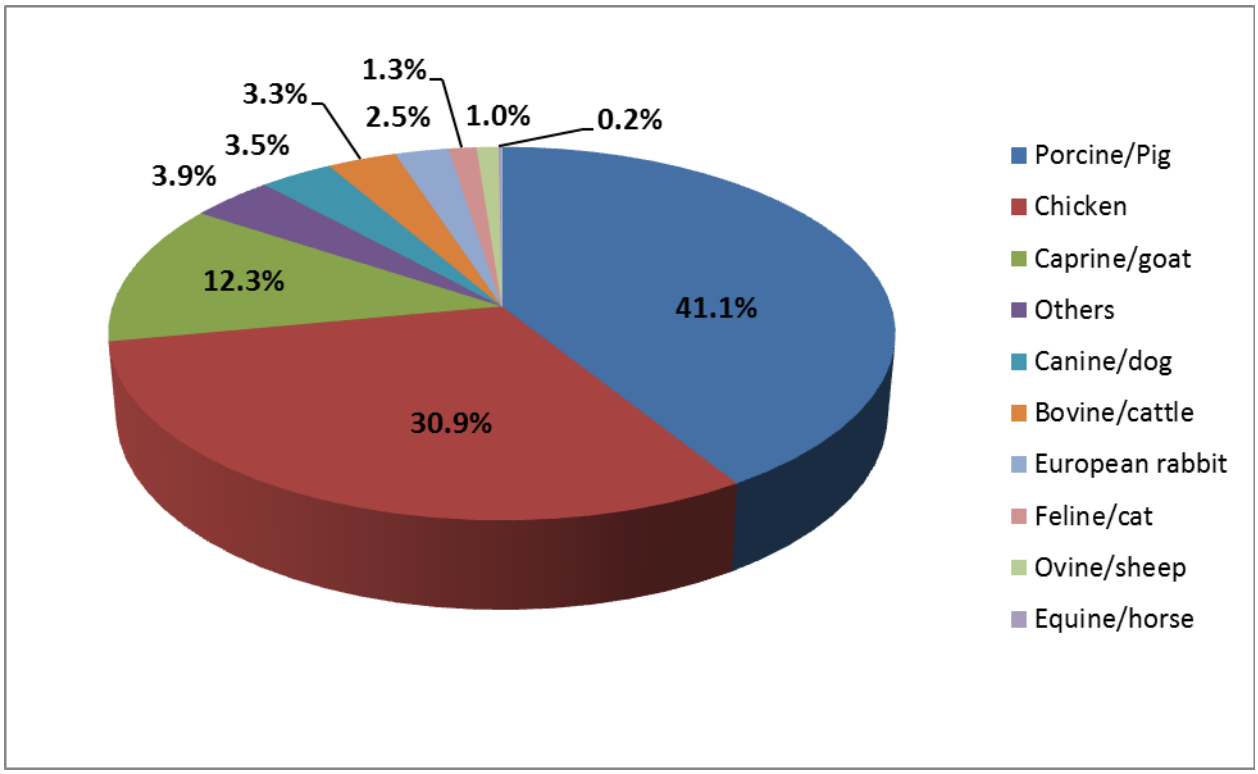
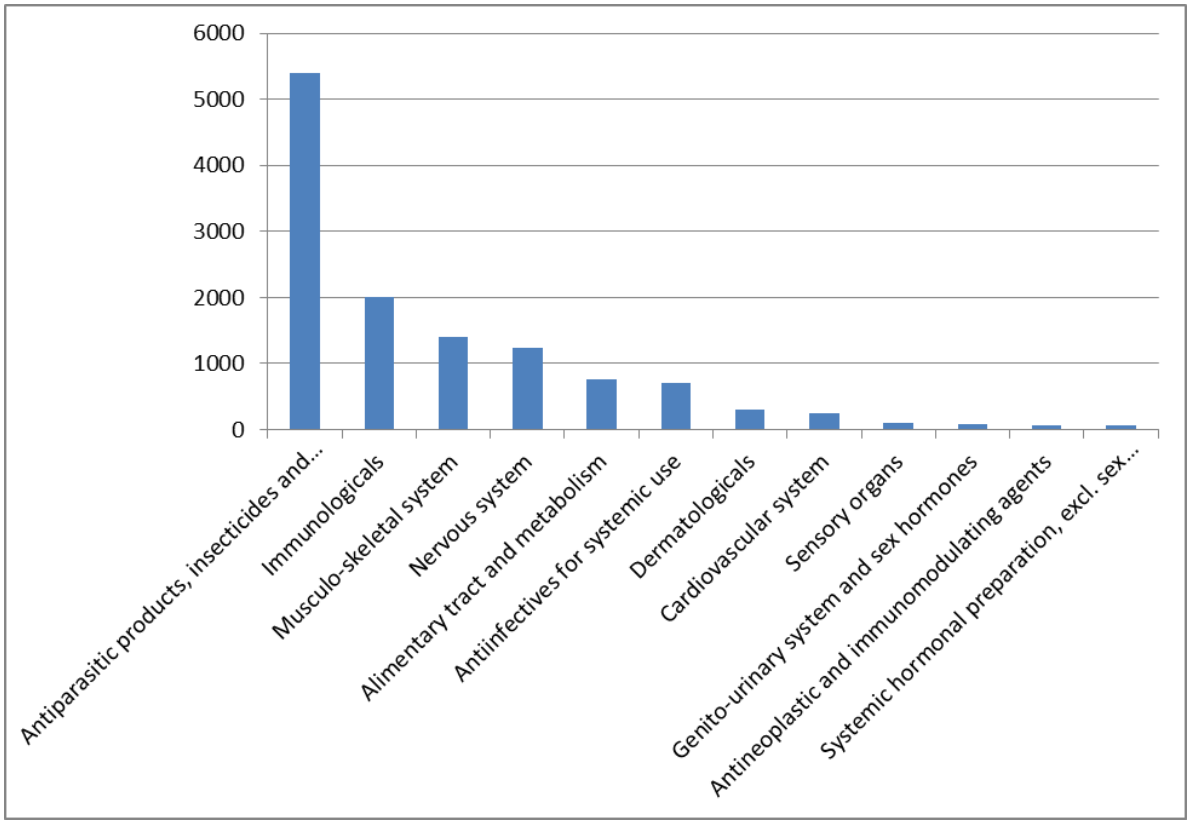
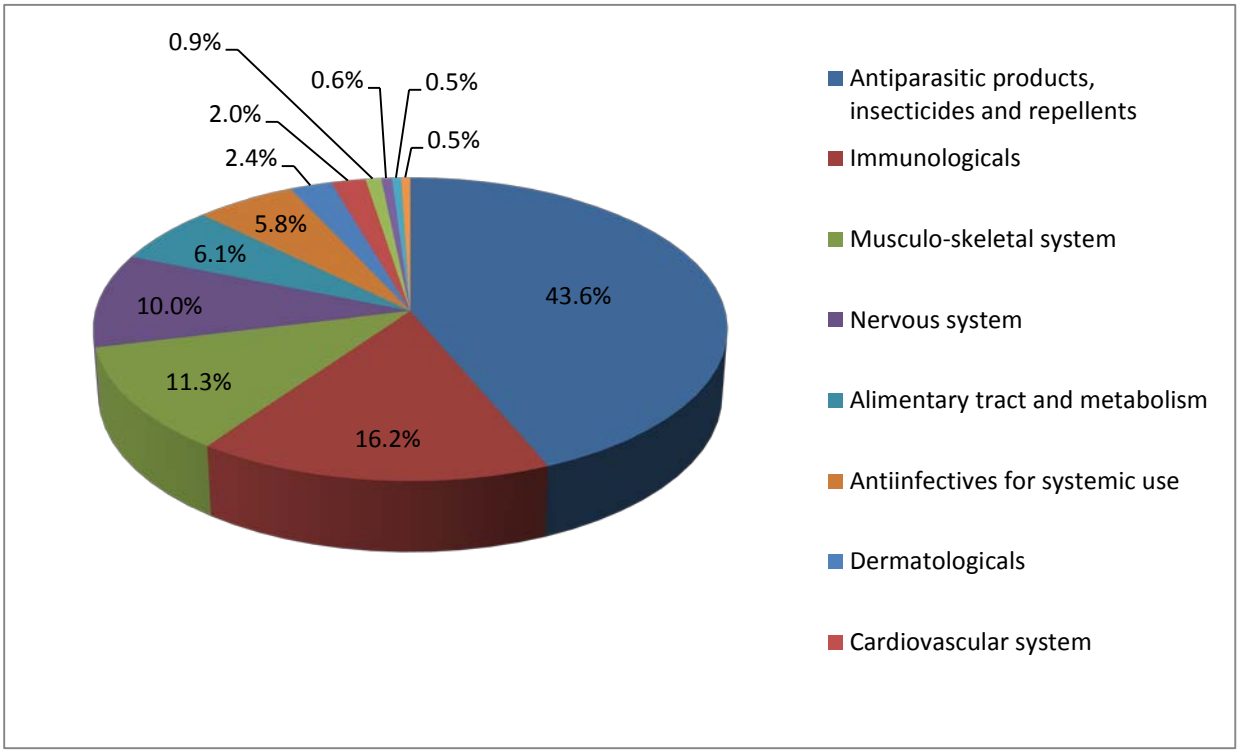


In the below charts, the reports of adverse events in various animal species and in human beings for centrally authorised products have been grouped according to the anatomical therapeutical chemical coding system (ATCvet; see http://www.whocc.no/atcvet/ for further explanations).

Graph 5: Number of adverse event reports classified by ATC coded type of product.



Graph 6: % of total adverse event reports classified by ATC coded type of product.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0.5%
2.0%
0.5%
2.4%
5.8%
6.1%
10.0%
43.6%
11.3%
16.2%
Antiparasitic products, insecticides and repellents
Immunologicals
Musculo-skeletal system
Nervous system
Alimentary tract and metabolism
Antiinfectives for systemic use
Dermatologicals
Cardiovascular system