EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use

Veterinary pharmacovigilance 2013

Public bulletin

1. Executive Summary

This public bulletin is primarily aimed at veterinarians and summarises the main outcome of post-marketing surveillance activities for veterinary medicinal products taken place during 2013 at the level of the European Medicines Agency (EMA), and therefore focuses on centrally authorised products. It includes recommendations to change the safety advice / warning statements and highlights on-going monitoring of several centrally authorised products, based on pharmacovigilance information. It also includes a summary of the discussions that have taken place at the European level regarding pharmacovigilance issues related to veterinary medicinal products authorised nationally. In the reporting period the assessment of the pharmacovigilance information for the centrally authorised medicinal products led to recommendations for amendments or new warnings in the product literature based on post-marketing adverse event data for a limited number of products.

Overall the pharmacovigilance system for veterinary medicinal products has matured and post-marketing surveillance has been strengthened through the increased reporting over the years and availability of all adverse event data in a central database together with the technical searching tools available. Further involvement of veterinarians as primary providers of their "field" experience with veterinary medicinal products and wider submission of adverse event reports, also for food-producing animals is encouraged.

2. Introduction

This is the 11th bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2013. The aim of this bulletin is to contribute to the public communication on veterinary medicinal products, particularly on the surveillance of the adverse events and safety issues of veterinary medicines in the European Union (EU). The bulletin is particularly addressed to veterinary health professionals, but also other to stakeholders.

All reports of adverse events that occurred in the EU concerning authorised veterinary medicinal products are collected and evaluated both by the marketing authorisation holder who places the

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product on the market and by the national competent authorities or the EMA. These reports can concern events such as death, life-threatening events or permanent lesions, reactions in humans (e.g. the veterinarian or the animal owner administering the product), or less serious events. Adverse event reports having occurred outside the EU are also collected and the marketing authorisation holder is obliged to provide these, 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 almost 111,000 reports of adverse events, approximately 69,000 of which occurred within the EU and 42,000 outside the EU.

The overall surveillance of the events is done through the evaluation of periodic safety update reports, which are a review of all adverse event reports having occurred in a set period, and is provided by the marketing authorisation holders as well as continuous monitoring of all pharmacovigilance data available that is in operation at the national competent authorities and the 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 medicines is 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 pharmacovigilance working party (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 matters that have been considered by the CVMP and the PhVWP-V during 2013.

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

The centrally authorised products are the 140 veterinary medicinal products authorised 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 can be obtained via 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 8,166 adverse event reports relating to exposure to centrally authorised products were received in 2013, concerning 7,796 adverse events in animals and 370 adverse events in humans, i.e. reporting largely at the same level as in 2012. Notably the majority of reports concerned companion animals, with adverse event reports in dogs and cats accounting for 86% of the reports in animal species received compared to 13% in cattle, pigs, chicken and goats. Further descriptive statistics regarding the reports received in 2013 can be found in Annex 1.

The EMA's CVMP and its PhVWP-V reviewed during 2013 in total 149 periodic safety update reports provided by the marketing authorisation holders.

With the increased number of electronic data available, it now also allows for signal detection at the level of the central EU database. Such signal detection takes place at certain intervals for each of the centrally authorised products and resulted in 2013 in 470 surveillance reports. During 2013, and as a result from the continuous surveillance of adverse events and the evaluation of periodic safety update

reports, the following regulatory actions were taken, which involved in particular changes to the product literature to include additional warnings:

Product name (active ingredient)	**Findings and recommendation to the marketing authorisation holder**	**Date issued**
Activyl (indoxacarb)	On the basis of a relative high number of reports that include neurological signs in cats it was recommended to add the following warning to the product literature: "In rare cases of licking the product, gastrointestinal signs (e.g. emesis, anorexia) or reversible neurological signs (e.g. incoordination, tremor, ataxia, mydriasis) have been observed in cats".	09/2013
CERTIFECT (amitraz, fipronil, methoprene)	On the basis of a relative high number of reports that included the sign "Pemphigus foliaceous" it was recommended to include the following warning to the product literature: "In very rare instances, certain sensitive dogs may develop skin irritation at the application site. Other forms of dermatitis including pemphigus-like conditions may occur in even rarer instances. Should this occur, contact your veterinarian promptly for treatment advice and discontinue use of the product."	06/2013
Equilis StrepE (live deletion mutant streptococcus equi strain tw928 (10exp9.0 to 10exp9.4)	Following a relative high number of reports that included diffuse oedematous swelling it was recommended to update the product literature with the following warning: "Further, an increase in rectal temperature up to 2°C may occur on the day of vaccination. In rare cases, inappetance, fever, ~~and~~ shivering and diffuse oedematous swellings (e.g. facial oedema, swollen muzzle/upper lip) may be observed. In very rare cases depression may develop."	09/2013
Leucogen (p45 FeLV-envelope antigen)	Following the observation of anaphylactic shock in a relative high number of reports it was recommended to update the product literature with the following warning: "In very rare cases (< 0.01%) anaphylactic reactions have been reported. In case of anaphylactic shock, appropriate symptomatic treatment should be administered".	12/2013
NOBIVAC MYXO-RHD (live myxoma vectored rhd virus strain 009)	Following reports of hypersensitivity reactions in pet rabbits it was recommended to conduct a post-authorisation safety study to collect safety data following the use of the product in pet rabbits. In addition it was recommended to update the product literature to include the following warnings: • serious hypersensitivity reactions which may be fatal; and	06/2013

	• the entire range of local reactions (e.g. injection site necrosis, injection site erythema, injection site scab, injection site hair loss, injection site pruritus, injection site pain, injection site crust and injection site abscess) and including clinical signs typical of mild forms of myxomatosis.	
SUVAXYN PCV (porcine circovirus recombinant virus (cpcv) 1-2, inactivated)	Following observations of anaphylactic reactions resulting in deaths it was recommended to update the product literature with the following warning: "Anaphylactic reactions are uncommon but may be lethal. In case of such reactions, appropriate treatment is recommended"	09/2013
SUPRELORIN (deslorelin, deslorelin acetate)	In relation to observations of potential lack of efficacy it was recommended to update the product literature with the following text: "Uncommonly (>0.1% to <1%), lack of expected efficacy has been reported in dogs (in the majority of reports a lack of reduction in testicle size was reported and/or a bitch was mated). Only testosterone levels (i.e. and established surrogate marker of fertility) could definitely confirm a lack of efficacy of the treatment. If lack of treatment is suspected, then the dog's implant (e.g. presence) should be checked."	02/2013

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:

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.
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.
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.
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.
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 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.
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.
Stronghold (selamectin)	Monitoring of reports that include potential lack of efficacy is on-going. No regulatory action is considered necessary at this stage.
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.

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.

The following issues with potential relevance to veterinarians in practice were discussed during 2013:

German pinchers / miniature pinchers and distemper vaccines.

Monitoring is continuing since 2012 regarding neurological symptoms being observed in pinchers being vaccinated, typically at the age of twelve weeks with a vaccine that contains a distemper component. The symptoms include ataxia and seizures and usually occur until about 9-12 days after the vaccination. Most dogs recover, although the symptoms sometimes are severe. The possible mechanism is yet unclear and regulatory measures regarding the potential products have not been issued at this stage.

Dissociative anaesthetics in Sphynx cats

The issue had arisen following correspondence from the Sphynx Club in France. The breed club had issued an information leaflet contraindicating the use of dissociative anaesthetics in Sphynx cats due to the risk of severe adverse events including paralysis and respiratory disorders, some of which resulted in fatalities. The French Agency for Veterinary Medicinal Products (ANMV), had initiated investigations into the issue, including convening an expert group and literature searches, to determine the scientific basis underlying the observed reactions. From the responses received from the national competent authorities that responded to the NUI, further investigations and data evaluation undertaken, and the conclusions of an *ad-hoc* expert group in France, there did not appear to be any scientific evidence or pharmacovigilance data to support specific contra-indication for the use of dissociative anaesthetics in Sphynx cats. The breed association has been notified accordingly about this conclusion.

***Salmonella gallinarum* field isolates from laying hens related to the vaccine strain SG9RF (Nobilis SG 9R)**

The PhVWP-V considered an article published by Vaccine (Volume 31, Issue 43, 9 October 2013, pages 4940-4945) on the use of the vaccine Nobilis SG 9R in relation to increased mortality rate occurring at a vaccinated farm in Belgium. The article raises the overall concern about the use of undefined strains as live vaccines and although it could not be demonstrated that the field strain had derived from the vaccine strain it was shown that the observed field strain differed by only a few single-base-pair substitutions compared to the SG9R vaccine strain. Hence the attenuation might have been reversed by spontaneous random mutations which could have become rapidly fixed in the bacterial population if there is strong selection pressure for virulence.

The licensing/marketing status for Nobilis SG 9R in Europe was established as follows:

- The vaccine is licensed and marketed in the following member states: Austria, Bulgaria, Czech Republic, Italy, Netherlands, Poland and Romania;
- The vaccine is still licensed but not marketed in the following member states: Greece, Belgium and Luxembourg

The national authorities were asked to take note of the publication.

Borrelia vaccine in dogs

Twelve reports of adverse reactions in dogs vaccinated with Trilyme have been sent by Swedish veterinarians. The reactions include injection site swellings, usually about 3-5 cm in diameter, but up to 15 cm in one case. Most dogs appeared unaffected by the swellings, but a few dogs also showed fever, tiredness and dullness. The swellings reported in dogs in Sweden are much larger than indicated in the SPC, which states "transitory swelling may be observed through palpation at the injection site (maximum diameter of 7 mm for a maximum of 5 days)". The issue is still under investigation.

Pentobarbital use for euthanasia and apparent delayed effect on foetus.

An adverse event report was discussed concerning euthanasia of a cow in the 7th month of pregnancy with pentobarbital. The foetus was meant to be removed from the cow for histological examination. However, when the foetus was extracted it was still alive with a strong heart beat 5 minutes after extraction. The foetus was euthanised separately 30 minutes after euthanasia of the cow. The national authorities were asked to take note and to consider the need for regulatory action.

5. Overall conclusions

The increasing EU data set of adverse events has strengthened the signal detection capabilities in particular with the introduction of new analysing tools during the last two years. The assessment of the pharmacovigilance information for the centrally authorised medicinal products in 2013 led to recommendations for amendments or new warnings in the product literature based on post-marketing adverse event data for a limited number of products. No other regulatory actions were necessary. This would 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. 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.

ANNEX 1: Descriptive analysis of reports received for centrally authorised veterinary medicinal products during 2013

A total of 8,166 reports relating to exposure to centrally authorised veterinary medicinal products were received in 2013, concerning 7,796 adverse events in animals and 370 adverse events in humans.

The adverse-event reports received concerned 107 products, which is approximately 71% of the 151 centrally authorised products with a valid marketing authorisation granted by the end of 2013.

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 7,796 reports in animals, 6,735 reports concerned companion animals, most frequently dogs (4,545) and cats (2,155), and 1,061 reports concerned food-producing animals.

Of all the reports received in 2013, 3,598 occurred in EU/EEA countries, of which 3,531 concerned animal adverse events and 67 concerned human adverse events. Most of the 4,568 reports received from third countries (4,265 concerning animals and 303 concerning humans) were from the United States (79%) and Canada (9%), with the remainder being, listed by numbers of reports received, from Australia, Brazil, Japan, Switzerland, New Zealand, Colombia, Mexico, Russia, South Africa, Ukraine, Argentina, South Korea, Thailand, Guatemala, Taiwan, China, Ecuador and Puerto Rico.

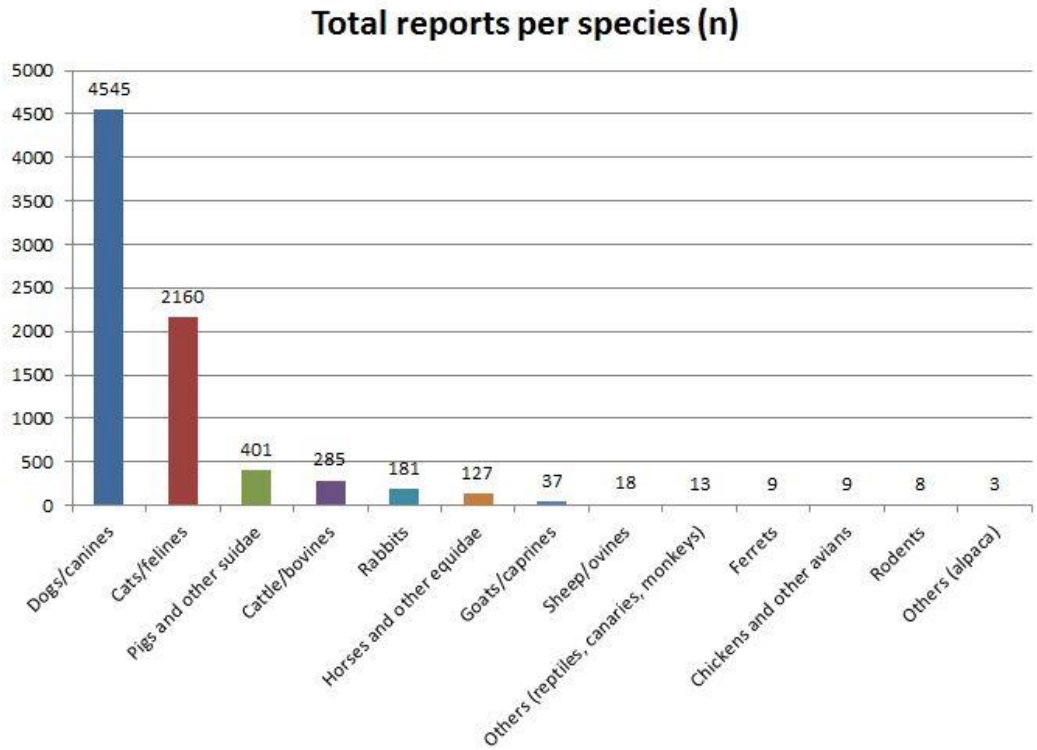
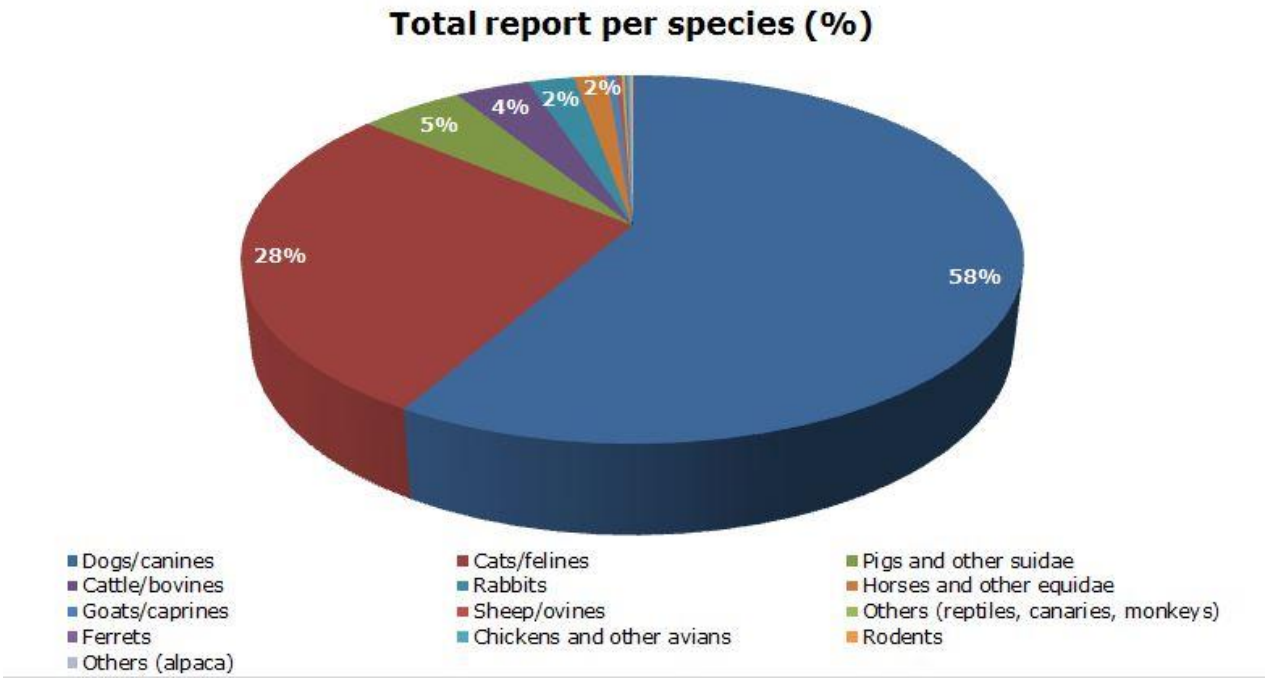
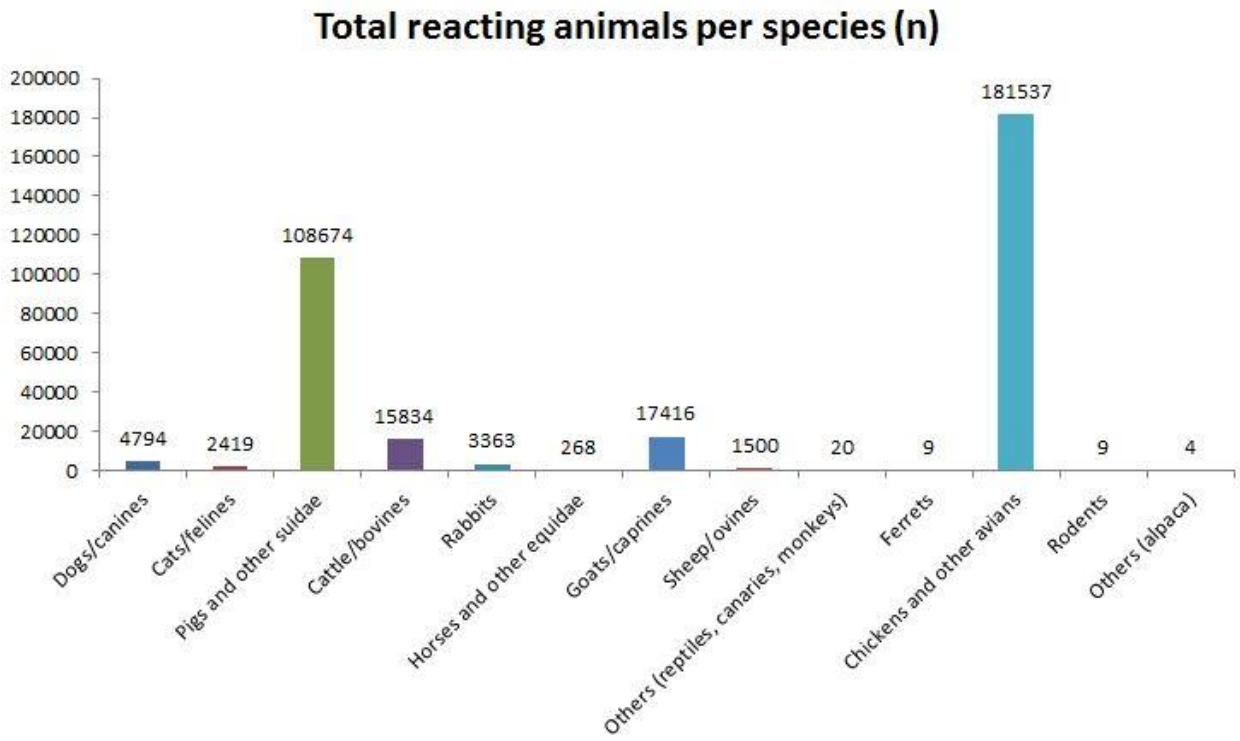
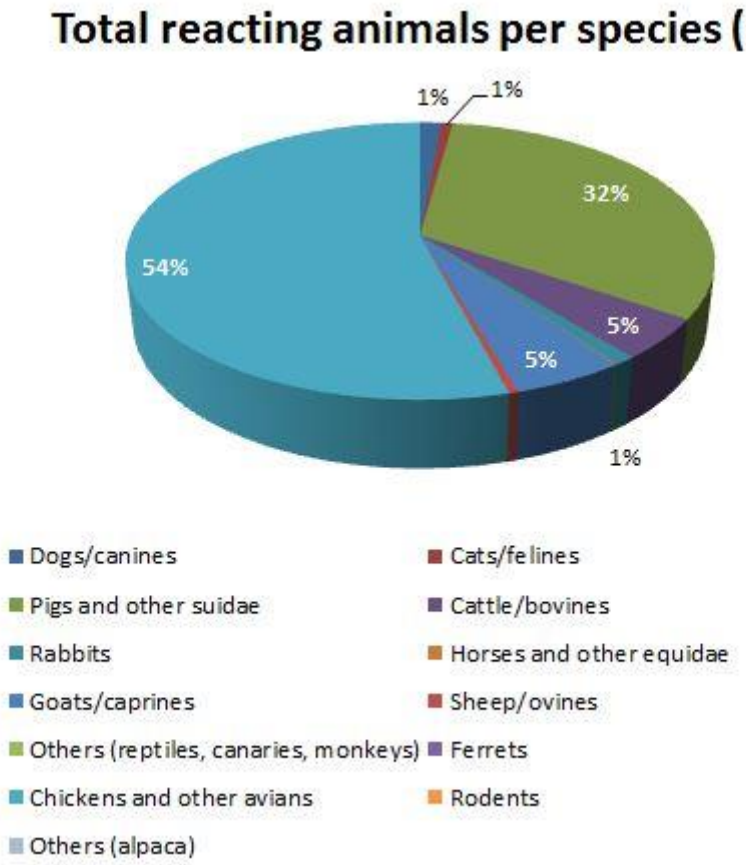


Table 1. Centrally authorised products: summary statistics on reports by target species, including reports in humans (Reports received between 1 January 2013 and 31 December 2013.)

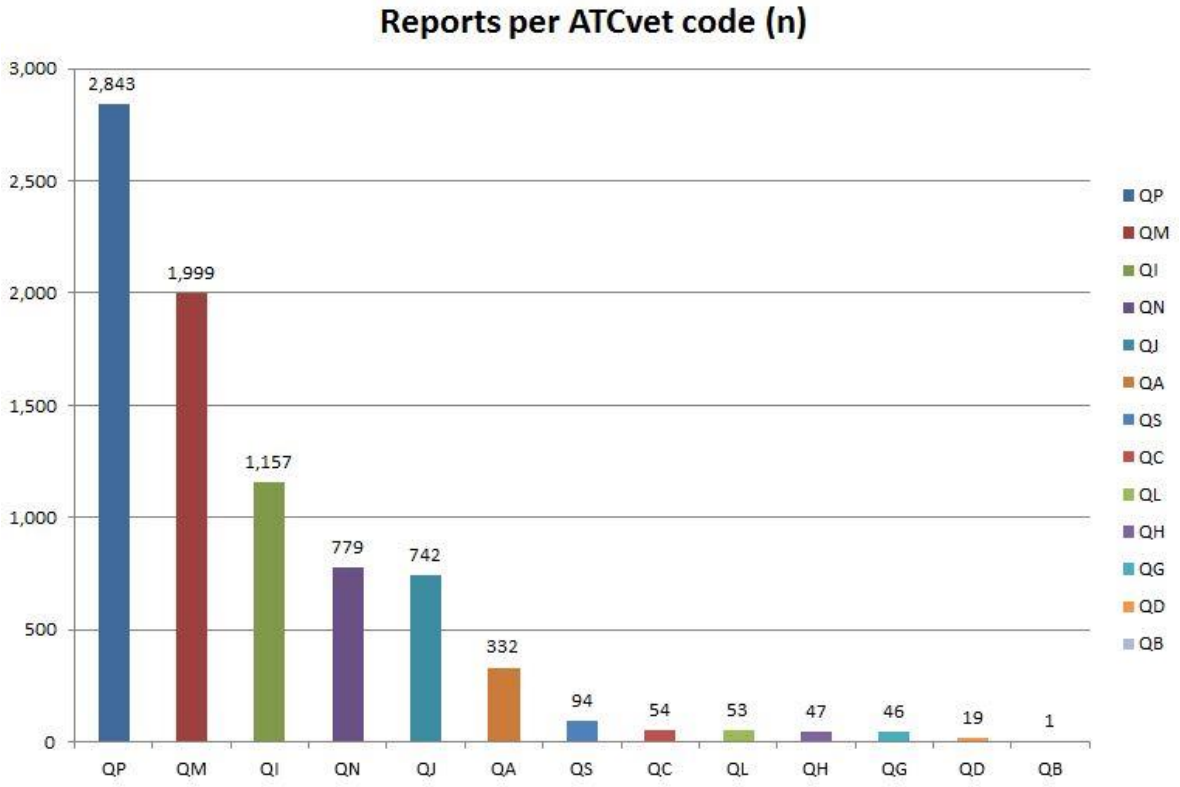
	Total reports (n)	Total reacting animals included in the reports (n)
Food-producing animals		
Sheep/ovines	18	1500
Pigs and other suidae	401	108674
Cattle/bovines	285	15834
Rabbits	181	3363
Horses and other equidae	127	268
Goats/caprines	37	17416
Chickens and other avians	9	181537
Others (alpaca)	3	4
Companion animals		
Dogs/canines	4545	4794
Cats/felines	2160	2419
Rodents	8	9
Ferrets	9	9
Others (reptiles, canaries, monkeys)	13	20
Human beings	370	N/A
All	**8166**	**335847**

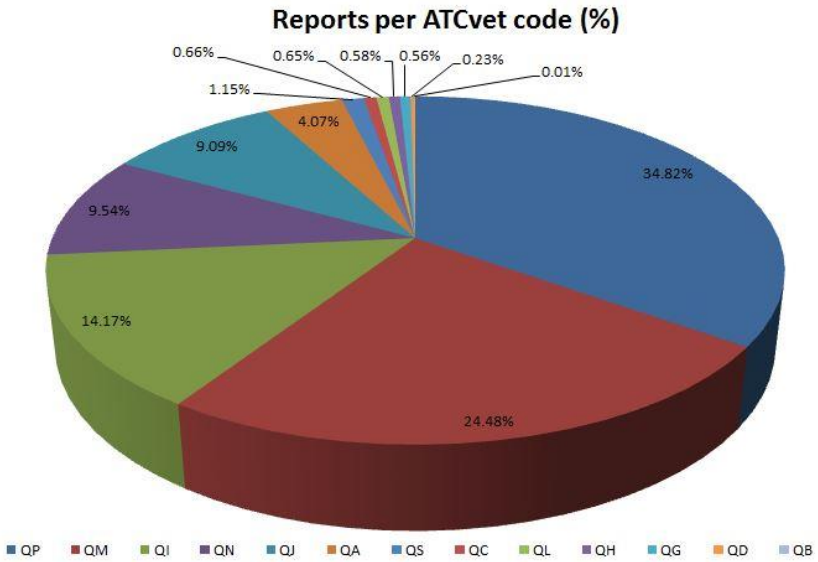



Total reacting animals per species (n)
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
4794
2419
108674
15834
3363
268
17416
1500
20
9
181537
9
4
Dogs/canines
Cats/felines
Pigs and other suidae
Cattle/bovines
Rabbits
Horses and other equidae
Goats/caprines
Sheep/ovines
Others (reptiles, canaries, monkeys)
Ferrets
Chickens and other avians
Rodents
Others (alpaca)


Total reacting animals per species (n)
1%
1%
32%
54%
5%
5%
1%
Dogs/canines
Cats/felines
Pigs and other suidae
Cattle/bovines
Rabbits
Horses and other equidae
Goats/caprines
Sheep/ovines
Others (reptiles, canaries, monkeys)
Ferrets
Chickens and other avians
Rodents
Others (alpaca)

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).





QA Alimentary tract and metabolism. QB Blood and blood-forming organs. QC Cardiovascular system. QD Dermatologicals. QG Genito-urinary system and sex hormones, QH Systemic hormonal preparation, excl. sex hormones and insulin. QI Immunologicals. QJ Antiinfectives for systemic use. QL Antineoplastic and immunomodulating agents. QM Musculo-skeletal system. QN Nervous system. QP Antiparasitic products, insecticides and repellents. QS Sensory organs.