7 February 2013
EMA/CVMP/PhVWP/717241/2012
Committee for Medicinal Products for Veterinary Use

Veterinary pharmacovigilance 2012

Public bulletin

1. Introduction

This is the 10th bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2012. 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). It is addressed to all stakeholders, and particularly to veterinary health professionals.

In the EU, all adverse-event reports concerning authorised veterinary medicinal products (VMPs) are collected and evaluated by national competent authorities. Reports that concern serious events like death, life-threatening events or permanent lesions are collated in a single database: EudraVigilance Veterinary (EVVet). This database also includes reports of serious and unexpected adverse events that occurred outside the EU, reported by the marketing-authorisation holder, when the product concerned is also authorised in the EU. EudraVigilance Veterinary is increasingly used for collecting reports of events that do not fall under the legal definition of serious, which is useful because these reports allow analysis to be performed using a more complete dataset. Electronic reporting became mandatory in November 2005, and EVVet now contains more than 90,000 reports of adverse events, approximately 59,000 of which occurred within the EU and 31,000 outside the EU.

Under current legislation, the Agency is responsible for the pharmacovigilance of centrally authorised VMPs, i.e. ones that have been granted an EU-wide marketing authorisation, whereas the surveillance of non-centrally authorised VMPs takes place at Member State level. However, procedures are also in place within the Agency's Committee for Medicinal Products for Veterinary Use (CVMP) and its Pharmacovigilance working party (PhVWP-V) for the assessment of adverse events relating to such products, where necessary.

This document gives an overview of the outcome of all pharmacovigilance matters that have been considered during 2012.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

© European Medicines Agency, 2013. Reproduction is authorised provided the source is acknowledged.

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

A total of 7,783 reports relating to exposure to centrally authorised veterinary medicinal products were received in 2012, concerning 7,361 adverse events in animals and 422 adverse events in humans.

The adverse-event reports received concerned 100 products, which is approximately 75% of the 132 centrally authorised products with a valid marketing authorisation granted by the end of 2012.

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 their causality assessment.

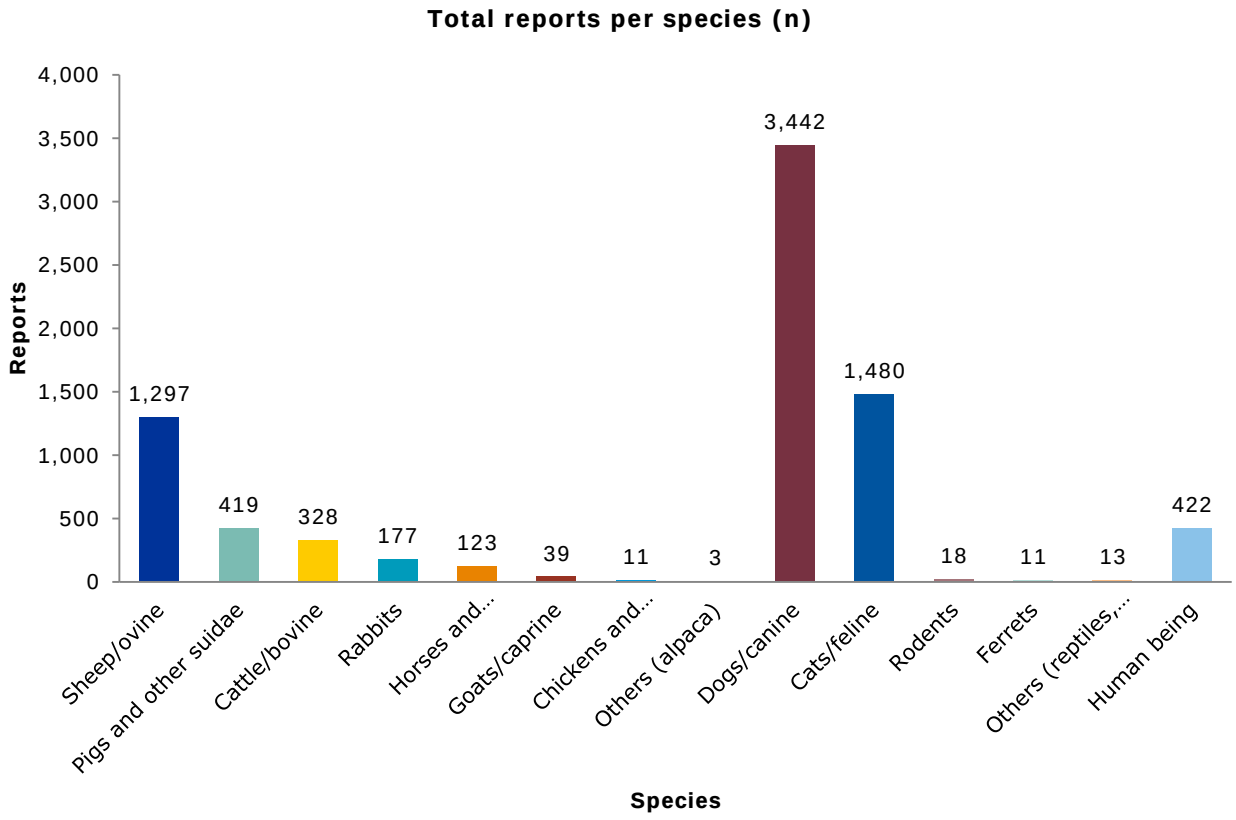
Of the 7,361 reports in animals, 4,964 concerned companion animals, most frequently dogs (3,442) and cats (1,480), and 2,397 concerned food-producing animals.

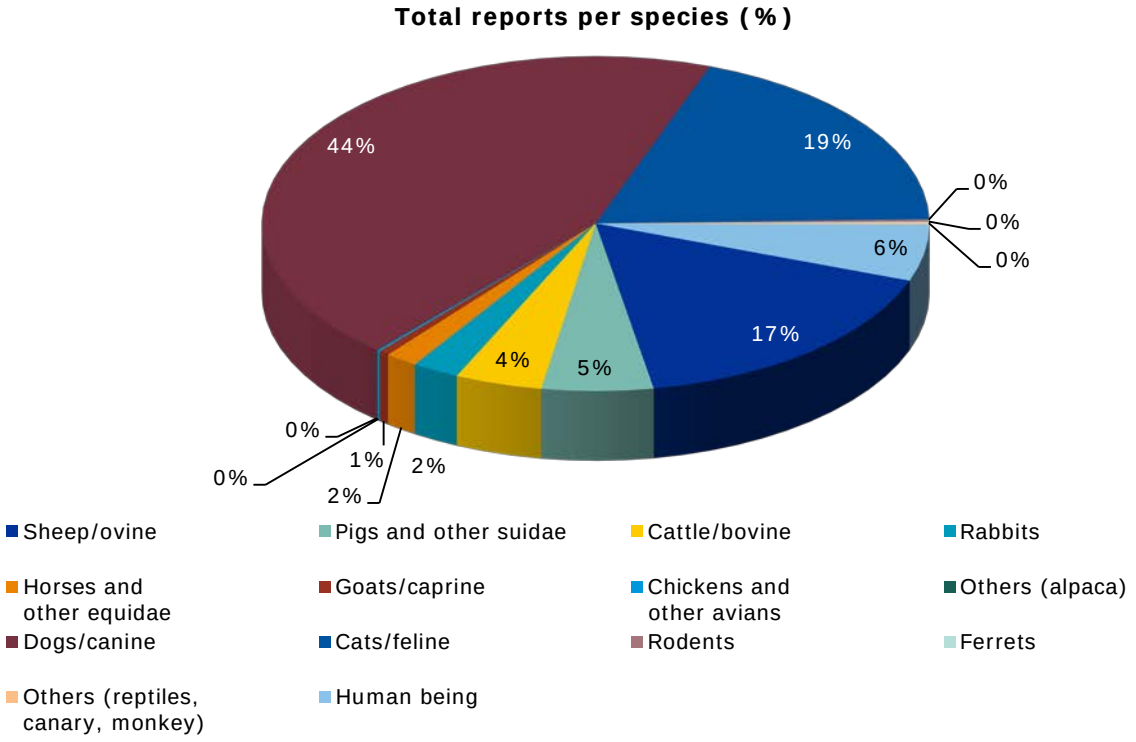
Of all the reports received in 2012, 3,944 occurred in EU/EEA countries, of which 3,861 concerned animal adverse events and 83 concerned human adverse events. Most of the 3,839 reports received from third countries (3,500 concerning animals and 339 concerning humans) were from the United States (79%) and Canada (9%), with the remainder being, listed by numbers of reports received, from Brazil, Australia, New Zealand, Japan, Switzerland, South Africa, Mexico, Colombia, Guatemala, Taiwan, Ukraine, Thailand, Ecuador, South Korea, Malaysia, Russia, Turkey, the Philippines, Puerto Rico and Venezuela.

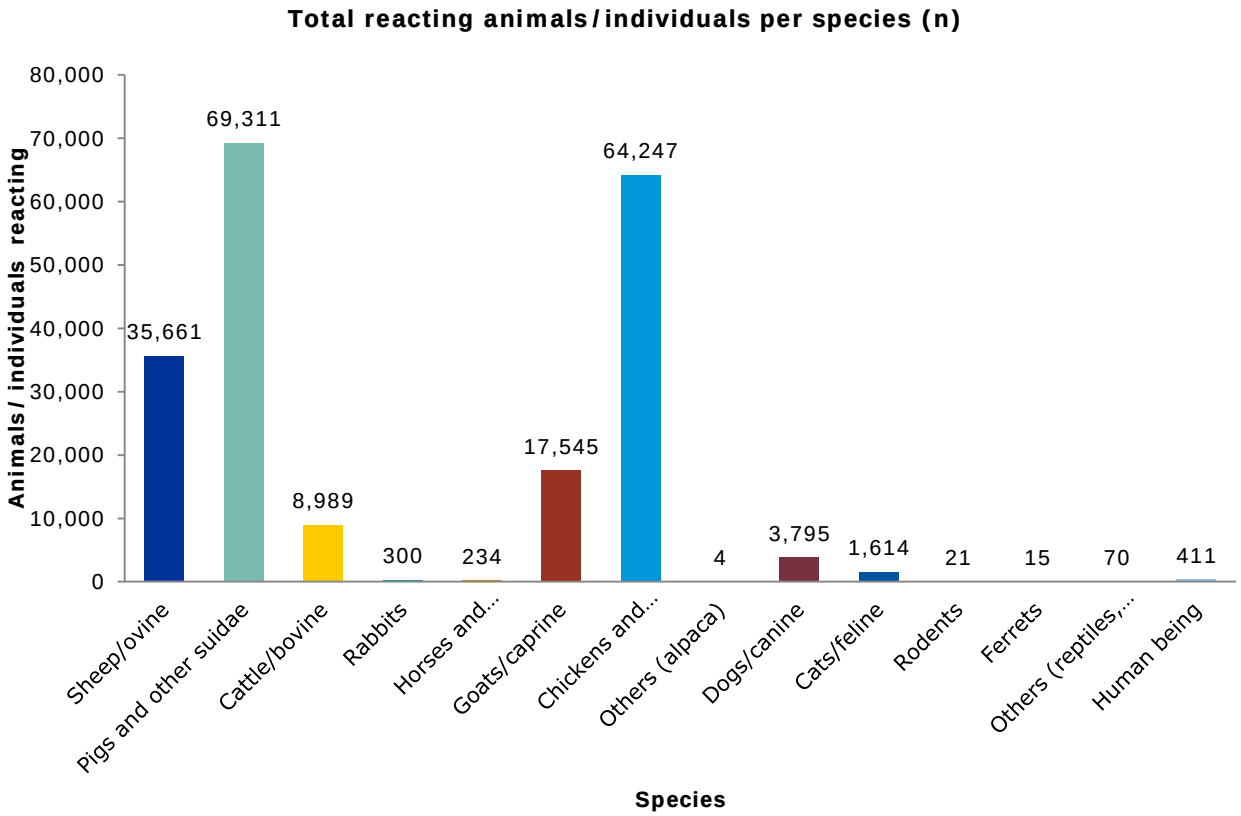
Table 1. Centrally authorised products: summary statistics on reports by target species, including reports in humans (Reports received between 1 January 2012 and 31 December 2012.)

	Total reports (n)	Total reacting animals (or individuals) included in the reports (n)
Food-producing animals		
Sheep/ovines	1,297	35,661
Pigs and other suidae	419	69,311
Cattle/bovines	328	8,989
Rabbits	177	300
Horses and other equidae	123	234
Goats/caprines	39	17,545
Chickens and other avians	11	64,247
Others (alpaca)	3	4
Companion animals		
Dogs/canines	3,442	3,795
Cats/felines	1,480	1,614
Rodents	18	21
Ferrets	11	15
Others (reptiles, canaries, monkeys)	13	70
Human beings*	422	411
All	**7,783**	**202,217**

* Some asymptomatic exposure reports have been received, although these were beyond the legal requirements.


Total reports per species (n)
Reports
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
1,297
419
328
177
123
39
11
3
3,442
1,480
18
11
13
422
Sheep/ovine
Pigs and other suidae
Cattle/bovine
Rabbits
Horses and...
Goats/caprine
Chickens and...
Others (alpaca)
Dogs/canine
Cats/feline
Rodents
Ferrets
Others (reptiles,...
Human being
Species


Total reports per species (%)
44%
19%
0%
0%
6%
0%
17%
4%
5%
0%
1%
2%
0%
2%
Sheep/ovine
Pigs and other suidae
Cattle/bovine
Rabbits
Horses and other equidae
Goats/caprine
Chickens and other avians
Others (alpaca)
Dogs/canine
Cats/feline
Rodents
Ferrets
Others (reptiles, canary, monkey)
Human being


Total reacting animals/individuals per species (n)
Animals/ individuals reacting
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
35,661
69,311
8,989
300
234
17,545
64,247
4
3,795
1,614
21
15
70
411
Sheep/ovine
Pigs and other suidae
Cattle/bovine
Rabbits
Horses and...
Goats/caprine
Chickens and...
Others (alpaca)
Dogs/canine
Cats/feline
Rodents
Ferrets
Others (reptiles,...
Human being
Species

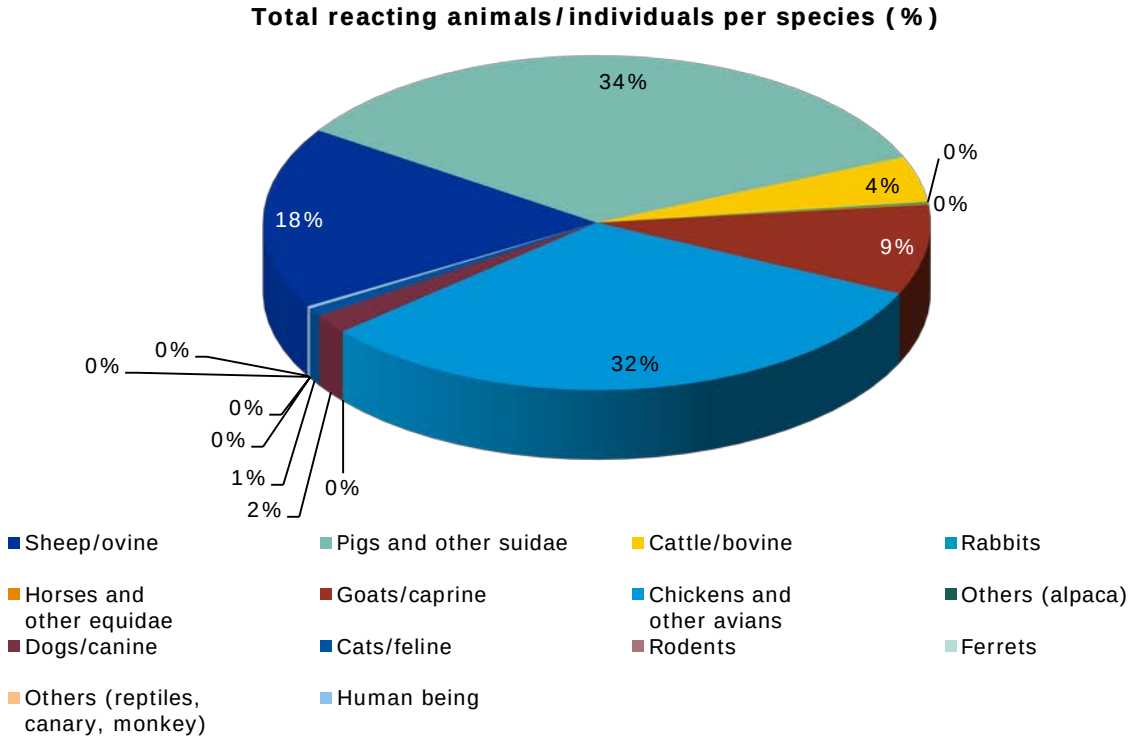
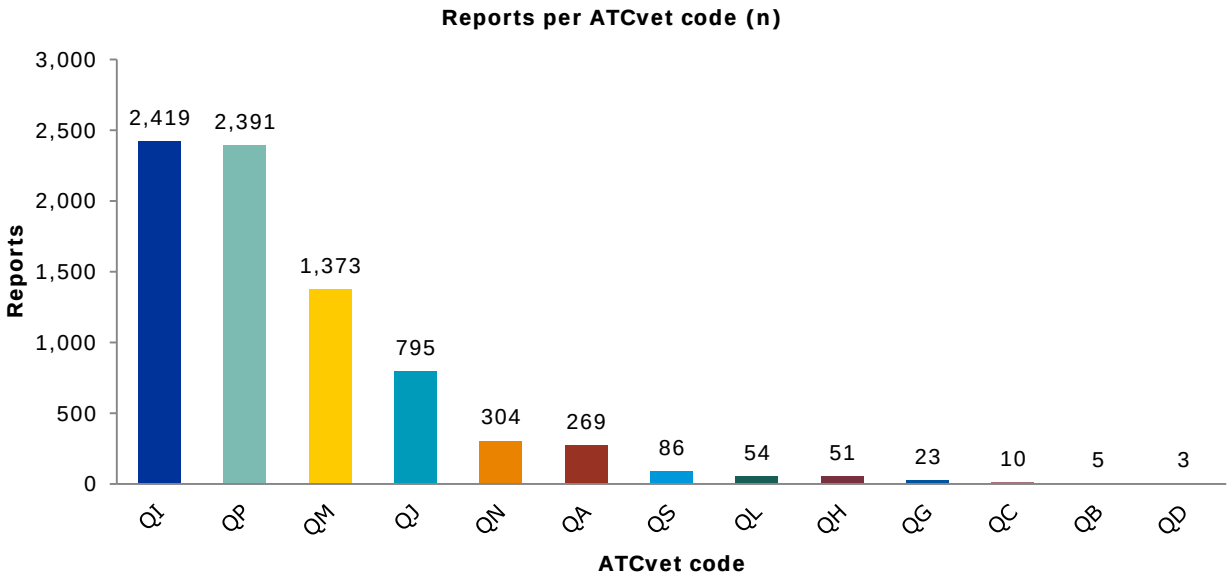
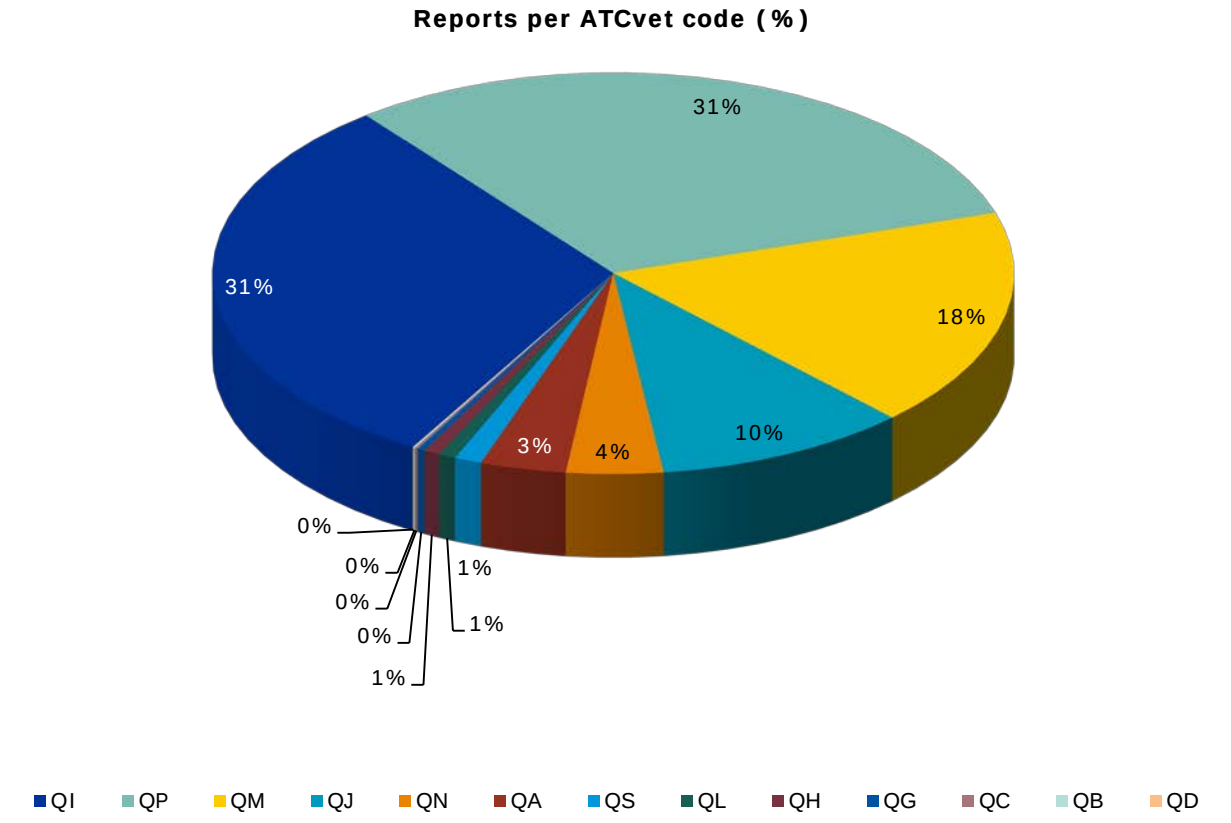

Total reacting animals/individuals per species (%)
34%
0%
4%
0%
18%
9%
32%
0%
0%
0%
0%
1%
2%
0%
Sheep/ovine
Pigs and other suidae
Cattle/bovine
Rabbits
Horses and other equidae
Goats/caprine
Chickens and other avians
Others (alpaca)
Dogs/canine
Cats/feline
Rodents
Ferrets
Others (reptiles, canary, monkey)
Human being

Table 2. Number of reports in animals and human beings for centrally authorised products grouped according to the ATCvet-group system (See http://www.whocc.no/atcvet/ for further explanations.)

ATCvet code	Sheep/ovines	Pigs and other suides	Cattle/bovines	Rabbits	Horses and other equides	Goats/caprines	Chickens and other avians	Other food-producing animals	Dogs/canines	Cats/felines	Rodents	Ferrets	Other companion animals	Human beings	Total
QA	-	-	-	-	-	-	-	-	195	55	-	-	-	19	**269**
QB	-	-	-	-	-	-	-	-	5	-	-	-	-	-	**5**
QC	-	-	-	-	-	-	-	-	9	1	-	-	-	-	**10**
QD	-	-	-	-	-	-	-	-	2	-	-	-	-	1	**3**
QG	-	-	-	-	-	-	-	-	21	-	-	-	-	2	**23**
QH	-	-	-	-	-	-	-	-	41	5	-	4	-	1	**51**
QI	1,282	355	66	152	59	37	7	-	160	270	-	-	-	31	**2,419**
QJ	3	59	210	5	52	1	1	1	94	306	2	-	-	61	**795**
QL	-	-	-	-	-	-	-	-	42	6	-	-	-	6	**54**
QM	1	5	28	9	12	-	2	-	975	316	4	1	6	14	**1,373**
QN	-	-	-	2	-	-	-	-	175	114	1		3	9	**304**
QP	11	-	24	9	-	1	1	2	1,638	407	11	6	4	277	**2,391**
QS	-	-	-	-	-	-	-	-	85	-	-	-	-	1	**86**
Total	**1,297**	**419**	**328**	**177**	**123**	**39**	**11**	**3**	**3,442**	**1,480**	**18**	**11**	**13**	**422**	**7,783**

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


Reports per ATCvet code (n)
Reports
3,000
2,500
2,000
1,500
1,000
500
0
2,419
2,391
1,373
795
304
269
86
54
51
23
10
5
3
QI
QP
QM
QJ
QN
QA
QS
QL
QH
QG
QC
QB
QD
ATCvet code


Reports per ATCvet code (%)
31%
31%
18%
10%
4%
3%
0%
0%
0%
0%
1%
1%
1%
QI
QP
QM
QJ
QN
QA
QS
QL
QH
QG
QC
QB
QD

In Table 2 and related 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). It is apparent from the table that most reports concern dogs, followed by cats, whereas there are fewer reports for food-producing animals (cattle, goats, chickens, horses, rabbits, pigs). The relatively high number of reports in sheep is in large part related to adverse events among animals that were vaccinated against bluetongue. It should be noted that the reports in dogs and cats usually concern only one or a few animals, whereas in the food producing animals, one report can concern a substantial number of animals. It is also apparent from Table 2 that there is a considerable number of adverse events reports in humans, who have been accidentally exposed to products authorised for veterinary use.

The adverse event reports received for some of the ATCvet groups are briefly commented upon below:

Antiparasitic agents (ATCvet group QP)

This is a heterogenous group of substances that are active against ectoparasites, endoparasites or both ecto- and endoparasites (endectocides). The substances are administered either dermally, as spot-on solutions, or orally, usually as tablets. Examples of adverse events are diarrhoea, lethargy, neurological disorders and (for spot-on solutions, additionally) dermal reactions. Examples of products within this group for which reports were received are Comfortis (spinosad; most reports in dogs, but also reports in cats), Certifect (fipronil / amitraz / S-methoprene; reports in dogs), Stronghold (selamectin; reports in dogs and cats), Advocate (imidacloprid / moxidectin; reports in dogs and cats), Profender (emodepside / praziquantel; reports in dogs and cats), Prac-Tic (pyriprole; most reports in dogs), Promeris Duo (methaflumizone / amitraz; reports in dogs), Halocur (halofuginone; reports in cattle) and Zolvix (monepantel; reports in sheep).

Non-steroidal anti-inflammatory drugs (NSAIDs) (ATCvet group QM)

This is an important group of substances, but it is also well known that treatments with these products may cause adverse events. The positive (therapeutic) effects of NSAIDs, i.e. the analgesic, anti-inflammatory, antipyretic and thrombocyte-aggregation-inhibiting effects, are related to inhibition of cyclooxygenase (COX). This mechanism also underlies the spectrum of adverse events that may occur, including injuries of the gastrointestinal mucosa, adverse events on the kidneys and the liver, and bleedings. Examples of products within this group for which reports were received are Metacam and its generics (meloxicam; most reports in dogs and cats, but also reports in other species, such as horse and cattle), Onsior (robenacoxid; reports in dogs and cats), Previcox (firocoxib; most reports in dogs) and Trocoxil (mavacoxib; reports in dogs).

Vaccines (ATCvet group QI)

Adverse events to vaccines are usually caused by anaphylactic reactions. The clinical signs can vary from relatively mild subcutaneous oedemas to severe anaphylactic shocks. Local reactions at the sites of the vaccinations are also quite common. Examples of vaccines for which reports were received are: Canileish (vaccine against Leishmania in dogs); the Purevax vaccine range in cats; horse vaccines such as ProteqFlu, ProteqFlu-Te and Equilis Prequenza; vaccines against bluetongue such as Bluevac BTV 8 and Bovilis Alsap 1-8 in cattle and sheep and Zulvac 8 Ovis in sheep; swine vaccines such as Ingelvac Circoflex, Porcilis PCV and Porcilis AR-T DF; the vaccine Vaxxitek HVT + IBD against Marek's disease and infectious bursal disease in chickens; and the vaccine Nobivac Myxo-RHD against myxomatosis and rabbit haemorrhagic disease.

Anti-infective agents (ATCvet group QJ)
Examples of adverse events to anti-infective agents are allergies, diarrhoea due to effects on the gastrointestinal microflora, and local site reactions following intramuscular or subcutaneous injections. Examples of anti-infective agents for which reports were received are Convenia (cefovecin; reports in cats and dogs), Naxcel (cetiofur; most reports in horse and cattle), Draxxin (tulathromycin; most reports in cattle), Zactran (gamithromycin; reports in cattle) and Zuprevo (tildipirosin; reports in cattle and swine).

Examples of products in other ATCvet groups for which reports of adverse events have been received include, within group alimentary tract (QA): Cerenia (maropitant; reports in dogs and cats) and Slentrol (dirlotapide; reports in dogs); within group hormones (QH): Suprelorin (deslorelin; reports in dogs); within group nervous system (QN): Dexdomitor (dexmedetomidine; reports in dogs and cats), Clomicalm (clomipramine; reports in dogs and cats) and Reconcile (fluoxetine; most reports in dogs); and within group sensory organs (QS): Posatex (orbifloxacin / mometasone / posaconazole; reports in dogs).

In **humans beings**, the majority of reports concern allergies after skin contact with animals treated with antiparasitic spot-on preparations for dogs or cats, such as Advocate, Certifect, Promeris Duo and Stronghold. There are also reports of adverse events after accidental exposure to other products, such as Naxcel and Metacam.

It should be highlighted that also Table 2 and the text above relate only to the analysis of reports for centrally authorised products ("Community" marketing authorisation), and may not reflect the relative occurrence of events observed for other veterinary medicines authorised in the different EU countries.

A new surveillance procedure for signal detection that makes use of electronic analysis tools for the periodic surveillance of all centrally authorised products was initiated in August 2011. During 2012, surveillance of all 132 centrally authorised products was performed. For three products, namely Stronghold, Suvaxyn PCV and Zuprevo, signals were detected and changes to the summary of product characteristics (SPC) (see Annex for details) were recommended. For two other products, the process is on-going, and a final decision will be taken in 2013.

3. Periodic safety update reports of centrally authorised products

Marketing-authorisation holders have the legal obligation to periodically provide summary reports on the safety of their products. These periodic safety update reports (PSURs) discuss and evaluate the overview of all adverse events (serious as well as non-serious) that were recorded during the period. They provide information on the frequency of occurrence of adverse events: the total amount of product sold and estimated number of animals treated are put into relation to the number of animals affected by an adverse event. They also include information on other aspects, such as lack of expected efficacy, environmental issues or residue violations. Based on its assessment of these PSURs, the Committee for Medicinal Products for Veterinary Use (CVMP) draws conclusions concerning the current benefit-risk balance of a product, and, on this basis, may consider that amendments to the product literature (e.g. addition of a warning) are necessary, and may require that they be made.

A total of 139 PSURs or PSUR addendum reports were received in 2012, and assessments were completed for a total of 134. After considering all pharmacovigilance data detailed in these PSURs, the CVMP concluded that the benefit-risk balance of the products concerned remained favourable. However, the Committee considered it necessary to amend the SPCs and product literature for 12 products, as detailed in Annex 1.

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 Agency. These procedures are not restricted to centrally authorised products, but are applicable to all veterinary medicinal products authorised within the EU. (Details of the two procedures are available in Volume 9B; see Section 5: Legal references.)

Some issues discussed in the RA and/or NUI systems during 2012 are summarised below.

In January, the PhVWP-V discussed an update of an NUI from Germany on **Nuflor (florfenicol) oral powder for pigs**. This is an antibiotic marketed in several Member States that is mixed in feed for treatment of airway infections in pigs. In Germany, diarrhoea, para-anal infections and deep necrolytic dermatitis have been observed in a large number of treated pigs. Florfenicol is also available as a pre-mix in feed, but there are no reports of adverse reactions in pigs treated with this preparation. It is possible that addition of florfenicol oral powder in the feed (which usually takes place at the farms) may result in a non-homogenous mixture, implying that some pigs may ingest a high overdose. The marketing-authorisation holder withdrew the product from the German market in 2012.

In May and November, the PhVWP-V discussed an update on **Pregsure BVD and bovine neonatal pancytopenia (BNP)**. BNP is caused by aplasia/hypoplasia of the bone marrow in calves. It affects primarily 1 to 3-weeks old calves, and the primary clinical signs are bleedings. The lethality is estimated to be over 80%. Pregsure BVD is an inactivated vaccine against bovine virus diarrhoea (BVD). Reports, primarily from Germany but also from several other countries, showed that BNP was mainly seen in calves from cows that had been vaccinated with Pregsure BVD. It was proposed that vaccination of the cows with Pregsure BVD results in the induction of alloreactive antibodies, which are transmitted to the new-born calves via the colostrum. The antibodies then react with antigens on thrombocytes and blood precursor cells in the calves, in turn causing aplasia/hypoplasia of the bone marrow. Following the suspicion that vaccinations of cows with Pregsure BVD may cause BNP in calves, the marketing of the product was stopped in all EU countries (via initiation of an Article 78 procedure of Directive 2001/82/EC). The marketing-authorisation holder withdrew the product from all countries. Since then, there has been a decline in number of BNP cases.

The production of the Pregsure BVD vaccine is performed in vitro in a medium containing a bovine cell-line (the Madin-Darby Bovine Kidney cells (MDBK) cell-line). This kind of cell-line is termed a homologous cell-line. It was proposed that presence of fragments of MDBK cells together with a potent adjuvant in the Pregsure BVD vaccine may promote formation of alloreactive antibodies in the cows. In their November 2012 meeting, the CVMP Immunologicals working party discussed whether the use of homologous cell-lines for the production of other vaccines or other immunological products might be a problem. The principal conclusion of a literature review was that, on the basis of the information available to date, it was not possible to make any recommendations concerning this matter. Therefore, no actions regarding other immunological products are needed at present. However, it was acknowledged that this issue may need to be revisited in future should new data and/or evidence emerge.

In July, the PhVWP-V discussed an NUI from Germany concerning **Cydectin 1% (moxidectin) and Footvax** (vaccine against footrot in sheep). It is stated in the product information (SmPC) for Footvax that Cydectin 1% should not be given to recently vaccinated animals, since they may then get anaphylactic reactions. A possible mechanism is that Cydectin 1% contains an excipient that may trigger the anaphylactic reaction. It was recommended that the marketing-authorisation holder clearly explain in the SPC and in other product literature why Cydectin 1% should not be given after the sheep have been vaccinated with Footvax.

In September, the PhVWP-V discussed an NUI from Finland on **Febrivac 3-Plus** (vaccine against virus enteritis, haemorrhagic pneumonia and *Clostridum botulinum* intoxications in minks). In Finland, a high frequency of injection-site reactions was reported concerning abscess formation in minks after vaccination. The injection-site reactions were considered likely to be attributed to the injection technique and handling, rather than a product related issue. The discussion will be finalised in 2013.

Also in September, the PhVWP-V discussed an NUI from Sweden on **breed-related sensitivity to vaccinations in German and miniature pinschers**, which had previously been discussed by the PhVWP-V in 2006. Adverse events had been reported mostly in Finland and Sweden; increasingly, however, similar events were being reported in other countries, including Norway, the United States and Australia. The events tended to be reported after dogs were vaccinated for the first time at twelve weeks of age and when the vaccine contained a distemper component. The reactions were not usually observed until about 9 to 12 days after the vaccinations. The reactions were characterised primarily by neurological signs, such as ataxia and seizures. Most dogs recovered, although the signs were sometimes severe. It was suggested that the mechanism was a vaccinal encephalitis and potentially related to an immunological characteristic in the relatively small pinscher populations. The time interval between vaccination and the adverse reactions makes it difficult to conclude on the causal relation. Consequently, the events may not be recognised as adverse ones, and may therefore not be reported. The discussion will be finalised in 2013.

5. Legal references

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

Volume 9B of The Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use.

Annex 1

Lists of amendments recommended in 2012 following pharmacovigilance surveillance and signal detection and/or assessment of PSURs or summary bridging reports and PSUR addendum reports in renewal procedures.

Summary of product characteristics (SPC) sections:

- 4.4 – Special warnings
- 4.5 – Special precaution(s) for use
- 4.6 – Adverse reactions (frequency and seriousness)
- 4.7 – Use during pregnancy and lactation or lay
- 4.10 – Overdose (symptoms, emergency procedures, antidotes)
- 5.1 – Pharmacodynamic properties

Product	SPC section	Recommendation to the marketing-authorisation holder (Addition, deletion or other changes shown in **bold** and ~~strikethrough~~)
Advocate	**4.6**	Use of the product may result in transient pruritus in cats. On rare occasions greasy fur, erythema and vomiting can occur. These signs disappear without further treatment. The product may, in rare cases, cause local hypersensitivity reactions. If the animal licks the application site after treatment, ~~**transient**~~ neurological signs**)** may be observed **in very rare cases** ~~**frequently**~~ (see section 4.10).
	4.10	After accidental oral ingestion **or overdose**, ~~**transient**~~ neurological signs **(most of which are transient**) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may occur in **in very rare cases** ~~**frequently**~~.
CaniLeish	**4.6**	After injection, moderate and transient local reactions may occur such as swelling, nodule, pain on palpation or erythema. These reactions resolve spontaneously within 2 to 15 days. **In very rare cases a more severe reaction at injection site (injection site necrosis, vasculitis) has been reported.**
CERTIFECT	**4.6**	Transient skin reactions at the application site (skin discolouration, local hair loss, itching, redness) and general itching or hair loss may occur on rare occasions. ~~**If dogs lick the application site after treatment**~~, **Lethargy, ataxia, emesis, anorexia, diarrhoea,** excessive salivation, ~~**vomiting**~~, hyperglycaemia, increased sensitivity to stimulation, ~~**lethargy**~~, bradycardia or bradypnea may ~~**also**~~ be observed. Signs are transitory and generally resolve without treatment within 24 hours.
Coxevac	**4.5**	**Under field conditions, vaccination with Coxevac has commonly been followed by a decrease in milk production in goats. Since stress could contribute to this adverse event, appropriate precautions should be taken to reduce stress as much as possible during the administration of the product.**

Product	SPC section	Recommendation to the marketing-authorisation holder (Addition, deletion or other changes shown in **bold** and ~~strikethrough~~)
Coxevac	**4.7**	**Under field conditions, vaccination with Coxevac has commonly been followed by a decrease in milk production in goats. Since stress could contribute to this adverse event, appropriate precautions should be taken to reduce stress as much as possible during the administration of the product**.
Econor	**4.4**	~~**None**.~~ **As an adjunct to treatment, good management and hygiene practices should be introduced in order to reduce the risk of infection and to control the potential build-up of resistance. Especially in the case of swine dysentery, a targeted early eradication programme of the disease should be considered.**
	4.5	**Special precautions for use in animals** Adverse ~~**drug**~~ reactions have occurred following the use of Econor. Their occurrence appears to be mainly associated with breed mixes that include Danish and/or Swedish Landrace. Extreme care should therefore be taken in the use of Econor in pigs of the Danish and Swedish Landrace breeds, and their crossbreeds thereof, especially in younger pigs. **When treating infections caused by *Brachyspira spp*., therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.** **Special precautions to be taken by the person administering the veterinary medicinal product to animals** ~~**When mixing the product and handling the final feed containing the product, direct contact with the skin and mucous membranes should be avoided. In case of accidental ingestion, seek medical advice immediately and show the product label.**~~ **Gloves should be worn when handling the veterinary medicinal product. When mixing the veterinary medicinal product and handling the final feed containing the veterinary medicinal product, direct contact with the skin and mucous membranes should be avoided. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.** People with known hypersensitivity to valnemulin should administer the veterinary medicinal product with caution.

<table>
<tr><th>Product</th><th>SPC section</th><th>Recommendation to the marketing-authorisation holder
(Addition, deletion or other changes shown in bold and ~~strikethrough~~)</th></tr>
<tr><td>Econor</td><td>5.1</td><td>
Valnemulin is an antibiotic belonging to the pleuromutilin group, which acts by the inhibition of the initiation of protein synthesis at the level of the bacterial ribosome.
Valnemulin has activity against a range of bacteria including those responsible for enteric and respiratory disease in pigs.
Valnemulin shows high activity against Mycoplasma spp. and spirochaetes such as Brachyspira hyodysenteriae and Brachyspira pilosicoli and Lawsonia intracellularis.
<table>
<tr><th>~~Species~~</th><th>~~MIC (Range) (µg/ml)~~</th><th>~~MIC$_{50}$ (µg/ml)~~</th><th>~~MIC$_{90}$ (µg/ml)~~</th></tr>
<tr><td>~~Mycoplasma hyopneumoniae~~
~~Brachyspira hyodysenteriae~~
~~Brachyspira pilosicoli~~
~~Lawsonia intracellularis~~</td><td>~~0.0009 – 0.125~~
~~0.025 – 4.0~~
~~0.0156 – 2.0~~
~~< 2.0 is the concentration likely to cause significant inhibition of intracellular growth~~</td><td>~~0.0025~~
~~0.2~~
~~0.0156~~</td><td>~~0.01~~
~~1.0~~
~~0.5~~</td></tr>
</table>
<table>
<tr><th>Species</th><th>MIC of wild-type population (µg/ml)</th></tr>
<tr><td>Brachyspira hyodysenteriae</td><td>≤0.125</td></tr>
<tr><td>Brachyspira pilosicoli</td><td>≤0.125</td></tr>
<tr><td>Lawsonia intracellularis</td><td>≤0.125</td></tr>
<tr><td>Mycoplasma hyopneumoniae</td><td>≤0.008</td></tr>
</table>
Valnemulin has little activity against Enterobacteriaceae, such as Salmonella spp. and Escherichia coli.
There appears to be no resistance development to valnemulin to date by M. hyopneumoniae and L. intracellularis.
There have been some increases of MICs of valnemulin against B. hyodysenteriae and to a lesser degree B. pilosicoli, some of which appear to have developed resistance.
Valnemulin binds to the ribosome and inhibits bacterial protein synthesis. Resistance development primarily occurs because of changes at the binding site associated with mutations of the ribosomal DNA genes.
</td></tr>
<tr><td>Meloxivet</td><td>4.6</td><td>Typical adverse reactions of NSAIDs such as loss of appetite, vomiting, diarrhoea, faecal occult blood, lethargy and renal failure have occasionally been reported. In very rare cases haemorrhagic diarrhoea, haematemesis, gastrointestinal ulceration and elevated liver enzymes have been reported.</td></tr>
<tr><td>Porcilis AR-T DF</td><td>4.6</td><td>In very rare cases adverse events of anaphylactic-type reaction and abortion have been reported.</td></tr>
</table>

Product	SPC section	Recommendation to the marketing-authorisation holder (Addition, deletion or other changes shown in **bold** and ~~strikethrough~~)
Procox	**4.5**	~~**Studies with emodepside indicate that the margin of safety in certain dogs of Collie or related breeds may be less than in other breeds. The tolerance of Procox in young puppies of these breeds has not been investigated, and the use of this veterinary medicinal product is therefore not recommended in such dogs.**~~ **Procox is not recommended to be used in dogs of Collie or related breeds that carry or are suspected to carry the mdr1 -/- mutation, because the tolerance of the product in mdr1 -/- mutant puppies has been shown to be lower than in other puppies.**
Stronghold	**4.6**	Exceptionally, as with other macrocyclic lactones, reversible neurological signs, **including seizures,** have been observed after use of the product.
Suprelorin	**4.4**	**In rare cases (>0.01 % to < 0.1 %), suspected lack of expected efficacy has been reported (in the majority of cases a lack of reduction of testicle size was reported and/or a bitch was mated but this did not result in pregnancy). Only testosterone levels (i.e. an established surrogate marker of fertility) could definitely confirm a lack-of-efficacy of the treatment. If suspicious of lack of treatment efficacy, then dog's implant (e.g. presence and condition) should be checked.** **Surgical or medical castration might have unexpected consequences (i.e. improvement or worsening) on aggressive behavior. Thus, dogs with sociopathic disorders and showing episodes of intra-specific (dog -to-dog) and/or inter-specific (dog to another species) aggressions should not be castrated either surgically or with the implant.**
	4.6	**In very rare cases (<0.01%), there has been transitory increased sexual interest, increased testicle size and testicular pain, immediately after implantation. During the treatment period, rare clinical effects (> 0.01% to < 0.1%) have been reported including hair coat disorders (e.g. hair loss, alopecia, hair modification), urinary incontinence, down-regulation associated signs (e.g. decrease in testicle size, reduced activity). In very rare cases, a testicle may be able to ascend the inguinal ring.** **In very rare cases (<0.01%), a transient behavioral change has been reported with the development of aggression (see- section 4.4 Special warnings).**
Suvaxyn PCV	**4.6**	Anaphylactic reactions are uncommon **but maybe lethal**. In case of such reactions, appropriate treatment is recommended. ~~**If left untreated, anaphylactic reactions might be lethal.**~~
Zuprevo	**4.5**	Administer strictly intramuscularly. **For this aim special attention should be paid to using the appropriate injection site and to selection of the appropriate needle size and length (adjusted to the size and weight of the animal).**

Product	SPC section	Recommendation to the marketing-authorisation holder (Addition, deletion or other changes shown in **bold** and ~~strikethrough~~)
Zuprevo	**4.6**	**In rare cases, individual shock reactions, with a potentially fatal outcome might occur.** In target animal safety studies, administration of the maximum recommended injection volume (5 ml) occasionally caused slight swellings at the injection site that were not painful on palpation. Swellings persisted for up to 3 days. Pathomorphological injection site reactions resolved completely within 21 days. During clinical trials, pain on injection and injection site swellings were seen very commonly in treated pigs. These swellings resolved within 1 to 6 days. ~~**During clinical trials, treatment caused shock symptoms in 2 out of 1048 animals. These symptoms quickly resolved in one animal, but led to death in the other animal.**~~