EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Union Pharmacovigilance Database: webinar on signal detection and analysis

EVV DWH Dashboard and Reports

Sample Methodology of Signal Detection

Presented by Laura Descalzo on 24 November 2021
Veterinary Risk and Surveillance Service

An agency of the European Union

Data analysis – example methodology (product based analysis)

Define baseline: Overview of data:
Number of reports, data distribution, eg. Species, geographic origin

Prioritisation:

- **Identify which AEs should be investigated**Focus on VeDDRA terms not included in the SPC taking into account:
  Relative frequency of the VeDDRA terms
  Nature and severity of the VeDDRA terms

- **Identify issues that might need urgent attention**
  Screen the data for issues that may require urgent consideration e.g. human reports, high numbers of animal deaths, MI events.

Consider the possible association with the product at report level for each of the signals investigated:

- Geographic origin
- Breed
- Age
- Other reactions reported
- Time to onset, detailed dose, and route of administration
- Off label use?
- Narrative

Many signals might be due to confounding factors. These are mainly of two types, confounding by disease (indication) and confounding by medication:

Confounded by disease
This is when it is considered that the AE might be regarded as symptoms of the disease the product has been administrated for, and not as a reaction to the product itself. However, it is important to consider that when the AE is typical for the indication it may also denote aggravation of the disease. Clinical judgment should be used.

Confounded by medication
This is when it is considered that the AE may be due to concomitant medication.

Population frequency of certain events
E.G epileptic seizures (happen randomly in the general population) and the baseline frequencies are not usually known. Hence they might appear as Aes, although they were not actually caused by the VMP

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Essential DATA systems

Union Product database	• QPPV • PSMF reference
Union Pharmacovigilance database	• AE reports • Data Warehouse
Signal Management reporting module	• Signals • Annual statements • Alerts

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Dashboards: product-based analysis

ADVERSE EVENT OVERVIEW

To obtain baseline data: Number of AERs per product and species, Number of animals affected, Number of fatalities

SIGNAL EVALUATION

To analyse the profile of affected animals (i.e. breed, age) for adverse events of interest (potential signs) and identify potential risk factors, effects of co-medication, geographical distribution or pharmaceutical form

SIGNAL DETECTION

To view the type of Adverse Events reported for a selected product or group of products (at SOC and PT) and to compare the frequency to the number of reports involving other products and other clinical signs = ROR / ROR(-)

DATA STRATIFICATION

To compare a product to products of the same class, or to identify and exclude certain products from the comparison (products with a disproportionate number of reports for a specific AE)

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EVV: Product data overview

UPD
Metacam 0.5 mg/ml – Oral suspension (cats, guinea pigs)
Metacam 0.5 mg/ml – Oral suspension (dogs)
Metacam 1 mg/ml – Chewable tablet (dogs)
Metacam 1.5 mg/ml – Oral suspension (dogs)
Metacam 2 mg/ml – Solution for injection (cats)

The **PI entries** are generated on the following strategies:

1. Product Name
2. Product Name + Strength
3. Product Name + Pharmaceutical form
4. Product Name + Strength + Pharmaceutical form

The **Product composition entries** are generated on the following strategies:

1. Active ingredient(s) name(s)
2. Active ingredient(s) name(s) + Strength(s)
3. Active ingredient(s) name(s) + Pharmaceutical form
4. Active ingredient(s) name(s) + Strength + Pharmaceutical form

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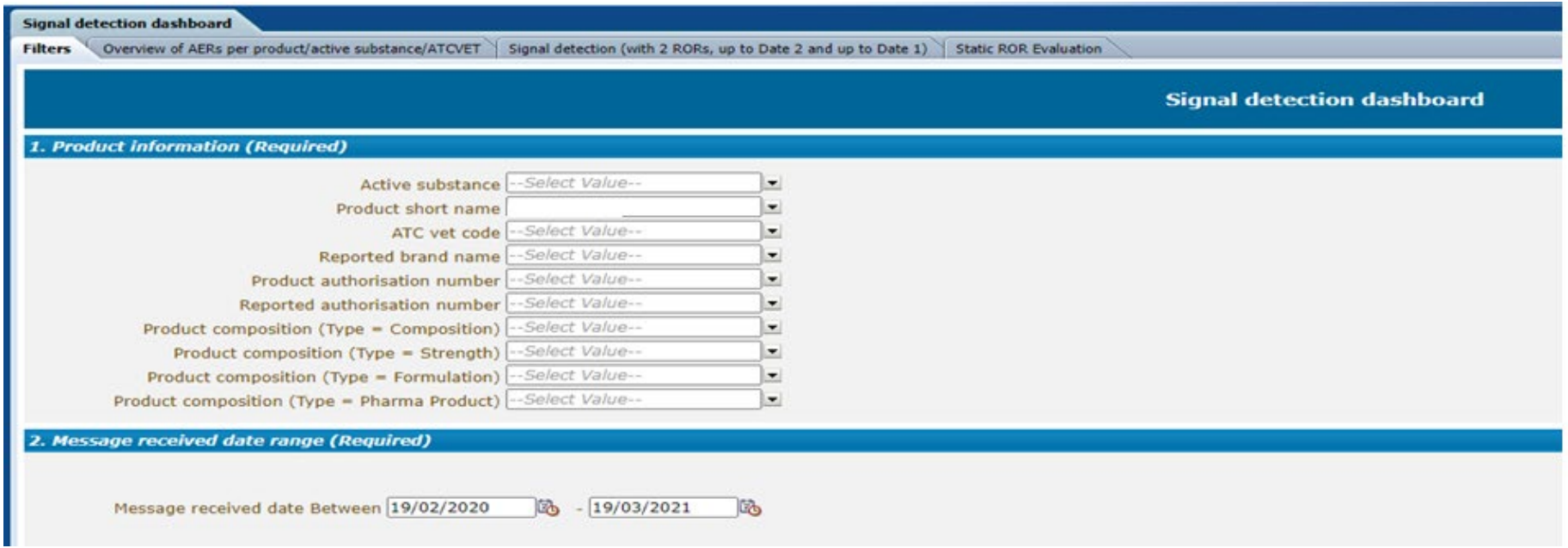
Data analysis – EVVET DWH

Filters selection page (1)



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Data analysis – EVVET DWH

Filters selection page (2)

3. Report filter (Required, only apply for signal detection and static ROR)

Human or animal ☑ Animal ☑ Human

4. Optional report filters

Age (hours) >= --Select Value-- <= --Select Value--
Age (days) >= --Select Value-- <= --Select Value--
Age (months) >= --Select Value-- <= --Select Value--
Age (years) >= --Select Value-- <= --Select Value--

Gender --Select Value--
Species --Select Value--
Breed --Select Value--
Occurrence region --Select Value--
Occurrence country --Select Value--
Organisation --Select Value--
Report type --Select Value--
Serious --Select Value--

Original received date Between -
Start date of reaction/event Between -
Authorisation procedure --Select Value--
Information type --Select Value--
Primary source categorisation --Select Value--
Is use according to label --Select Value--
Exclude lack of efficacy ☐ Yes
Hide known VedDRA terms ☐ Yes

Is off label

Indication ☐ Yes ☐ No
Product expired ☐ Yes ☐ No
Storage ☐ Yes ☐ No
Treatment ☐ Yes ☐ No
Other issue ☐ Yes ☐ No

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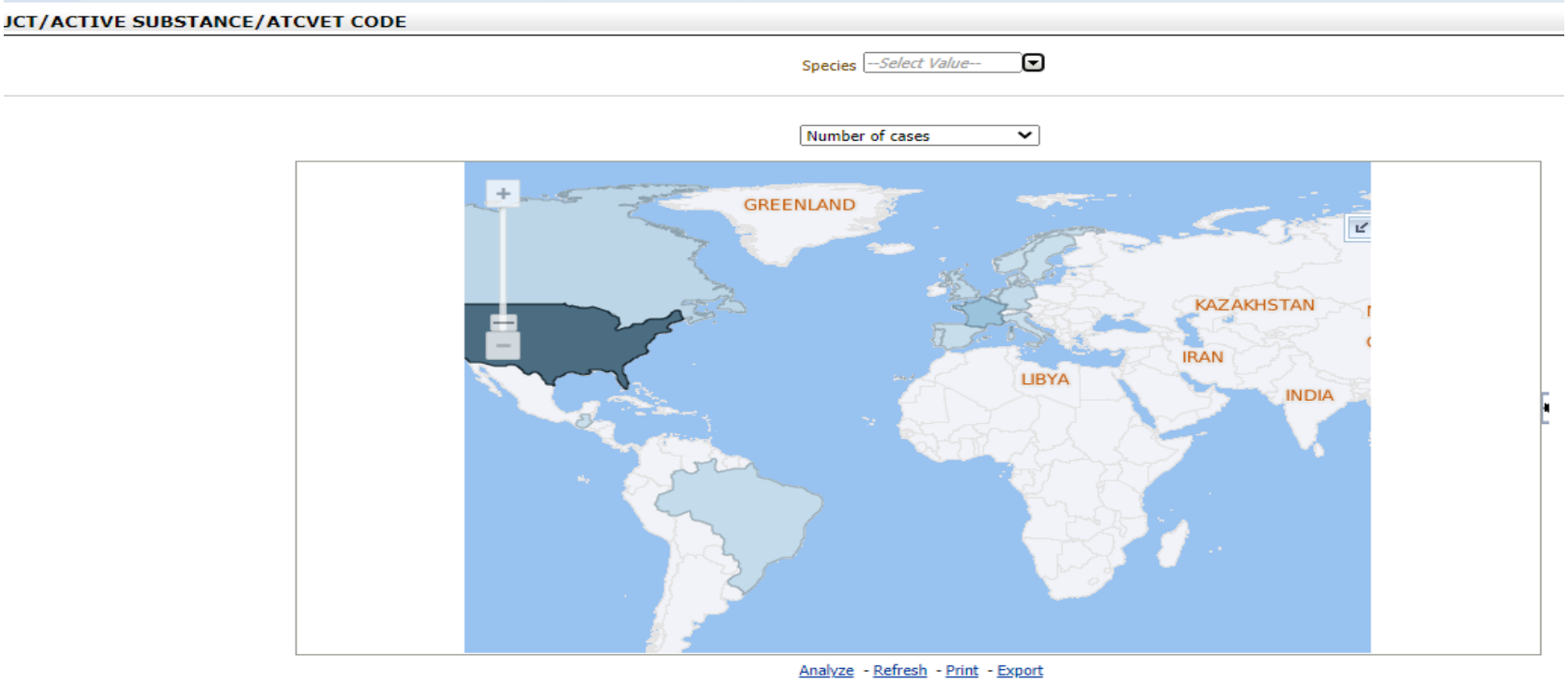
Data analysis – EVVET DWH



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Data analysis – EVVET DWH

Product Hierarchy Level Medicinal product shortname

		Human or animal	Animal				Human		Number of cases	Number reacted
		Seriousness	Yes		No		Unknown			
			Number of cases	Number reacted	Number of cases	Number reacted	Number of cases	Number reacted		
Medicinal product shortname	Occurrence region	Occurrence country								
	EEA	Belgium			1	1			1	1
		Denmark			1	1			1	1
		France	25	25	33	43	1	1	59	69
		Germany	5	11	5	5	1	1	11	17
		Italy	2	2					2	2
		Netherlands	2	2	1	1			3	3
		Norway			1	1			1	1
		Portugal	4	4					4	4
		Spain	6	7					6	7
		Sweden			1	1			1	1
	Non EEA	Australia	2	2					2	2
		Brazil	9	9					9	9
		Canada	19	19					19	19

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Data analysis – EVVET DWH

Signal detection with 2 RORs – type of Aes reported for product or substance

Product Hierarchy Level Medicinal product shortname

Date 1: 19/02/2020
Date 2: 19/03/2021

Species Cat

Medicinal product shortname	VedDRA SOC name	VedDRA PT name	Number of cases between date 1 and date 2	Number reacted between date 1 and date 2	ROR (-) until date 2	ROR until date 2	ROR (+) until date 2
	Behavioural disorders	Aggression	2	2	1.53	1.80	2.14
		Anxiety	2	2	1.50	1.78	2.12
		Behavioural disorder NOS	5	5	1.14	1.35	1.59
		Grooming disorder	5	7	12.23	14.88	18.10
		Hallucination	0		N/A	N/A	N/A
		Hyperactivity	13	15	5.53	6.62	7.93
		Self mutilation	1	1	N/A	N/A	N/A
		Vocalisation	5	5	1.61	1.91	2.26
	Blood and lymphatic system disorders	Other blood disorder NOS	0		N/A	N/A	N/A
		Other coagulation abnormality	1	1	N/A	N/A	N/A
	Cardio-vascular system disorders	Bradycardia	0		N/A	N/A	N/A
		Cardiac arrest	0		N/A	N/A	N/A
		Cardiac insufficiency	0		N/A	N/A	N/A
		Circulatory shock	1	1	N/A	N/A	N/A
		Hypotension	0		3.27	3.92	4.70
		Murmur	0		N/A	N/A	N/A
		Pericardial effusion	1	1	N/A	N/A	N/A
		Tachycardia	3	3	2.07	2.45	2.90

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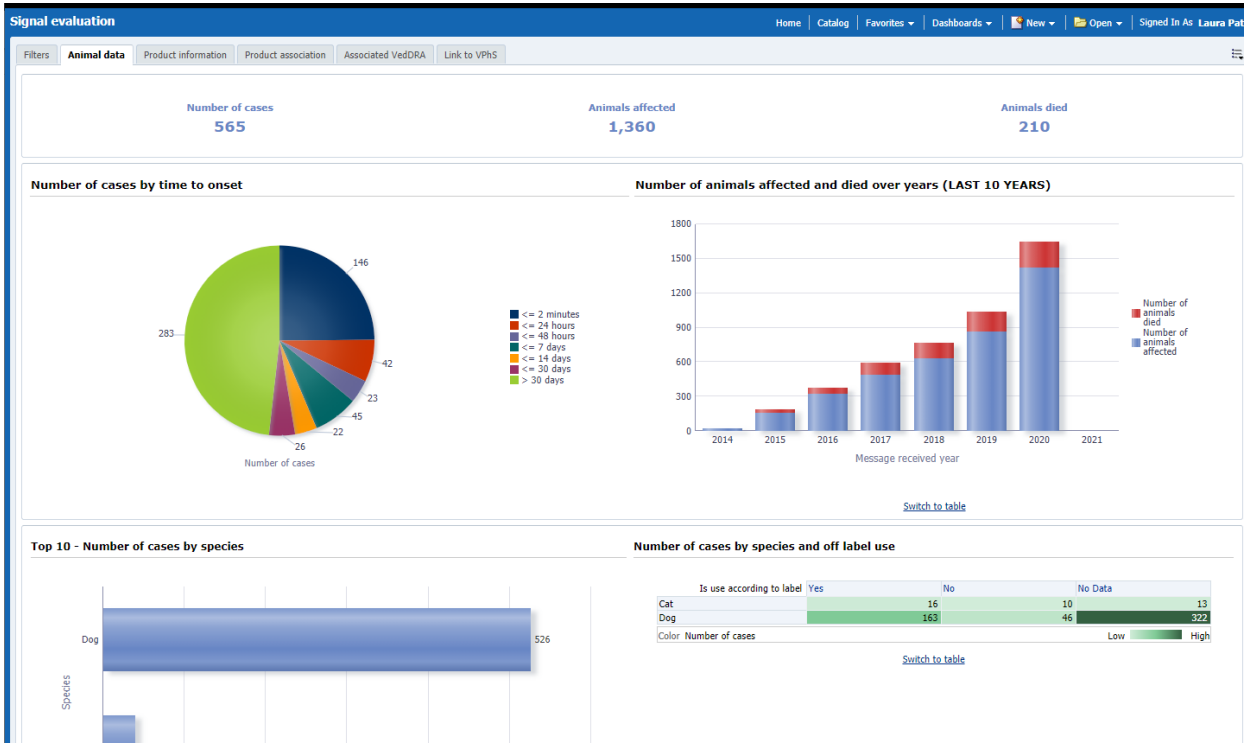
Data analysis – EVVET DWH

Signal evaluation: species/breed, age, weight, time to onset, off-label use analysis



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Data analysis – EVVET DWH

Number of cases by species and breeds

Species Dog

Age range	Number of cases	Number of animals affected	Number of animals died
0-0.49 years	11	11	4
0.5-0.99 years	14	14	2
1-6.99 years	279	279	21
13 and over years	33	33	6
7-12.99 years	151	152	40
Unknown	38	832	128

Species Dog

Weight range	Number of cases	Number of animals affected	Number of animals died
0-4.999 kg	100	895	141
10-24.999 kg	160	160	20
25-44.999 kg	133	133	25
45-69.999 kg	16	16	4
5-9.999 kg	116	116	11
70 and over kg	1	1	0

Species Dog Age range 0-0.49 years

Breed	Number of cases	Number of animals affected	Number of animals died
Alaskan Malamute	1	1	0
Chihuahua	1	1	0
Collie - Border	2	2	0
Crossbred Canine/dog	4	4	2
Shepherd Dog - German	1	1	1
Spaniel - Cocker American	1	1	0
Unknown	1	1	1

Species Dog Weight range 0-4.999 kg

Breed	Number of cases	Number of animals affected	Numbe
Akita	1	1	
Beagle	2	2	
Berger Picard or Sheepdog - Picardy	1	1	
Borzoi	1	1	
Boxer (German Boxer)	2	2	
Chihuahua	8	8	
Collie - Border	2	2	
Crossbred Canine/dog	19	19	
Dachshund - Miniature	1	1	
Dog (other)	7	7	
Maltese	5	5	
Papillon - Spaniel - Continental Toy (with erect ears or with dropped ears (Phaléne))	2	2	
Pekingese	1	1	
Pointing Dog - Hungarian Short-haired (Vizsla)	1	1	
Poodle - Toy	1	1	
Pug	1	1	
Retriever - Golden	1	1	
Retriever - Labrador	1	1	

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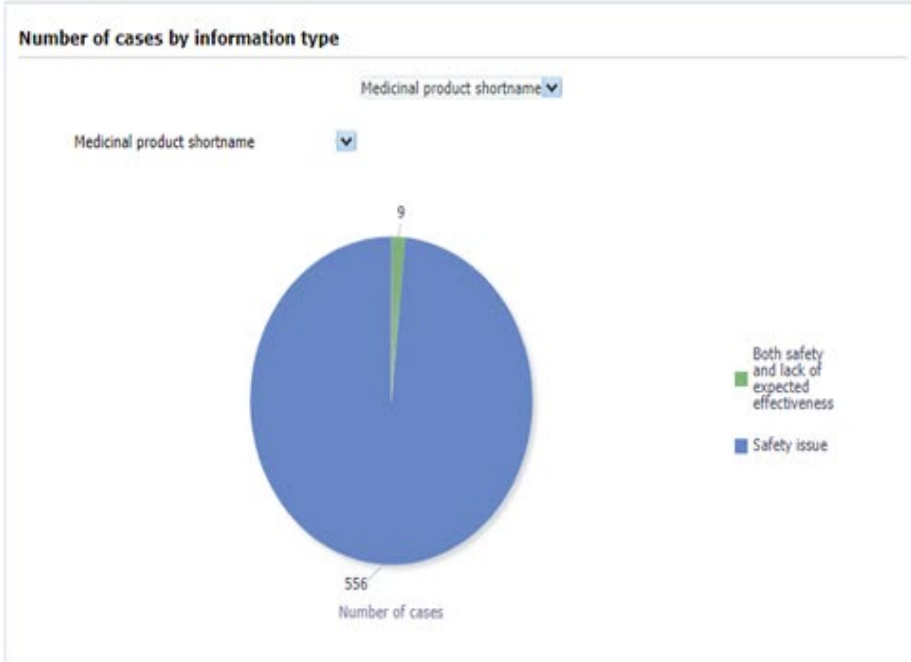
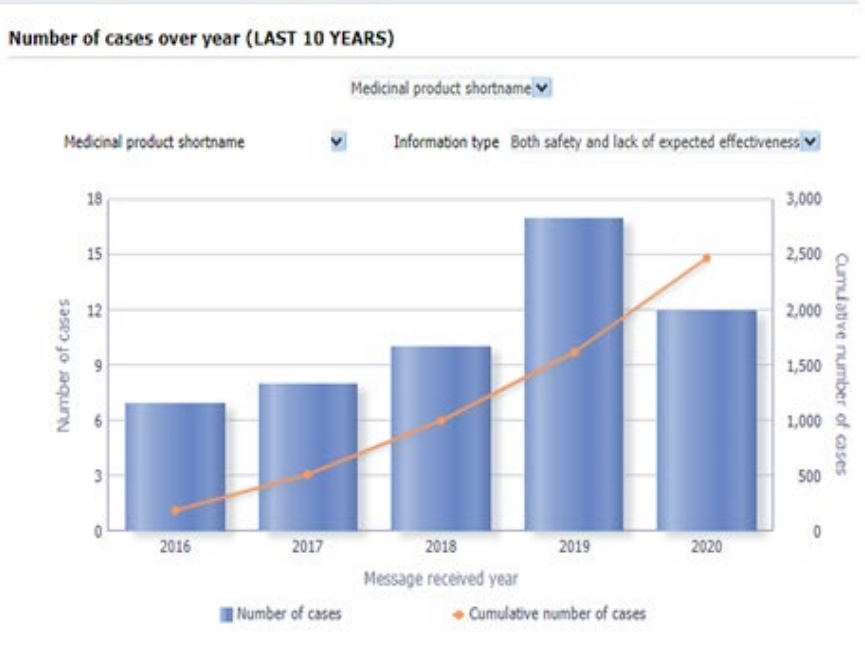
Data analysis – EVVET DWH

Product information (Geographical, information type and pharma form breakdown)





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Data analysis – EVVET DWH

Product information (Geographical, information type and pharma form breakdown)

Number of animals affected by pharmaceutical form or active substance

Pharmaceutical product form

Species Cat

Information type Safety issue

			Animal			Number of AERs	Number of animals affected	Number of animals died
Pharmaceutical product form	Occurrence region	Occurrence country (U)	Number of AERs	Number of animals affected	Number of animals died			
CHEWABLE TABLET	Non EEA	UNITED STATES	3	3	0	**3**	**3**	**0**
SPOT-ON SOLUTION	EEA	FRANCE	2	2	0	**2**	**2**	**0**
		GERMANY	2	2	1	**2**	**2**	**1**
	Non EEA	AUSTRALIA	3	3	1	**3**	**3**	**1**
		BRAZIL	1	1	1	**1**	**1**	**1**
		CANADA	1	1	0	**1**	**1**	**0**
		NEW ZEALAND	1	1	1	**1**	**1**	**1**
		SOUTH AFRICA	2	2	1	**2**	**2**	**1**
		UNITED KINGDOM	1	1	0	**1**	**1**	**0**
		UNITED STATES	25	25	4	**25**	**25**	**4**
Grand Total			**39**	**39**	**9**	**39**	**39**	**9**

Return - Analyze - Print - Export

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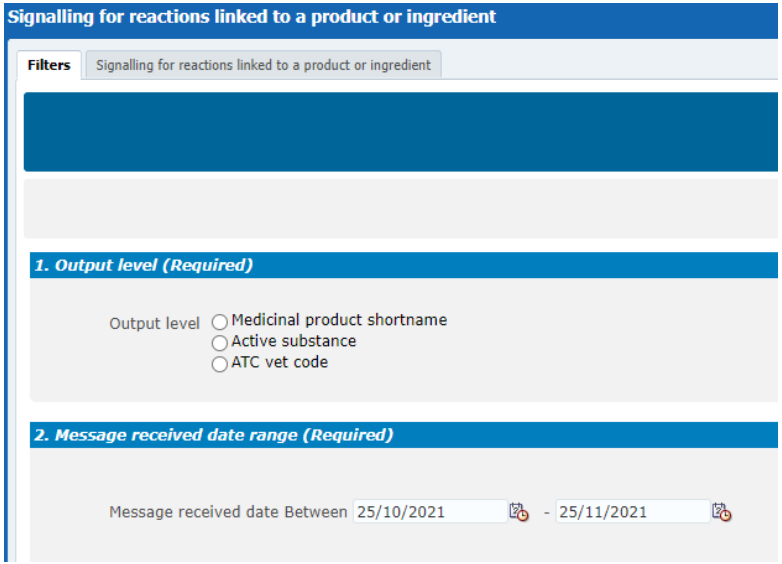
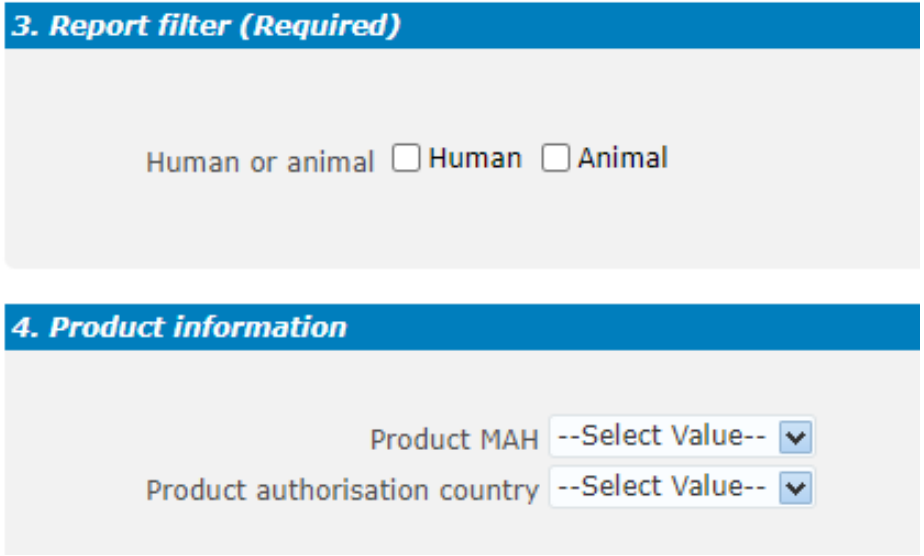
Live Demo

Data analysis – EVVET DWH

Continuous monitoring (signalling report)





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Data analysis – EVVET DWH

Continuous monitoring (signalling report)

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Data analysis – EVVET DWH

Continuous monitoring (Signalling report)

Date 1: 01/10/2020
Date 2: 15/10/2020

Species Dog

Medicinal product shortname	VedDRA SOC name	VedDRA PT name	Go to signal evaluation dashboard	Number of cases between date 1 and date 2	Number reacted between date 1 and date 2	ROR (-) until date 2	ROR until date 2	ROR (+) until date 2	Number of cases until date 1	Number reacted until date 1	ROR (-) until date 1	ROR until date 1	ROR (+) until date 1	Total number of cases
	Digestive tract disorders	Emesis	Link	15	15	1.37	1.40	1.43	3050	3,934	1.37	1.41	1.44	3148
	Neurological disorders	Ataxia	Link	16	16	2.16	2.22	2.27	1767	2,565	2.16	2.21	2.27	1856
		Convulsion	Link	22	22	3.18	3.26	3.34	2727	3,552	3.18	3.26	3.34	2892
	Systemic disorders	Anorexia	Link	16	16	2.31	2.37	2.43	2664	3,505	2.31	2.37	2.42	2747
		Death	Link	24	24	1.72	1.76	1.80	2800	3,944	1.71	1.75	1.79	2922
		Lack of efficacy	Link	26	26	0.26	0.26	0.27	1273	1,414	0.26	0.26	0.27	1414
		Lethargy	Link	20	20	1.95	1.99	2.04	3404	4,287	1.94	1.99	2.04	3512
	Systemic disorders	Lack of efficacy	Link	15	34	5.54	6.24	7.02	729	1,214	5.49	6.19	6.97	805
	Digestive tract disorders	Diarrhoea	Link	13	13	0.34	0.34	0.35	1676	1,987	0.34	0.34	0.35	1766
		Emesis	Link	43	43	0.39	0.39	0.40	4612	4,926	0.39	0.39	0.40	4866
	Neurological disorders	Convulsion	Link	11	11	0.21	0.22	0.22	1133	1,397	0.21	0.22	0.22	1171
	Systemic disorders	Death	Link	11	11	0.11	0.11	0.11	1069	1,383	0.11	0.11	0.11	1142
		Lack of efficacy	Link	285	289	14.84	15.18	15.52	36657	37,165	14.99	15.33	15.68	38170
		Lethargy	Link	14	14	0.17	0.17	0.18	1924	2,205	0.17	0.17	0.18	1986
	Behavioural disorders	Vocalisation	Link	11	11	0.61	0.63	0.65	441	441	0.60	0.62	0.64	476
	Digestive tract disorders	Diarrhoea	Link	30	34	1.07	1.09	1.11	3442	3,827	1.07	1.09	1.11	3596
		Emesis	Link	65	66	1.35	1.37	1.39	8955	9,377	1.35	1.37	1.40	9378
	Neurological disorders	Ataxia	Link	21	21	0.48	0.49	0.50	1526	1,776	0.48	0.49	0.50	1619
		Convulsion	Link	25	26	0.78	0.79	0.81	2728	2,975	0.78	0.79	0.81	2848
		Muscle tremor	Link	11	11	0.60	0.61	0.63	1114	1,130	0.60	0.61	0.63	1172
	Respiratory tract disorders	Tachypnoea	Link	13	13	0.65	0.66	0.68	806	1,045	0.64	0.66	0.68	852
	Skin and appendages disorders	Pruritus	Link	25	31	2.48	2.54	2.61	3373	3,819	2.50	2.56	2.63	3535
	Systemic disorders	Anorexia	Link	33	33	0.71	0.72	0.73	3183	3,458	0.70	0.72	0.73	3329
		Death	Link	12	13	0.18	0.18	0.18	1305	1,713	0.18	0.18	0.18	1365
		Lack of efficacy	Link	208	263	1.78	1.81	1.84	15292	17,223	1.78	1.81	1.84	16585
		Lethargy	Link	38	38	0.62	0.63	0.64	4447	4,743	0.62	0.63	0.64	4640
	Digestive tract disorders	Diarrhoea	Link	16	16	2.51	2.60	2.70	802	833	2.52	2.61	2.71	889
		Emesis	Link	47	48	2.77	2.88	3.00	1663	1,716	2.75	2.87	2.99	1851
	Neurological disorders	Convulsion	Link	11	11	0.53	0.55	0.57	204	206	0.52	0.53	0.55	239
	Systemic disorders	Lack of efficacy	Link	22	23	0.30	0.31	0.32	475	552	0.29	0.30	0.31	587
		Lethargy	Link	15	16	1.11	1.15	1.19	784	802	1.12	1.16	1.20	851
	Digestive tract disorders	Emesis	Link	11	13	1.67	1.73	1.80	1104	1,304	1.67	1.74	1.81	1165
	Digestive tract disorders	Diarrhoea	Link	12	15	1.62	1.67	1.72	925	1,087	1.61	1.66	1.71	966
		Emesis	Link	23	26	1.43	1.48	1.52	1805	1,958	1.43	1.47	1.52	1903
	Immune system disorders	Allergic oedema	Link	19	19	5.46	5.65	5.84	1074	1,146	5.45	5.64	5.83	1162
		Anaphylaxis	Link	16	16	3.83	3.96	4.10	808	832	3.81	3.93	4.07	897
	Skin and appendages disorders	Pruritus	Link	11	11	1.26	1.30	1.34	391	409	1.24	1.28	1.32	423
	Systemic disorders	Anorexia	Link	13	13	1.84	1.90	1.95	1306	1,447	1.84	1.90	1.96	1369
		Hyperthermia	Link	14	14	4.62	4.78	4.94	994	1,062	4.61	4.77	4.93	1048
		Lethargy	Link	23	23	2.36	2.43	2.51	2238	2,413	2.36	2.43	2.51	2346
	Systemic disorders	Lack of efficacy	Link	16	16	1.60	1.67	1.74	1614	1,748	1.60	1.67	1.74	1666
	Neurological disorders	Ataxia	Link	15	15	2.86	2.97	3.08	774	796	2.86	2.96	3.08	823
		Convulsion	Link	31	31	13.33	13.99	14.68	2242	2,308	13.34	14.00	14.70	2366
	Digestive tract disorders	Emesis	Link	12	13	0.87	1.01	1.18	33	33	0.76	0.90	1.05	67
	Neurological disorders	Convulsion	Link	21	22	13.94	17.49	21.94	116	117	14.21	18.12	23.12	212

Rows 1 - 45 (All Rows)

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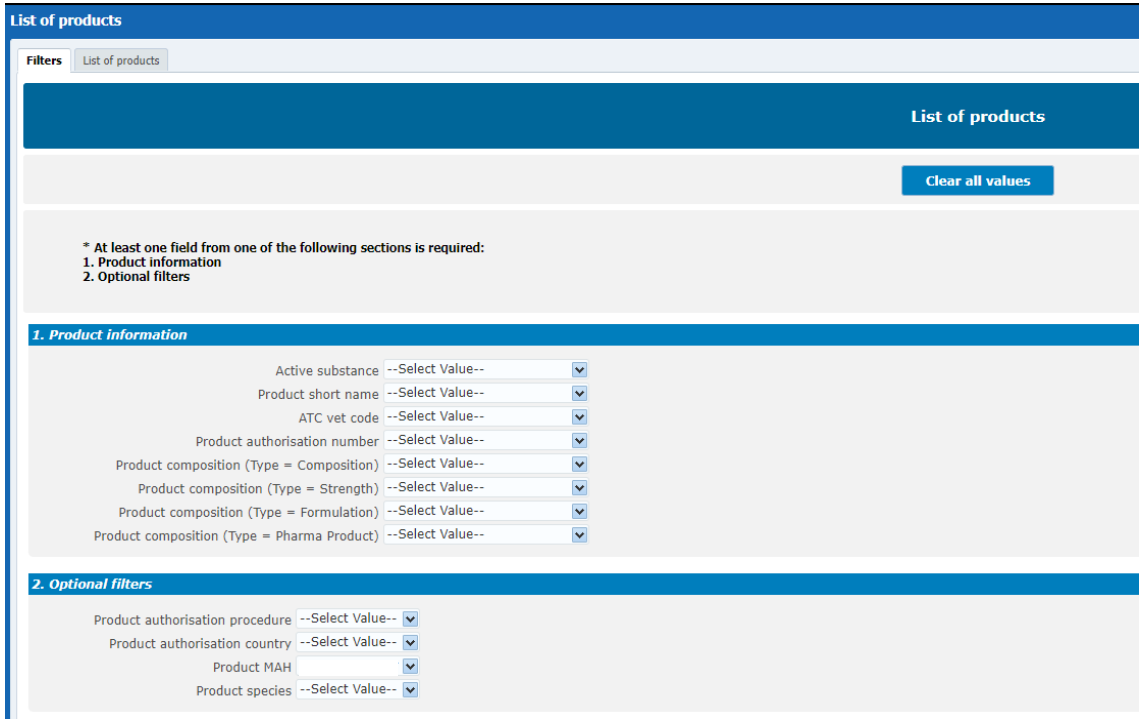
Data analysis – EVVET DWH

Continuous monitoring (List of products)



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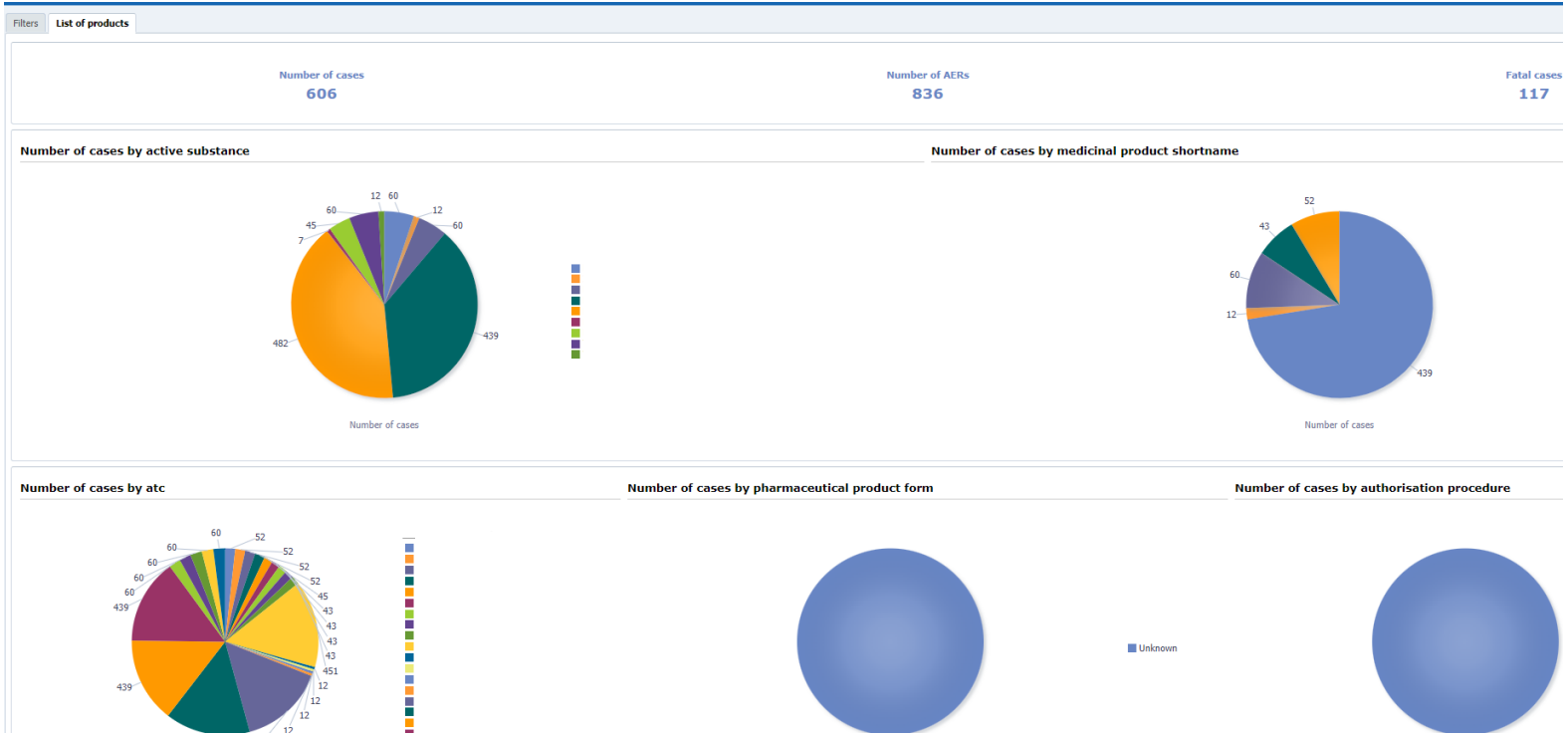
Continuous monitoring (List of products)



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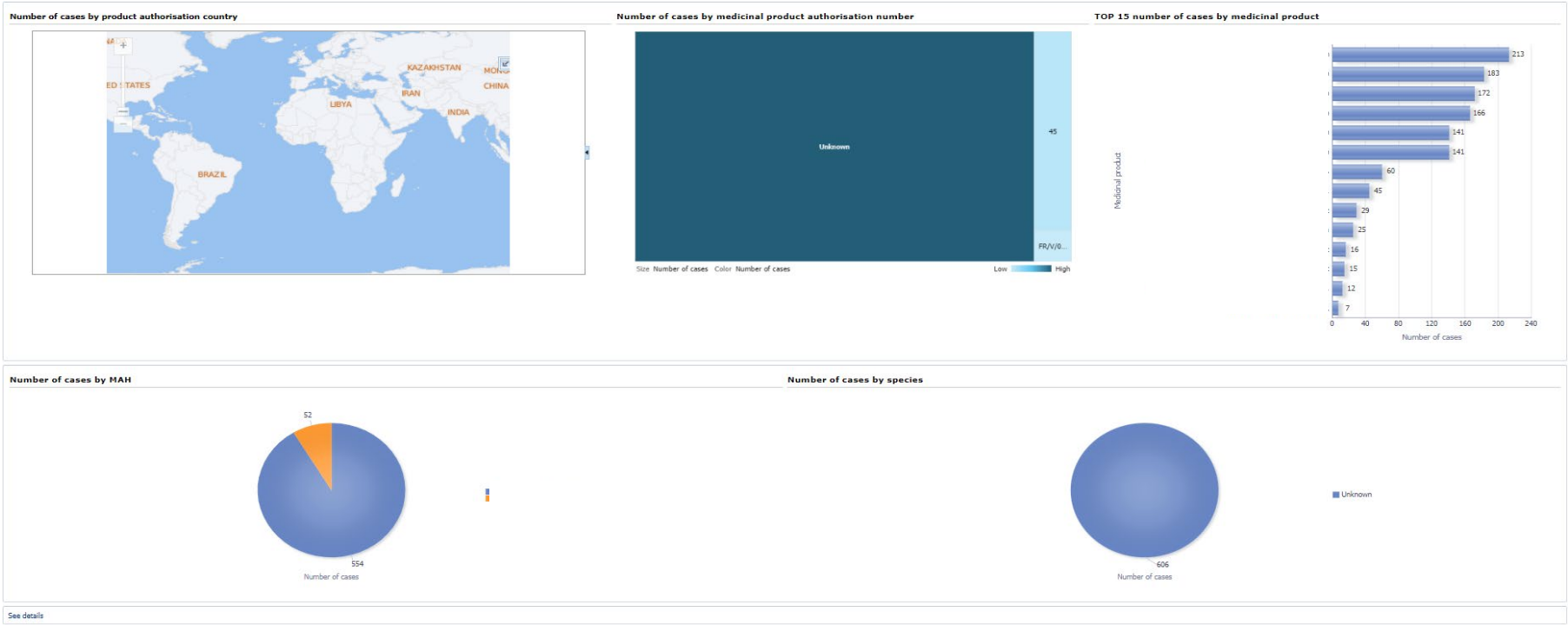
Continuous monitoring (List of products)



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Data analysis – EVVET DWH

Potential emerging safety issue

We will go through a set of practical questions for a concrete product and reaction, in this case a signal has been found for **product A** for the VeDDRA term **recumbency**

❑ How many cases for product A have occurred?

- ✓ The user goes to dashboard "Adverse Event Overview" and selects product A in the first prompt in the filter "Product Short name";
- ✓ Enter the "Message Received Date range" as required, ensuring that the dates that include the whole period when product A has been on the market are selected;
- ✓ Select "VeDDRA Hierarchy, VeDDRA PT name = Recumbency" and tick the box for "animal" and then run the query

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Data analysis – EVVET DWH

Potential emerging safety issue

A signal has been found for **Product A** for the VeDDRA term **recumbency**.

❑ Where have the majority of the cases occurred? How many animals have been affected?

- ✓ In the "Adverse Event Overview", the user clicks on "Animal/Human adverse events overview" which is a link to the signal detection dashboard;
- ✓ It will automatically navigate to the "Overview of human/animal AERs" per product/active substance/atcvet code tab.

❑ Are other products involved?

- ✓ Go to the "Signal evaluation" dashboard and select product A in the first prompt in the filter "product short name".
- ✓ Enter the "message received date range" as required *e.g.* last 5 years.
- ✓ Select "VeDDRA Hierarchy, VeDDRA PT name = Recumbency". Tick the box for "animal" in the 4th prompt and then run the query. Go to the "product association" tab

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Data analysis – EVVET DWH

Potential emerging safety issue

A signal has been found for **product A** for the VeDDRA term **recumbency**. The following questions emerge in a standard analysis process:

❑ **How many animals treated with product A, have died? How many of those have been euthanised?**

✓ "Adverse event overview" query gives you the number of animals died (select product A, click the "animal" box and make sure to select the dates that include the whole period when product A has been on the market);

✓ To see the number of animals euthanised, select the VeDDRA term LLT "Death by euthanasia".

❑ **How many cases have been reported between 01/03/2019 and 31/05/2019 and how many cases in total? How many new cases are we receiving daily?**

✓ "Adverse event overview"" select product A and select the dates.

✓ In the column "Number of cases (Period specified)", you have the n. of cases for specified period. To see the total n. of cases, either remove the date filters, or go to "see details". In the column "N. of cases (Total ALL)" you have the n. of total cases in the database per VeDDRA term;

✓ In the column "N. of cases (Case count (filter not applied)" you have the n. of total cases for the product;

✓ For monitoring new data (not follow-ups), select the filter "New cases".

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Data analysis – EVVET DWH

Potential emerging safety issue

A signal has been found for p**roduct A** for the VeDDRA term **recumbency**. The following questions emerge in a standard analysis process:

❑ **Which other products are associated with recumbency? Which product has the highest number of cases of recumbency after product A?**

- ✓ Go to the "Data stratification" dashboard and select "VeDDRA terms, VedDRa PT name = Recumbency";
- ✓ Then click on "and", then select "VeDDRA term PT = Death";
- ✓ Tick the box for "Animal" then run the query by clicking on "Adverse events by VeDDRA terms. The first graph will give you the answer.

❑ **Which other signs have been reported together with recumbency? Which pair has the highest count?**

- ✓ Go to the dashboard "Signal Evaluation" and select Product A in the first prompt in the filter "Product short name";
- ✓ Enter the "Message received date range" as required *e.g.* last 5 years;
- ✓ Tick the box for "animal" in the 3rd prompt;
- ✓ Select "VeDDRA Hierarchy, VedDRa PT name = Recumbency" and go to "Associated VeDDRA".

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Any questions?

Further information

Vetchange.programme@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

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