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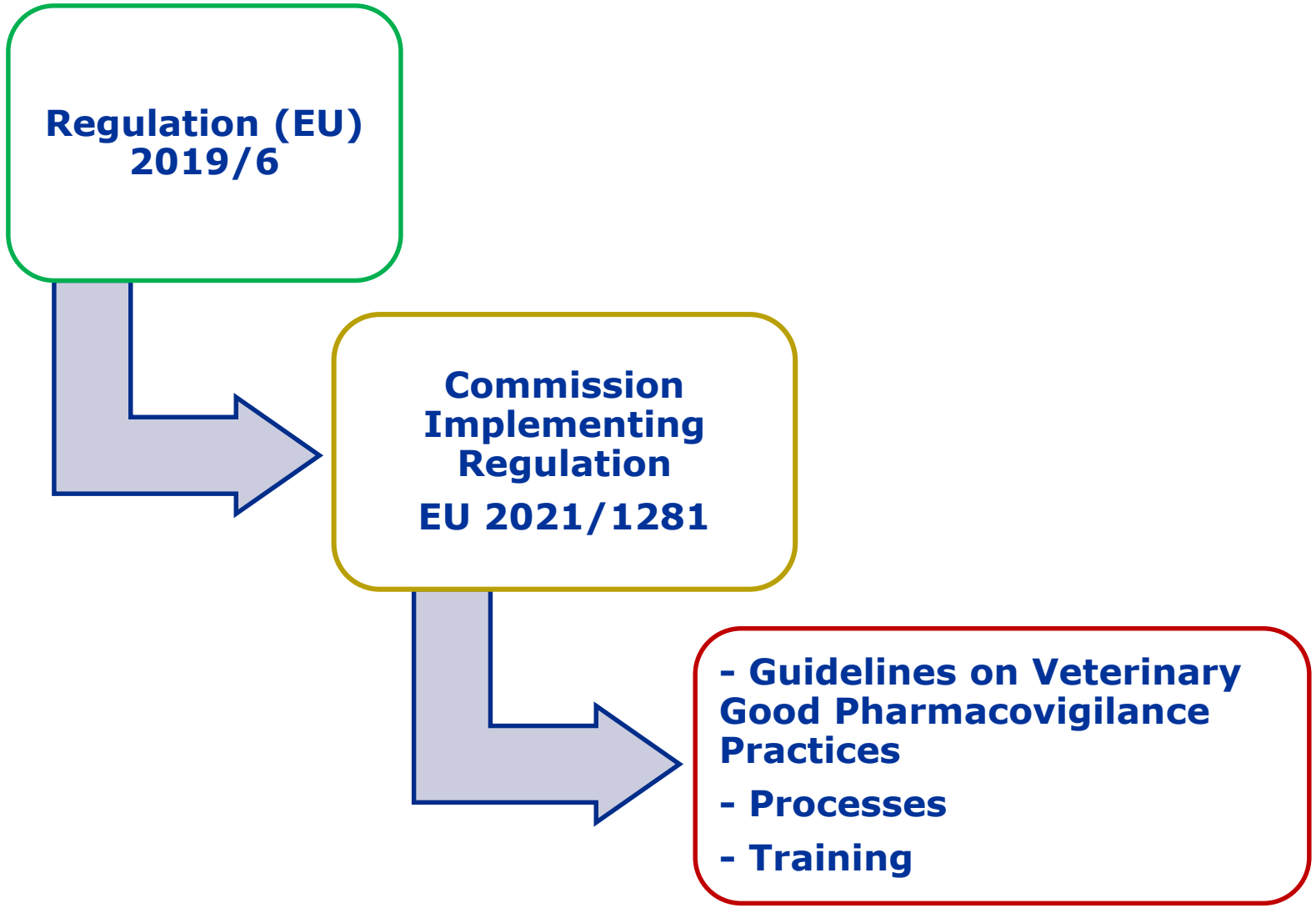
SCIENCE MEDICINES HEALTH

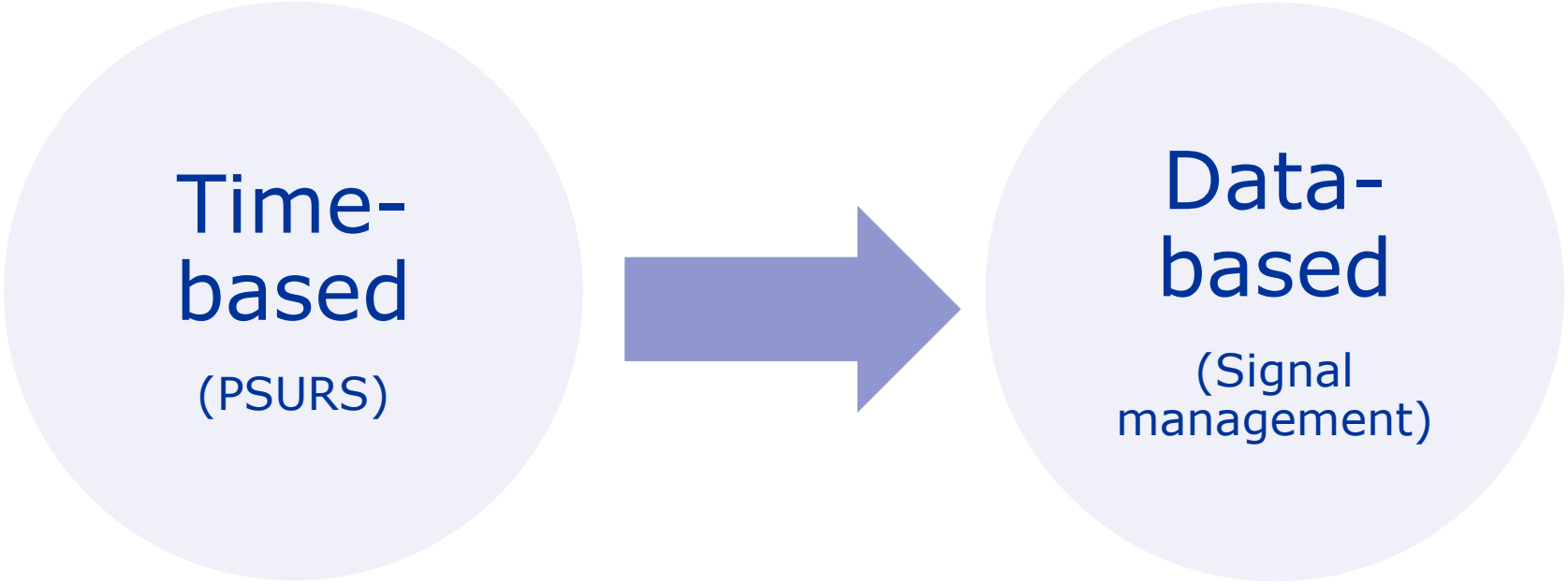
Changes in pharmacovigilance, signal detection and surveillance

Jos Olaerts



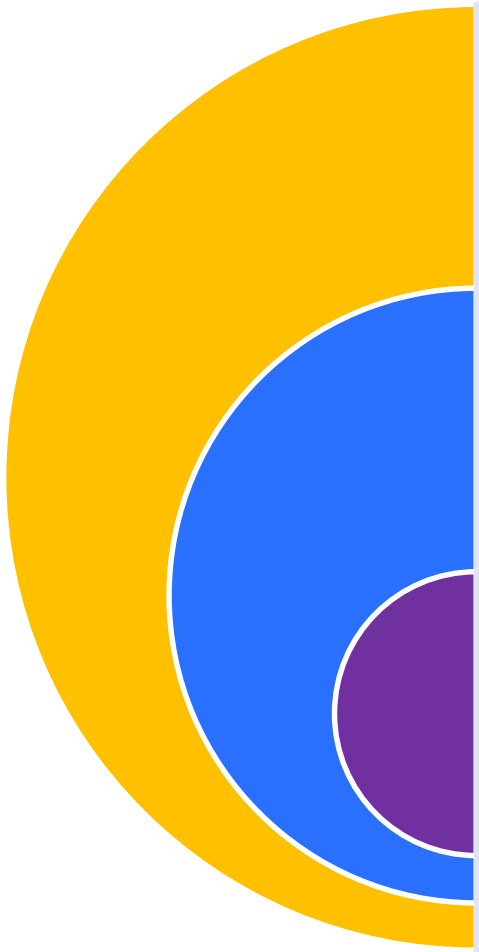
PhV Pillars

- **AE collection and recording**
  - 30 days + non-serious cases
  - Yearly sales (+ estimation of exposed Number of target species)
- **Continuous AE analysis by MAH (signal management)**
  - Using EVVET database or own database (+ 1 yearly SD analysis on EVVET)
  - Yearly MAH statements + SM outcomes submitted to database
- **Regulator oversight through**
  - PhV Inspections
  - Risk based signal surveillance by regulators
  - Ad-hoc targeted surveillance
- **Pharmacovigilance Master File (+ Quality Management System)**



(However: annual statements (2) + sales)

Essential DATA systems



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

PhV related activities (“Burden”)

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- Systems
- Processes
- Training
- Signals

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AER recording – EVV

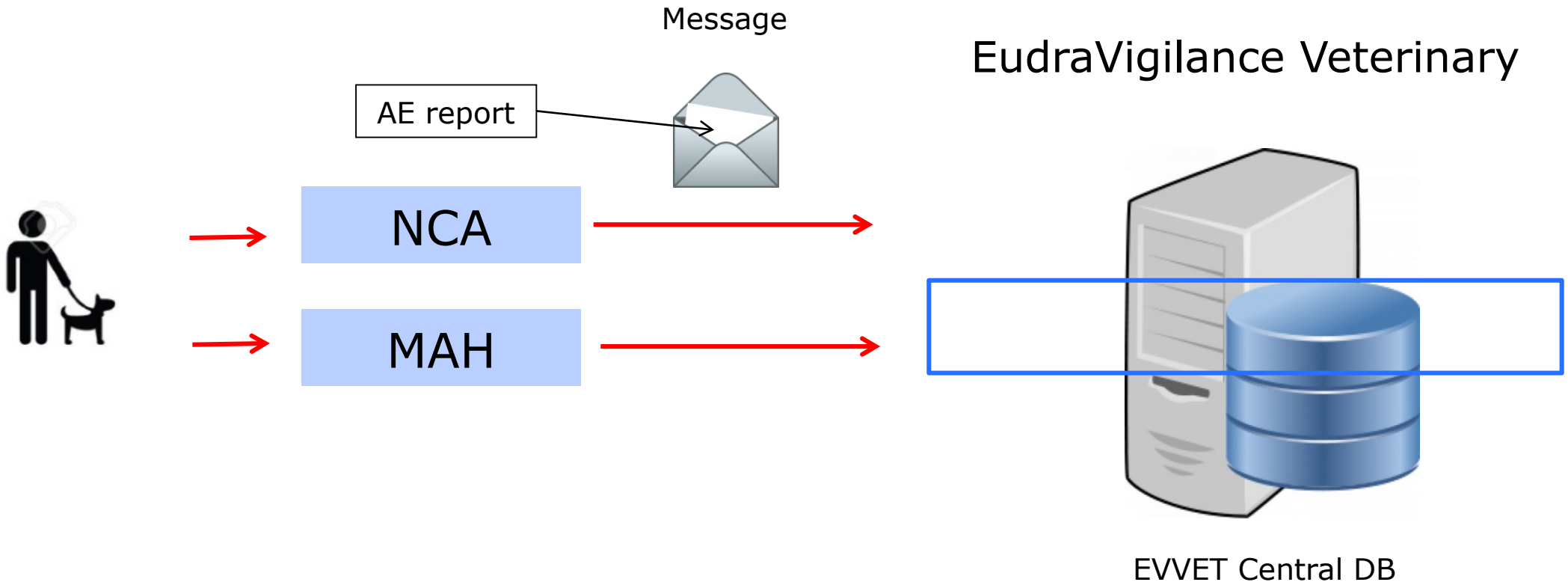
Laura Descalzo

Regulation (EU) 2019/6 vs Volume 9B of The Rules Governing Medicinal Products in the European Union

Main differences

- All suspected adverse event reports (AERs) recorded directly to EVV
- Timeframe for AERs recording in EVV: 30 calendar days
- No difference between serious and non-serious adverse events for reporting obligations and signal detection, however the field 'Serious AE' is mandatory in EVV (Yes, No)
- Requirement for collection and recording of any observation of a lack of efficacy of a veterinary medicinal product (VMP) following its administration to an animal, whether or not in accordance with the summary of product characteristics
- Requirement for collection and recording of environmental incidents (NEW DEFINITION)
- Requirement for collection and recording of any unfavourable and unintended reaction in an animal to a medicinal product for human use

MESSAGING FLOW
ALL reports



LOGIN– EVVET (1)

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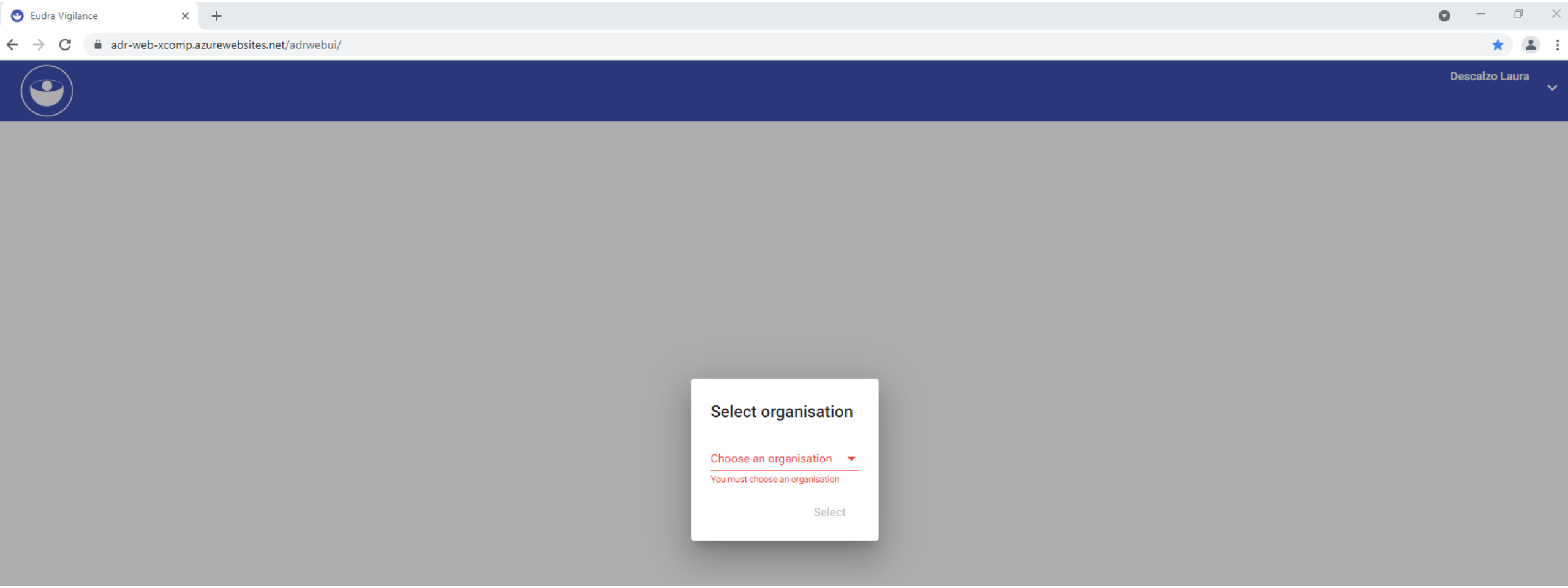

LOGIN– EVVET (2)

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AERs Mailbox

Descalzo Laura
Eudravigilance Veterinary

Create and Send | Search AE Reports | Search AE Messages

Search

New | Import XML | Export XML | Validate | Validate and Send

- AE Message 1
  - AE Report #1
    - A - Administrative and Identification Information
      - A.2 Marketing Authorization Holder (MAH)
      - A.3 Person(s) Involved in AER
      - A.4 AER Information
    - B - Description of Animal Data Information

AE Message

Batch Identifier *

This field is required

Batch Sender Identifier

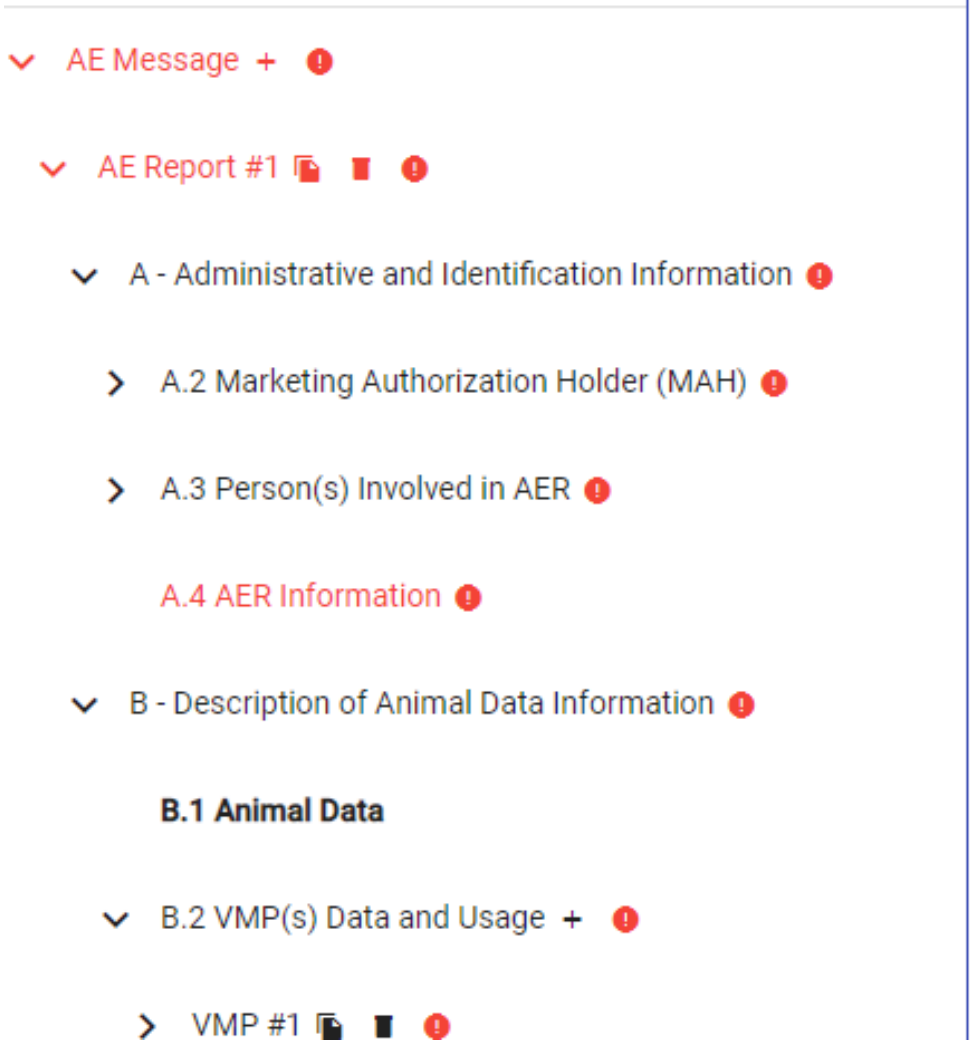
(EVVETTBL) Eudravigilance Veterinary

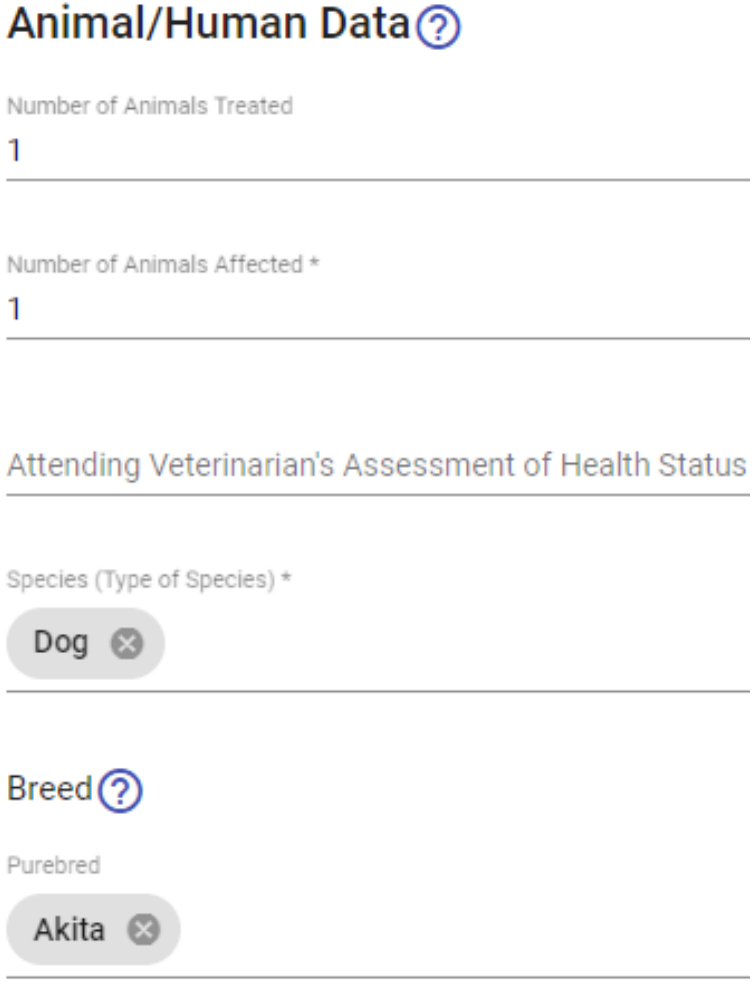
Batch Receiver Identifier *

Date of Batch Creation *

2021/10/19 17:37:05

AE REPORTING– EVVET (1)





AE REPORTING – EVVET (2)

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- B.1 Animal Data
- B.2 VMP(s) Data and Usage +
  - VMP #1
    - B.2.1 Registered or Brand Name
    - B.2.2 Active Ingredient(s) +
    - B.2.3 Lot Number +
    - B.2.4 Who Administered the VMP
    - B.2.5 Use According to Label
    - B.3.9 Previous Exposure to the VMP
    - B.3.10 Previous AE to VMP
    - B.4 Dechallenge-Rechallenge Information
- **B.3 Adverse Event Data**
- B.5 Assessment of AE
- B.6 Report Number(s) of Linked Report(s)
- B.7 Supplemental Documents

AE REPORTING – EVVET (3)

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Narrative of AE *

This field is required

Adverse Clinical Manifestations

AER Term Name *	Number of Animals	Accuracy of the Number of Animals *
Application site abscess	1	Actual
Lethargy	1	Actual

+ Add

Choose a Date Format *: Day, Month and Year

Date of Onset of AE (AE Start Date) *: 2021/03/02

Length of Time between Exposure to VMP & Onset of AE: <12 hours

Duration of AE

Duration (Time): 3

AE REPORTING – EVVET (4)

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Label Usage

Use According to Label

Was the animal underdosed?

Explanation for Off-Label Use

Was the treatment regimen Off-label?

Was the target species Off-label?

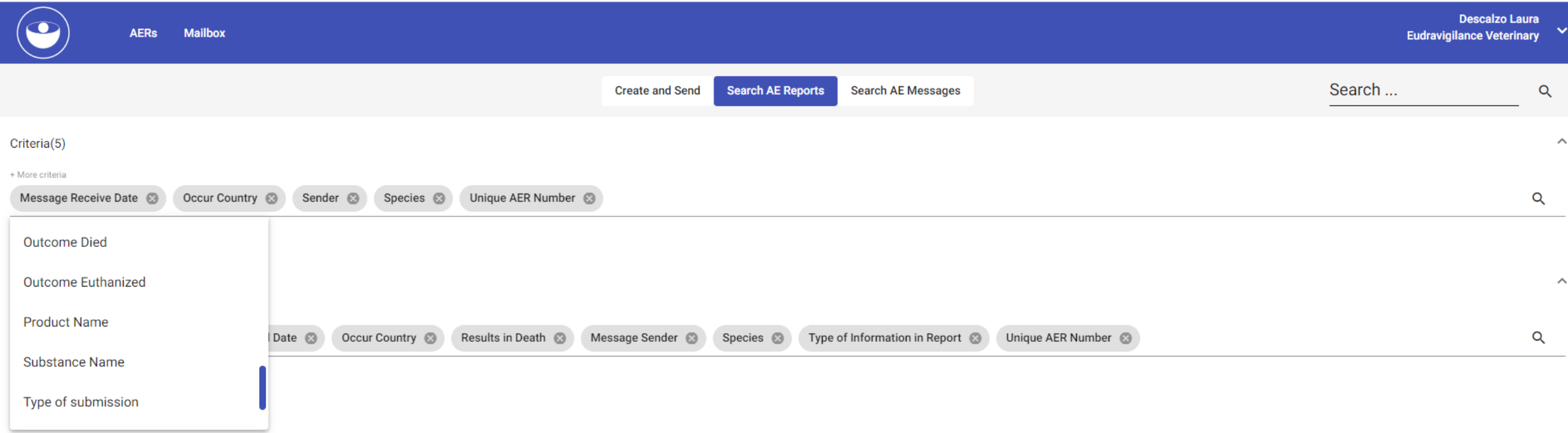
Was the indication Off-label?

Was the route of administration Off-label?

Was the storage condition Off-label?

Was the animal overdosed?

Search for Messages and AERs



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EVV DWH Dashboard and Reports

19 – March - 2021

Searching flow: where to begin?

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As a general rule, if the user wants…

ADVERSE EVENT OVERVIEW

To get a simple overview of the data for a product, substance, group of products

SIGNAL DETECTION

To view data for product, active substance, group of products in order to check for potential signals

SIGNAL EVALUATION

To evaluate signals (age, time to onset, off label use, geographical distribution, pharmaceutical form, other products involved, other VedDRA terms)

DATA STRATIFICATION

To exclude outliers or simply narrow a query for comparison purposes

ADVERSE EVENT BETWEEN 2 PERIODS

To compare data for 2 time periods

LINE LISTING

To list the cases for a product, substance, group of products, MAH, country

SIGNALING FOR REACTIONS

To monitor data for MAH/NCA products or substances (weekly, monthly)

LIST OF PRODUCTS

To monitor number of cases (by active substance, product, pharmaceutical form, ATC, authorization country, number, MAH, species)

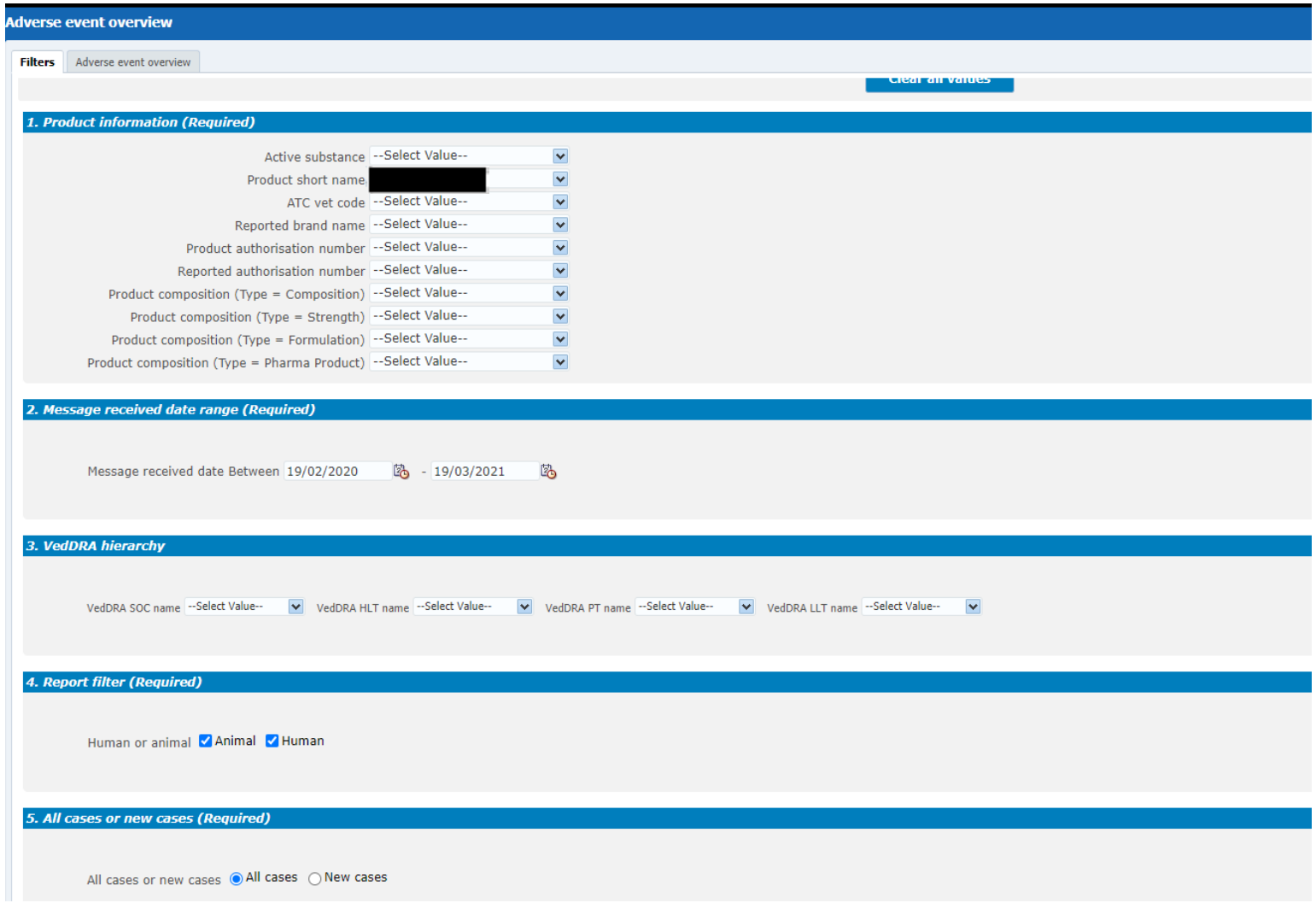
Dashboards: how to get an overview of data for a product/substance/ group of products

ADVERSE EVENT OVERVIEW

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

Adverse Event Overview

Filters page selection

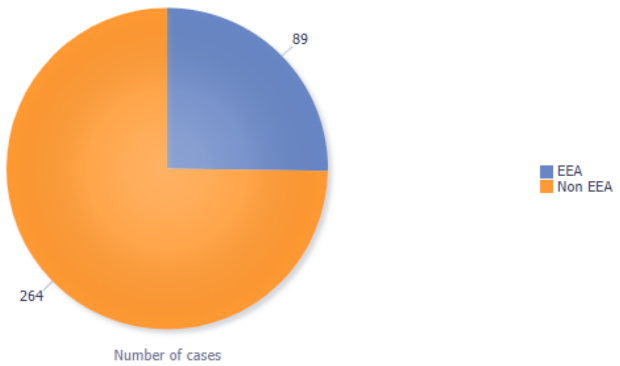


Adverse Event Overview

Filters | **Adverse event overview**

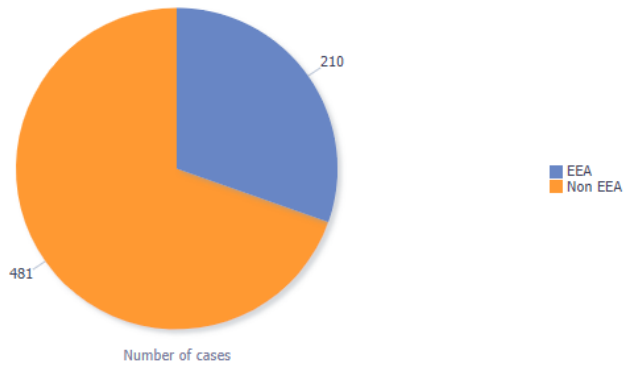
Number of cases	Animals affected	Fatal cases	Animals died
353	370	46	57

Number of cases by region (Specified period)



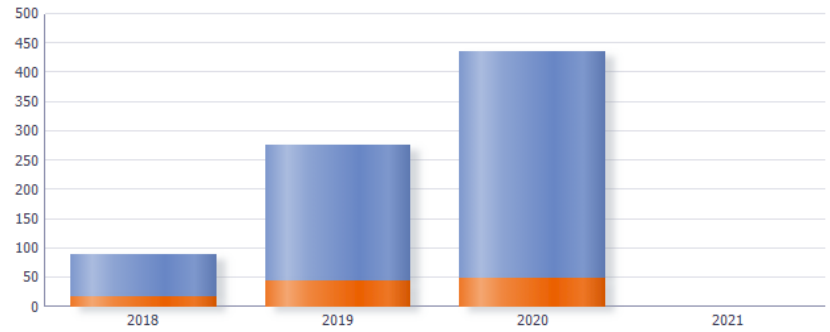
* Occurence region filter not applied

Number of cases by region (All cases)

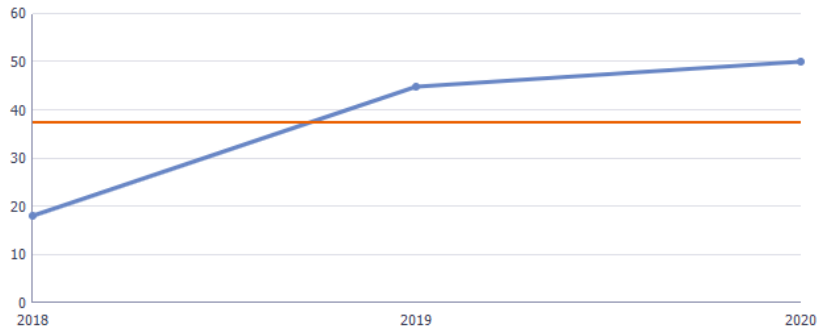


* Occurence region and message received date filters not applied

Number of cases and fatal cases (LAST 10 YEARS)



Number of fatal cases over average (LAST 10 YEARS)



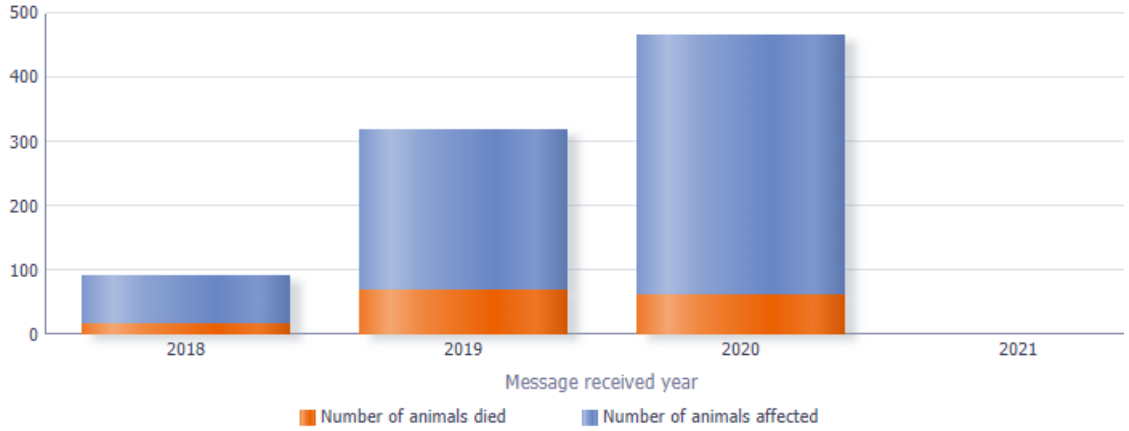
Adverse Event Overview

Number of cases by species and VedDRA SOC over product

	Cat	Dog	Human
Application site disorders		2	
Behavioural disorders	22	45	
Blood and lymphatic system disorders	1	4	
Cardio-vascular system disorders	5	19	1
Digestive tract disorders	10	109	5
Ear and labyrinth disorders	3	1	
Endocrine system disorders		3	
Eye disorders	1	18	
Hepato-biliary disorders		3	
Immune system disorders	2	16	1
Investigations	4	58	
Musculoskeletal disorders	2	26	
Neurological disorders	27	190	2
Renal and urinary disorders	1	16	
Reproductive system disorders	1	3	
Respiratory tract disorders	19	27	1
Skin and appendages disorders	15	15	1
Systemic disorders	34	140	1
Unclassifiable event		1	

* Species and VedDRA hierarchy filters not applied

Number of animals affected and animals died (LAST 10 YEARS)



*Message received date filter not applied

See details

Links to signal detection reports

Animal/Human adverse events overview

ROR calculations based on number of animals reacted*

*Please fill in at least one field from VedDRA terms

Link to data stratification report

Adverse events overview for associated products

Adverse Event Overview

Product Hierarchy Level Medicinal product shortname **VedDRA Hierarchy Level** VedDRA PT name

Species Cat

Medicinal product shortname	VedDRA SOC name	VedDRA PT name	ROR (AER)	ROR (+) (AER)	ROR (-) (AER)	Number of animals affected	Number of cases (period specified)	Number of NON EEA cases (period specified)	Number of EEA cases (period specified)	Number of cases (Total ALL)	Number of NON EEA cases	Number of EEA cases	Number of cases (Total ALL reactions)	Number of fatal cases (period specified)	Number of fatal cases	Case count (AERs)	Reaction count	Case count by product (filter applied)	Case count (filter not applied)	Reaction count total	Percentage of reactions	Percentage of cases	Known VedDRA terms code	Number of AERs (ROR)
[redacted]	Behavioural disorders	Aggression	N/A	N/A	N/A	2	2		2	3		2	153			2	1	68	691	123	0.81	2.94	0	2
		Anxiety	N/A	N/A	N/A	2	2		2	3		2	153			2	1	68	691	123	0.81	2.94	0	2
		Behavioural disorder NOS	1.27	1.65	0.98	5	5		5	9		5	153			5	2	68	691	123	1.63	7.35	0	5
		Grooming disorder	15.30	22.19	10.55	7	5	2	3	9	2	3	153			5	1	68	691	123	0.81	7.35	0	5
		Hyperactivity	6.83	9.10	5.13	15	13	2	11	31	2	11	153			13	4	68	691	123	3.25	19.12	0	13
		Self mutilation	N/A	N/A	N/A	1	1		1	1		1	153			1	1	68	691	123	0.81	1.47	0	1
		Vocalisation	2.47	3.24	1.88	5	5	1	4	9	1	4	153			5	2	68	691	123	1.63	7.35	0	5
	Blood and lymphatic system disorders	Other coagulation abnormality	N/A	N/A	N/A	1	1		1	2		1	153			1	1	68	691	123	0.81	1.47	0	1
	Cardio-vascular system disorders	Circulatory shock	N/A	N/A	N/A	1	1		1	2		1	153			1	1	68	691	123	0.81	1.47	0	1
		Pericardial effusion	N/A	N/A	N/A	1	1		1	1		1	153			1	1	68	691	123	0.81	1.47	0	1
		Tachycardia	2.26	2.99	1.70	3	3	1	2	9	1	2	153			3	1	68	691	123	0.81	4.41	0	3
	Digestive tract disorders	Diarrhoea	N/A	N/A	N/A	2	2	1	1	8	1	1	153			2	1	68	691	123	0.81	2.94	0	2
		Digestive tract disorder NOS	N/A	N/A	N/A	1	1		1	1		1	153			1	1	68	691	123	0.81	1.47	0	1
		Dysphagia	N/A	N/A	N/A	1	1	1		1	1		153			1	1	68	691	123	0.81	1.47	0	1
		Emesis	0.52	0.67	0.40	5	5	1	4	18	1	4	153			5	1	68	691	123	0.81	7.35	0	5
		Hypersalivation	N/A	N/A	N/A	2	2	1	1	7	1	1	153			2	1	68	691	123	0.81	2.94	0	2
		Intestinal disorder NOS	N/A	N/A	N/A	1	1		1	1		1	153			1	1	68	691	123	0.81	1.47	0	1
		Intestinal stasis	N/A	N/A	N/A	1	1	1		1	1		153			1	1	68	691	123	0.81	1.47	0	1
		Nausea	N/A	N/A	N/A	1	1		1	3		1	153			1	1	68	691	123	0.81	1.47	0	1
		Paralytic ileus	N/A	N/A	N/A	1	1		1	1		1	153			1	1	68	691	123	0.81	1.47	0	1
	Ear and labyrinth disorders	Ear canal disorder	N/A	N/A	N/A	1	1		1	1		1	153			1	1	68	691	123	0.81	1.47	0	1
		Internal ear disorder	N/A	N/A	N/A	2	2		2	2		2	153			2	2	68	691	123	1.63	2.94	0	2
	Eye disorders	Blepharospasm	N/A	N/A	N/A	1	1		1	1		1	153			1	1	68	691	123	0.81	1.47	0	1
	Immune system disorders	Anaphylaxis	N/A	N/A	N/A	2	2		2	2		2	153			2	1	68	691	123	0.81	2.94	0	2
	Investigations	Abnormal necropsy finding	N/A	N/A	N/A	1	1		1	2		1	153			1	1	68	691	123	0.81	1.47	0	1

Rows 1 - 25

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Signal Management

Laura Descalzo & Jos Olaerts

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 reactions of interest (potential signs) and identify potential risk factors, effects of co-medication, geographical distribution or pharmaceutical form

SIGNAL DETECTION

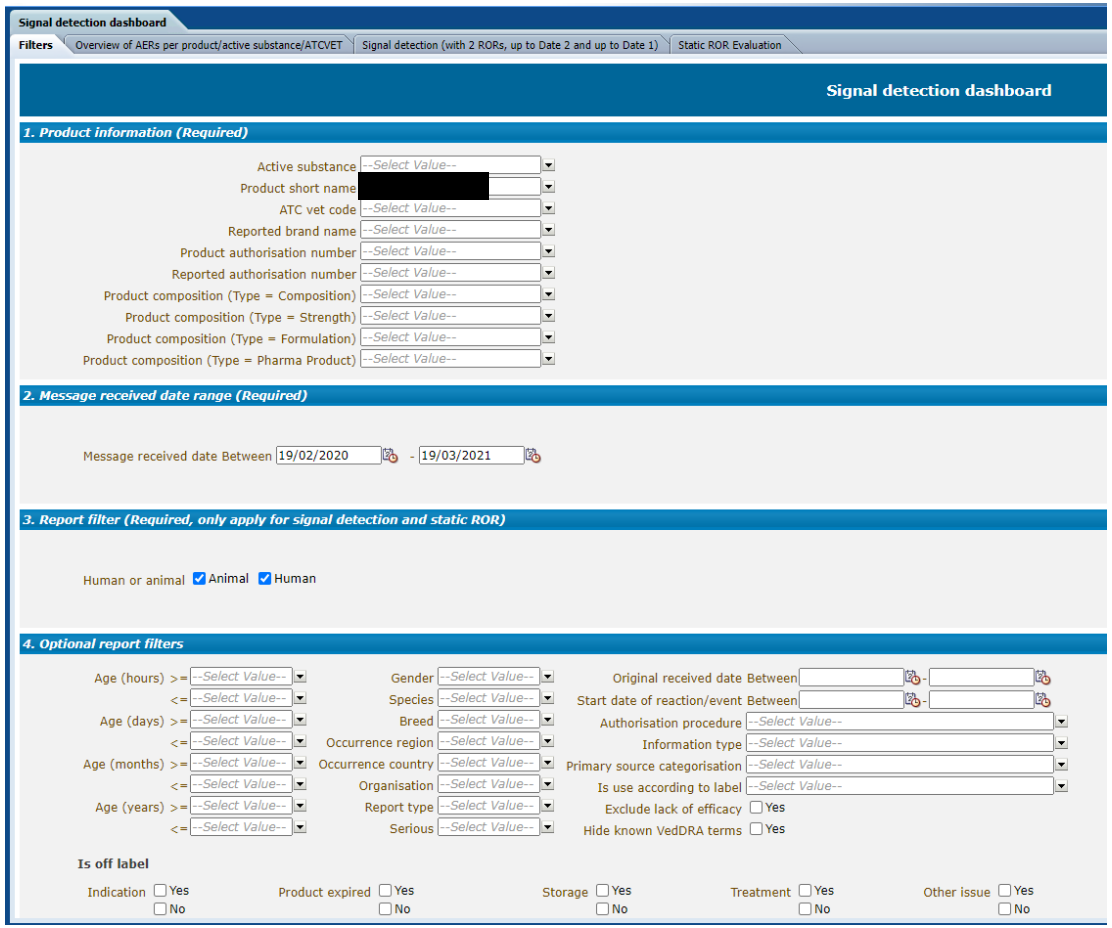
To view the type of Adverse Events reported for a selected product or group of products (at SOC and PT) and to compare the frequency to the number of reports involving other products and other clinical signs = ROR / ROR(-)

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)

Signal Detection

Filters selection page



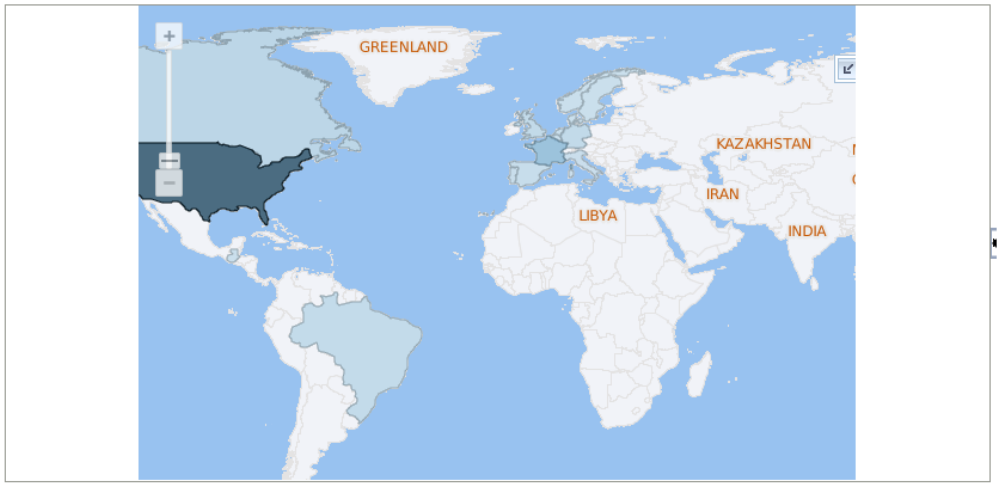
Signal Detection

Overview of AERs per product/active substance/ATC Vet code

JCT/ACTIVE SUBSTANCE/ATCVET CODE

Species --Select Value--

Number of cases



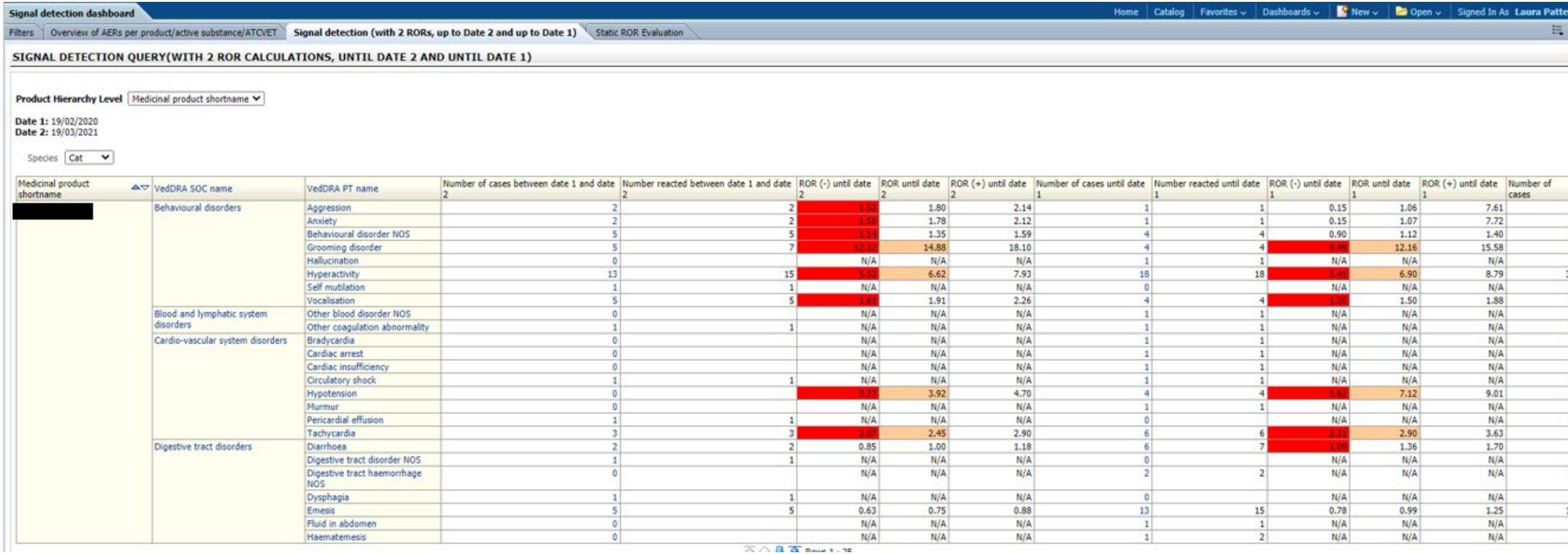
Analyze - Refresh - Print - Export

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								
[redacted]	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

Signal Detection

Signal detection with 2 RORs up to date 2 and up to date 1



Signal detection dashboard

Home | Catalog | Favorites | Dashboards | New | Open | Signed In As Laura Patte

Filters | Overview of AERs per product/active substance/ATCVET | Signal detection (with 2 RORs, up to Date 2 and up to Date 1) | Static ROR Evaluation

SIGNAL DETECTION QUERY(WITH 2 ROR CALCULATIONS, UNTIL DATE 2 AND UNTIL DATE 1)

Product Hierarchy Level: Medicinal product shortname

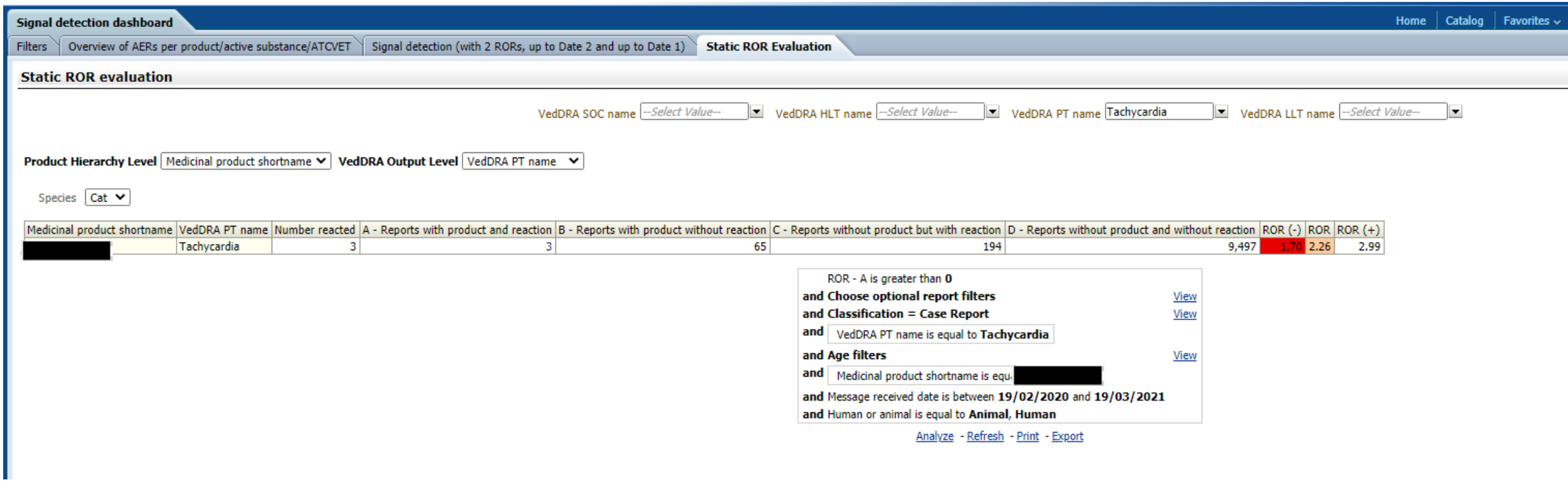
Date 1: 19/02/2020
Date 2: 19/03/2021

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	Number of cases until date 1	Number reacted until date 1	ROR (-) until date 1	ROR until date 1	ROR (+) until date 1	Number of cases
[redacted]	Behavioural disorders	Aggression	2	2	1.52	1.80	2.14	1	1	0.15	1.06	7.61	
		Anxiety	2	2	1.50	1.78	2.12	1	1	0.15	1.07	7.72	
		Behavioural disorder NOS	5	5	1.14	1.35	1.59	4	4	0.90	1.12	1.40	
		Grooming disorder	5	7	12.22	14.88	18.10	4	4	9.46	12.16	15.58	
		Hallucination	0		N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Hyperactivity	13	15	5.52	6.62	7.93	18	18	5.41	6.90	8.79	
		Self mutilation	1	1	N/A	N/A	N/A	0		N/A	N/A	N/A	
		Vocalisation	5	5	1.61	1.91	2.26	4	4	1.20	1.50	1.88	
	Blood and lymphatic system disorders	Other blood disorder NOS	0		N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Other coagulation abnormality	1	1	N/A	N/A	N/A	1	1	N/A	N/A	N/A	
	Cardio-vascular system disorders	Bradycardia	0		N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Cardiac arrest	0		N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Cardiac insufficiency	0		N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Circulatory shock	1	1	N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Hypotension	0		3.27	3.92	4.70	4	4	5.61	7.12	9.01	
		Murmur	0		N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Pericardial effusion	1	1	N/A	N/A	N/A	0		N/A	N/A	N/A	
		Tachycardia	3	3	2.07	2.45	2.90	6	6	2.31	2.90	3.63	
	Digestive tract disorders	Diarrhoea	2	2	0.85	1.00	1.18	6	7	1.05	1.36	1.70	
		Digestive tract disorder NOS	1	1	N/A	N/A	N/A	0		N/A	N/A	N/A	
		Digestive tract haemorrhage NOS	0		N/A	N/A	N/A	2	2	N/A	N/A	N/A	
		Dysphagia	1	1	N/A	N/A	N/A	0		N/A	N/A	N/A	
		Emesis	5	5	0.63	0.75	0.88	13	15	0.78	0.99	1.25	
		Fluid in abdomen	0		N/A	N/A	N/A	1	1	N/A	N/A	N/A	
		Haematemesis	0		N/A	N/A	N/A	1	2	N/A	N/A	N/A	

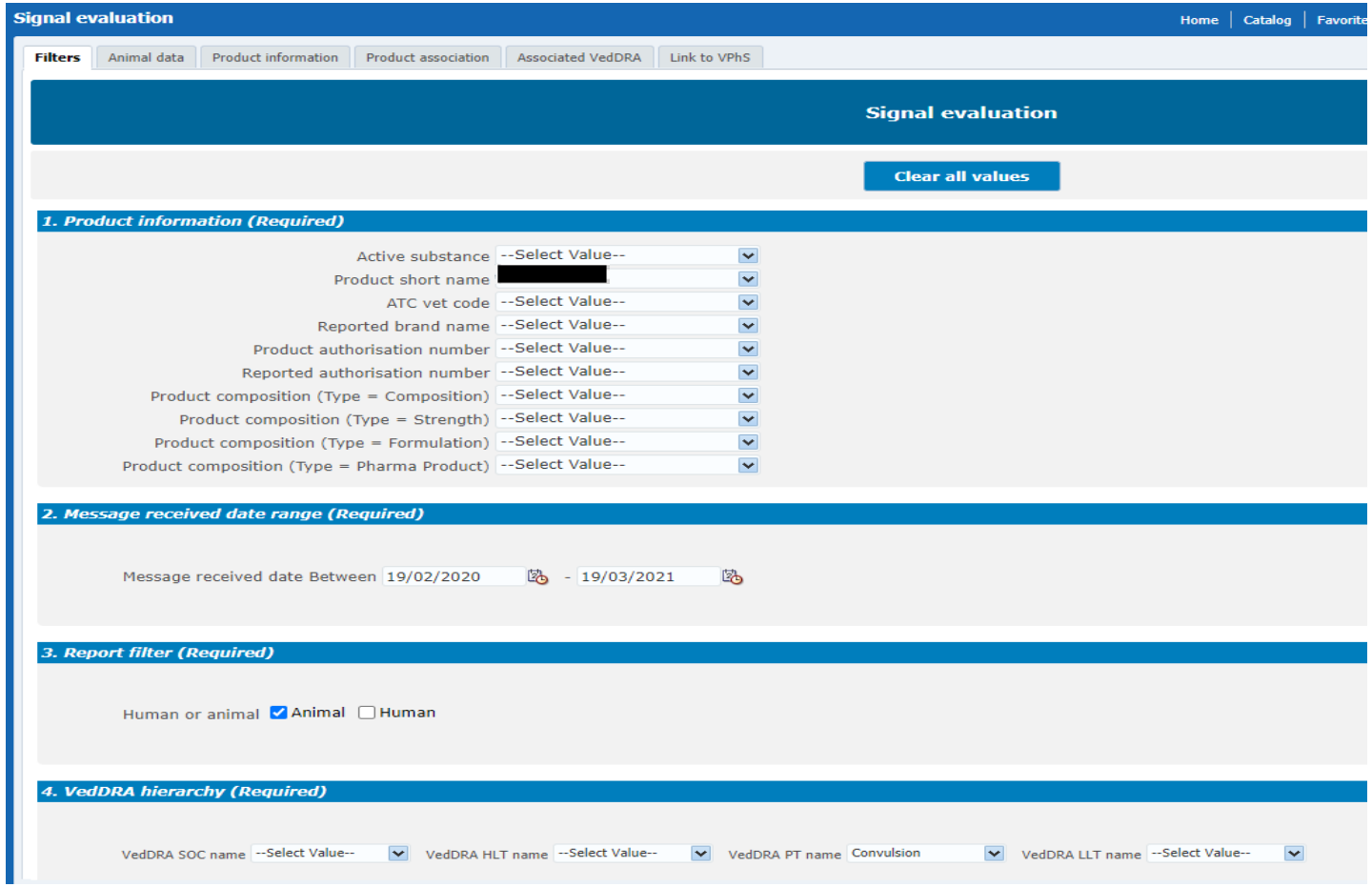
Signal Detection

Static ROR Evaluation (e.g. may help identify masking if C very high)



Signal evaluation

Filters selection page

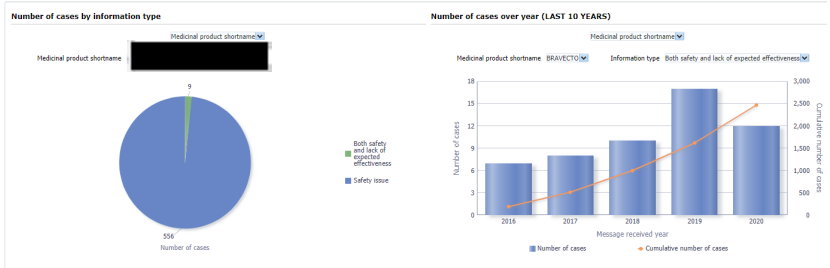


Signal evaluation

Animal Data (species/breed, age, weight, time to onset, off label use analysis)

Signal evaluation

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



Number of animals affected by pharmaceutical form or active substance

Pharmaceutical product form

Species Cat

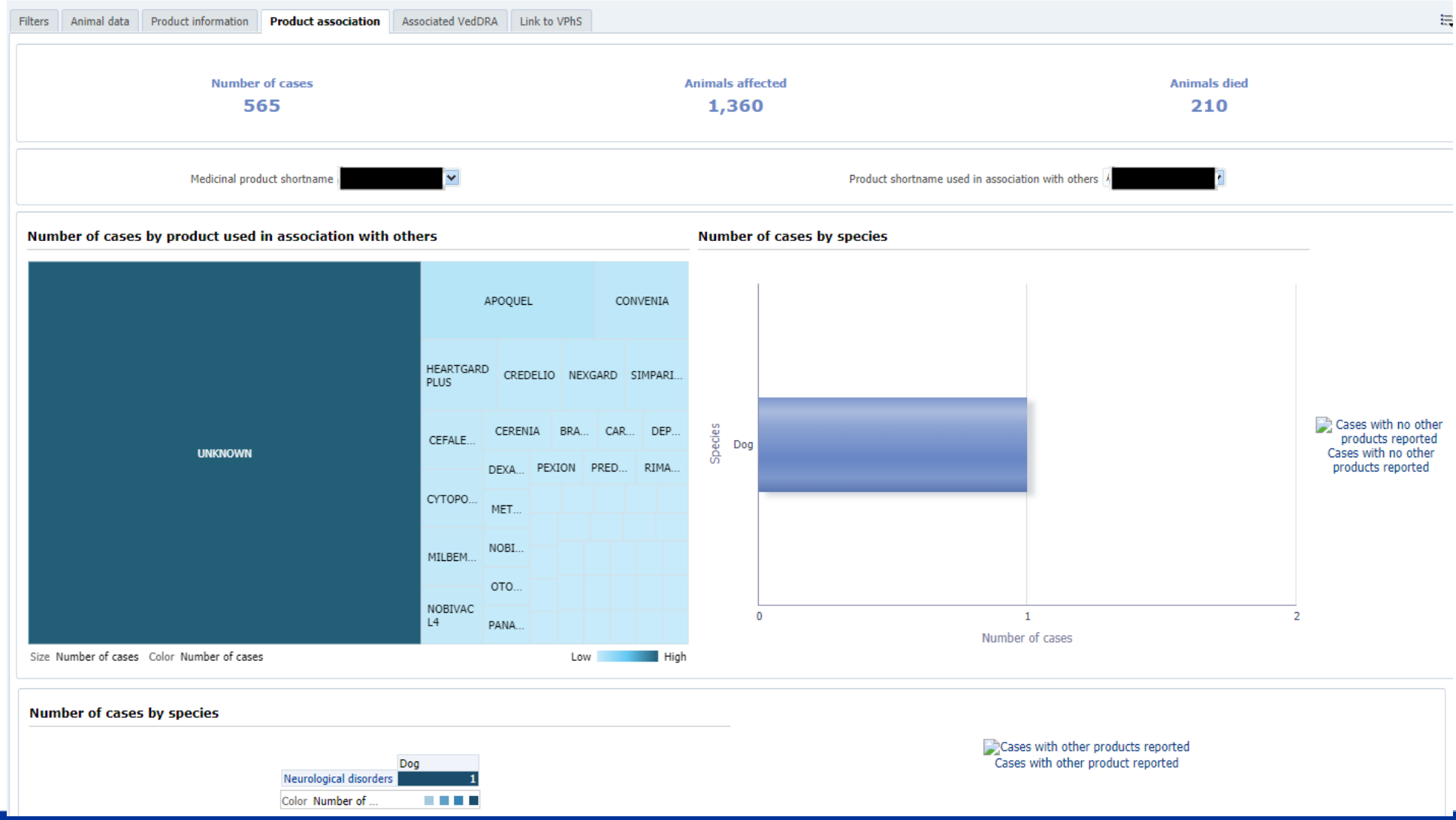
Information type Safety issue

			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

Signal evaluation

Product association (were there other products administered to the same animal(s)?)



Signal evaluation

Associated VedDRA (other VedDRA terms involved)

Species Dog

Medicinal product shortname	VedDRA SOC name	Associated vedDRA SOC name	Reaction count	Reaction count total for the combination	Number of cases	Total Number of cases (VedDRA)	ROR (-) for the combination
[redacted]	Application site disorders	Neurological disorders	3	234	5	30	

Overall approach to signal management by MAHs

*A **signal** is defined as information that arises from one or multiple sources, including observations and experiments, which **suggests** a potentially **new** causal association, or a new aspect of a known causal association between an intervention and an **adverse event** or a set of related adverse events, that is judged likely to justify further **investigation** of possible causality (Article 1(c) of the Implementing Act)*

- The focus should be on identifying **new** information
- A signal is an hypothesis; it does not always translate into a definitive causal association
- Not all signals represent risks or require further regulatory actions

DATA ANALYSIS – EXAMPLE METHODOLOGY

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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, or high numbers of animal deaths.

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

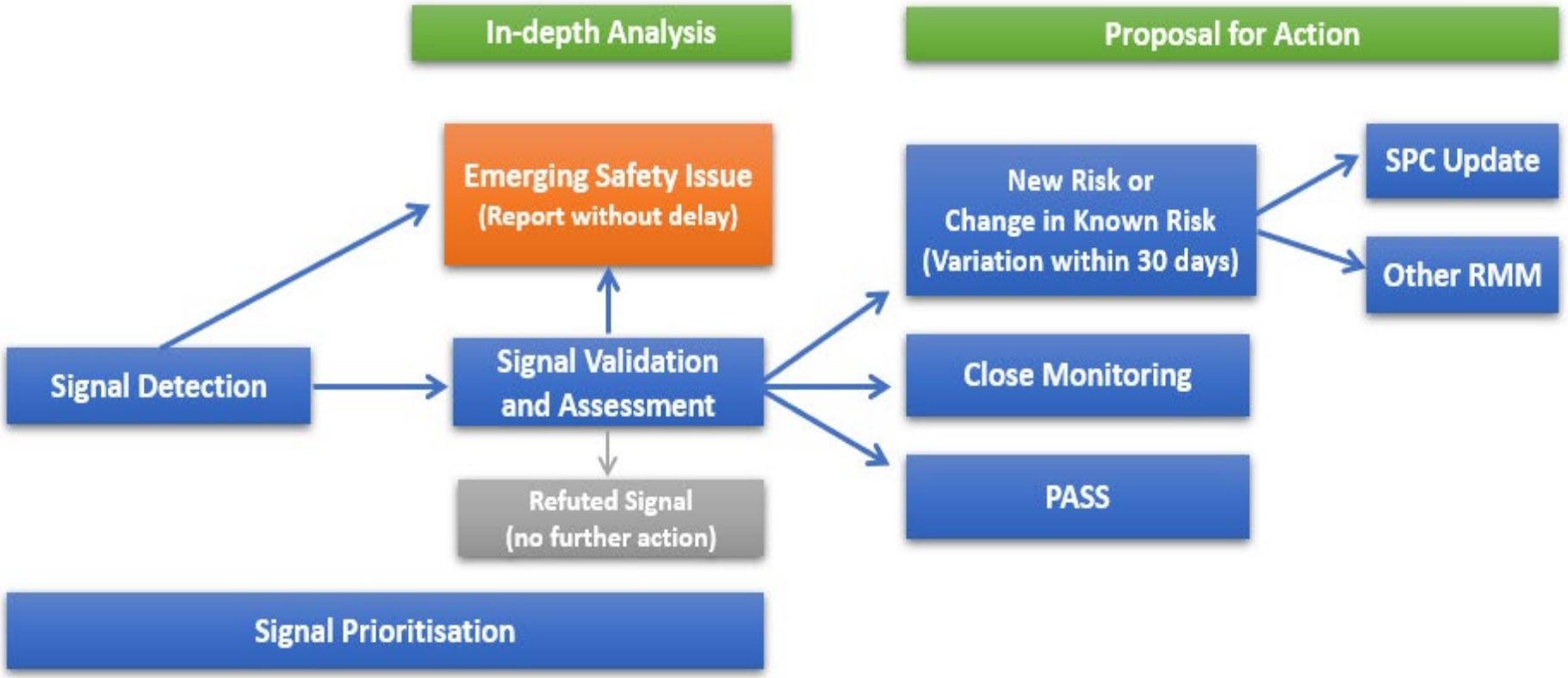
- Geographic origin
- Breed
- Age
- Other reactions reported
- Time to onset, detailed dose, and route of administration
- Off label use?
- Narrative

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.

Pharmacovigilance data analysis – Signal management



Medically Important Events (MIE) list

MIE PTs	Species association #	Excluded LLTs ¤
Abdominal pain	Horse	Abdominal cramp, Abdominal discomfort, Praying position, Stomach cramp, Tense abdomen
Abomasitis	Ruminant, Camelid	
Abortion	All	
Acute mastitis	Ruminant, Camelid, Horse	
Anaphylaxis	All	
Anorexia	Horse	
Apnoea	All	
Birth defect	All	
Blindness	All	
Bone marrow hypoplasia	All	
Cardiac arrest	All	
Cardiac insufficiency	All	
Circulatory shock	All	
Collapse NOS	All	
Coma	All	
Convulsion	All	
Deafness	All	
Death	All	Unexplained death, Unrelated death
Diabetes mellitus	All	
Dyspnoea	All	
Epileptic seizure	All	
Fish asphyxia	Fish	
Fish body deformity	Fish	
Haemolytic anaemia	All	
Haemorrhagic gastroenteritis	All	
Heart block	All	
Hepatic failure	All	
Hypersensitivity reaction	All	Allergic pruritus, Allergic reaction, Allergic skin reaction, Allergy NOS
Hypocalcaemic condition	Ruminant, Camelid	
Hypomagnesaemic condition	Ruminant, Camelid	
Impaired hearing	All	
Impaired vision	All	
Ketosis	Ruminant, Camelid	
Laminitis	Horse	
Loss of consciousness	All	
Lying down	Horse, Ruminant, Pig, Camelid	
Metastatic neoplasia	All	
Metritis	Horse, Ruminant, Camelid	
Moribund	All	
Multi-organ failure NOS	All	
Myoglobinuria (Horses only)	Horse	
Paralysis	All	
Paresis	All	
Perinatal mortality	All	
Recumbency	Horse, Ruminant, Pig, Camelid	
Renal insufficiency	All	
Reticulitis	Ruminant, Camelid	
Stillbirth	All	
Suspected infectious agent transmission	All	

How to decide on the frequency of monitoring

*Marketing authorisation holders shall perform signal management using a **risk-based approach** and monitor the data with a **frequency proportionate to the identified risk**. The risk-based approach shall take into account the following topics: **type of product**, length of **time on the market** and **stability of the pharmacovigilance profile**, **identified** and **potential risks** and the **need for additional information**. The risk-based approach shall be applied to determine the methodology, extent and frequency of the signal management process and the rationale shall be documented.*

Article 17(3), Commission Implementing Regulation 2021/1281

Overall approach to signal management by MAHs

- Signal management is a **continuous** process throughout the product life-cycle
  - MAHs are expected to continuously monitor the safety of their products
  - Continuous monitoring of the Union Pharmacovigilance Database
  - Risk-based approach
- Transition from time-based into a **data-driven** pharmacovigilance system
- **Flexibility** and sound **scientific** and **clinical judgement** should always be applied

Practical aspects of signal detection

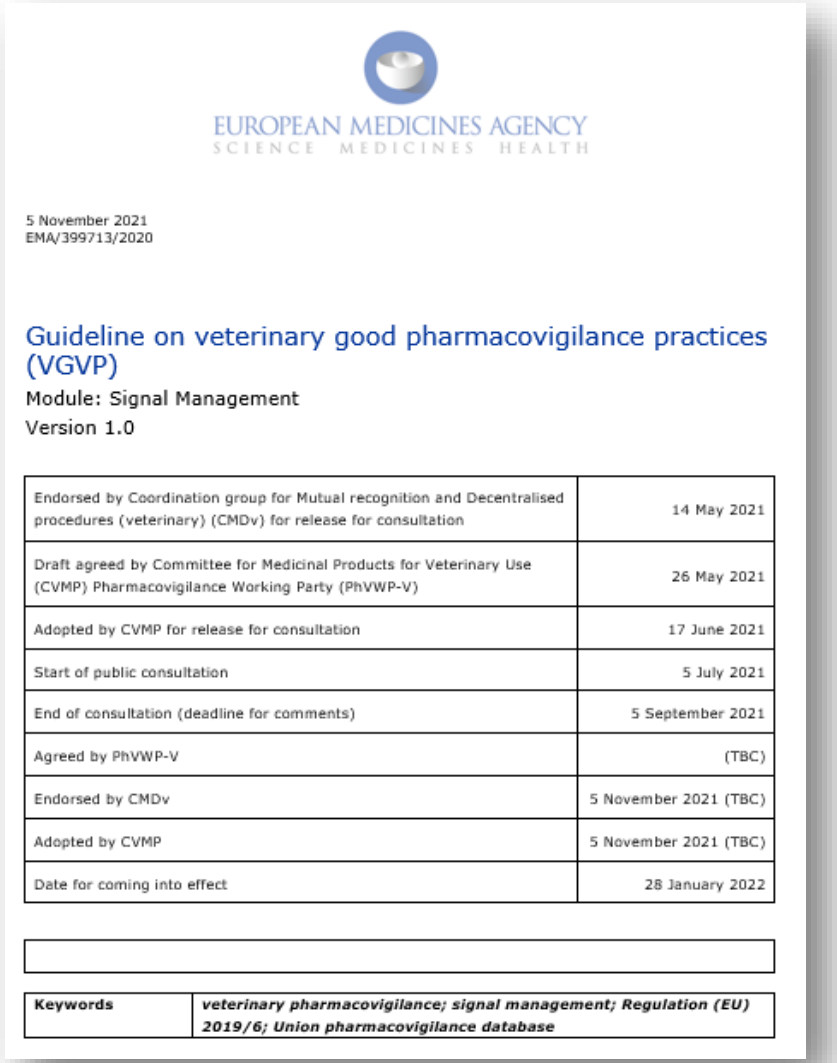
Statistical analyses in signal detection should always be complemented by qualitative review of the cases.

PhV – signal management – underlying basics

- **Clinical judgment:**
  - Injection site reaction, anaphylactic type reaction.
  - Rare events, long-term effects, confounding factors concomitant products, underlying disease, possible interaction
  - Observational data versus prospective study
- Signal Detection advantage:
  - facilitates lifecycle overview
  - Relative comparison (however skewed dataset)

Signal Management Guideline

- Veterinary good pharmacovigilance practices (VGVP) on Signal Management
- Provides general methodological principles, describes the roles, responsibilities and procedural aspects
- Date for coming into effect **28 January 2022**
- Glossary for definitions



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SCIENCE MEDICINES HEALTH

5 November 2021
EMA/399713/2020

Guideline on veterinary good pharmacovigilance practices (VGVP)

Module: Signal Management

Version 1.0

Endorsed by Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMDv) for release for consultation	14 May 2021
Draft agreed by Committee for Medicinal Products for Veterinary Use (CVMP) Pharmacovigilance Working Party (PhVWP-V)	26 May 2021
Adopted by CVMP for release for consultation	17 June 2021
Start of public consultation	5 July 2021
End of consultation (deadline for comments)	5 September 2021
Agreed by PhVWP-V	(TBC)
Endorsed by CMDv	5 November 2021 (TBC)
Adopted by CVMP	5 November 2021 (TBC)
Date for coming into effect	28 January 2022

Keywords	***veterinary pharmacovigilance; signal management; Regulation (EU) 2019/6; Union pharmacovigilance database***

Annual submission statements

Commission Implementing Regulation (EU) 2021/1281

Article 19 (1) ***Conclusion on the benefit-risk balance***

Marketing authorisation holders shall annually record a conclusion on the benefit-risk balance for each of their products in the Union pharmacovigilance database and confirm that the signal management process has been conducted

	Benefit-risk balance
X	I confirm that the benefit-risk balance remains unchanged

	Adherence to GVPV guidelines
X	I confirm that the signal management process has been conducted in compliance with the pharmacovigilance guidelines published by the Agency (VGVP) and all assessed signals have been submitted

Overview of comments and changes

Still to be clarified

Due dates for annual submission (ATC vet based + existing workshare)

Regulatory procedures

Incidence / sales data – to be further developed and agreed (legal deadline 2023)

To be clarified during training sessions

Guidance on the possibilities for grouping

How to use the MI terms for prioritisation

Queries available for MAHs and how to perform analyses, perform signal management and take advantage of the full dataset

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Pharmacovigilance system and PSMF

Presented by Laura Descalzo on 30 March 2021

An agency of the European Union

COMMISSION IMPLEMENTING REGULATION (EU) 2021/1281

- CHAPTER 1 GENERAL PROVISIONS AND PHARMACOVIGILANCE SYSTEM

Article 2 Pharmacovigilance system & Article 3 Qualified person responsible for pharmacovigilance)

- CHAPTER 2 QUALITY MANAGEMENT SYSTEM (Articles 4-9)
- CHAPTER 4 THE PHARMACOVIGILANCE SYSTEM MASTER FILE (Articles 21 – 25)
- CHAPTER 5 CONTROLS AND INSPECTIONS BY COMPETENT AUTHORITIES (Articles 26- 27)

Complemented by VGVP Modules on Controls and Pharmacovigilance inspections & on Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files

Main changes and simplifications

Past - present

- DDPS describing the PhV system
- DDPS filed in every MAA (variations)
- DDPS assessed and verified at inspection

EU Member State where PSMF is located to lead the inspection (Supervisory Authority)

Delegation & Worksharing

PhV inspection outcome, captured in the database, valid for all EU

Avoid duplication, adjust scope and frequency of inspections (risk-based approach)

Future

- PSMF describing the PhV system, tool for QPPV oversight, audit/inspections
- PSMF kept by MAH not in MA dossier
- PSMF summary in MA dossier

Summary of the pharmacovigilance system master file

The summary of the pharmacovigilance system master file shall contain the following information:

(a) the pharmacovigilance system master file reference number;

(b) the pharmacovigilance system master file location;

(c) name, contact details and place of operation of the qualified person responsible for pharmacovigilance;

(d) the signed statement referred to in Article 22(2)(b), point (i);

(e) the type of record management system used for adverse events reports including the name of the database, if applicable

Pharmacovigilance system master file (PSMF) (1)

- The PSMF is not just a requirement laid down in the legislation, should be **a useful tool for the MAH and QPPV to facilitate oversight**, contribute to the management of and improvement(s) to the pharmacovigilance system.
- The PSMF will be **kept by the MAH/QPPV *(not part of the MA dossier),*** a copy should be available to competent authorities upon request.
- PSMF does not need to be printed as hard copy in the physical location. It can be kept electronically and be accessible in an electronic format (printable and searchable).
- PDF and other document formats, such as Excel files for certain annexes acceptable. For the main body of the PSMF, formats to allow version control.
- Content of the annexes to the pharmacovigilance system master file (PSMF): the use of other systems, where the required information is kept, as an alternative for annex /list generation will be considered, as long as these alternative systems fulfil the same objectives. MAH may update the PSMF on a periodic basis, to reduce burden provided that significant changes, important for PV oversight are tracked on an *ad hoc* basis .

Training - Good Vigilance Practice (until Jan 2022)

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Topic	Elements	Target	Format	Timeline
Adverse event collection and recording	Regulatory framework and topics to highlight Demo session on EVV (Log-in, AE recording, AE search and download, Duplicate management)	NCAs + MAHs	Webinar (recorded and published)	10/11/2021
Signal detection and analysis	SD process. ROR Querying the Dbase	NCAs + MAHs	Webinar (recorded and published)	23-24/11/2021
PhV systems and their PhV system master files and quality management systems + PhV Inspections - Introduction and principles	PSMF elements Inspections process	NCAs + MAHs	Webinar (recorded and published)	8/12/2021
Signal management process		NCAs	Webinar (recorded and published)	09/12/2021
Adverse event collection and recording	Regulatory framework and topics to highlight Demo session on EVV (Log-in, AE recording, AE search and download, Duplicate management)	NCAs + MAHs	Webinar (recorded and published)	13/01/2022 (tbc)
Signal detection, evaluation and yearly reporting (1)	SD process. ROR Querying the Dbase	NCAs + MAHs	Webinar (recorded and published)	18-19/01/2022 (tbc)