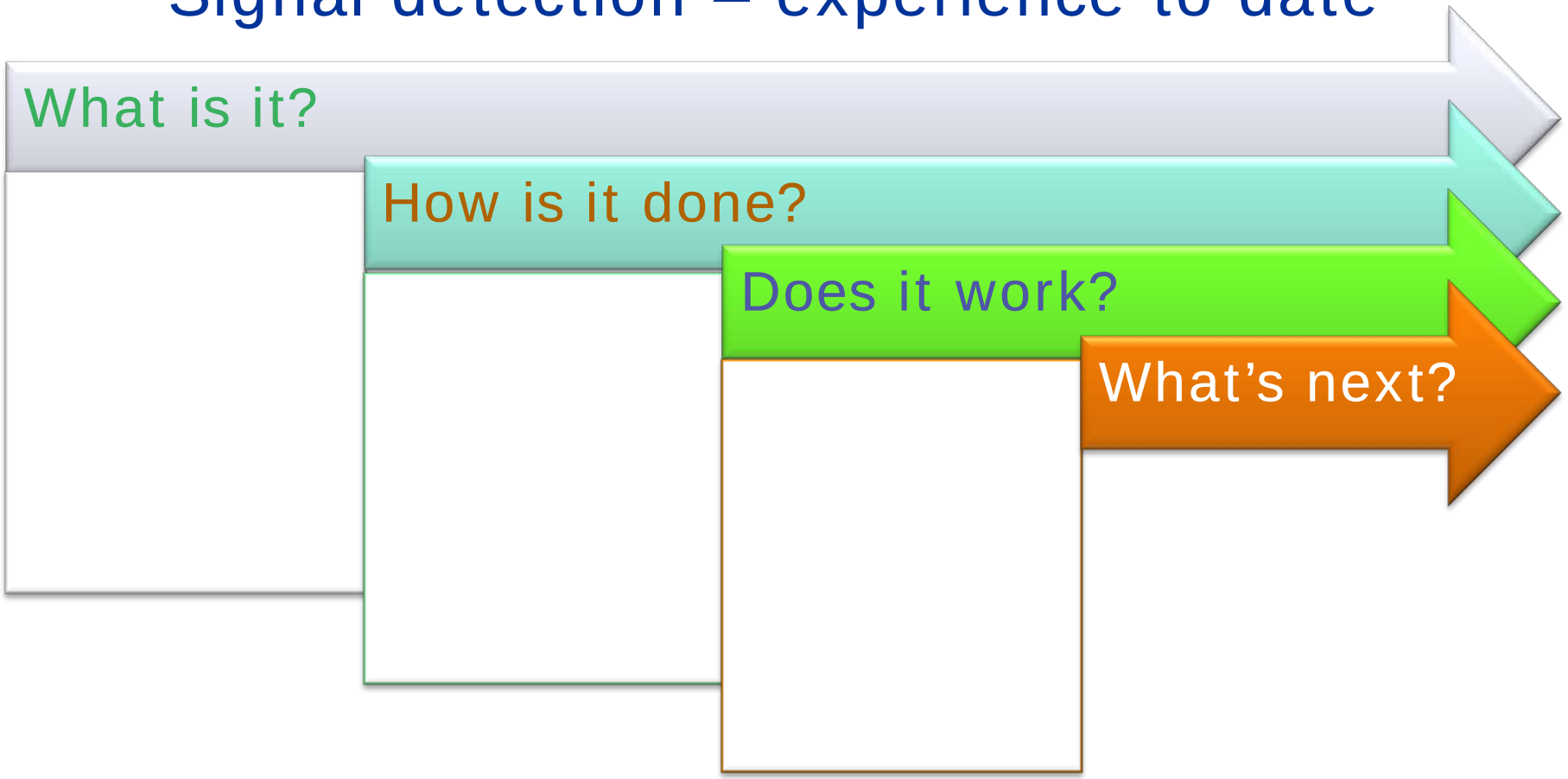
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Signal detection – experience to date

EMA / IFAH-Europe Info Day

Presented by Jos Olaerts on 13 March 2015

Signal detection – experience to date



Definition of signal detection

Council for International Organisations of Medical Sciences Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010):

SIGNAL *= information that* ***arises from one or multiple sources*** *(including observations and experiments), which suggests a* ***new potentially causal association****, or a* ***new aspect of a known association****, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify* ***verificatory*** *action.*

Volume 9B of The Rules Governing medicinal Products in the European Union

*One of the aims of pharmacovigilance is the detection of **new** safety signals in relation to the use of VMPs. A signal should be considered as information reported on a **possible causal** relationship between an adverse event and a VMP, the relationship being unknown or previously incompletely documented.*

The regular review and analysis of adverse events in a pre-defined time period for one specific VMP in one particular species might lead to the identification of potential signals when, for example:

- *an increase in the **number** of adverse events in a short period is observed,*
- *an increase in the **frequency** of a particular clinical sign is recorded, compared with the expected frequency for that sign,*
- ***new** unidentified clinical signs are highlighted,*
- *a potential impact on **public or animal health** is suspected.*

Signal detection

Causal relationship

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12 December 2013
EMA/CVMP/PhVWP/901279/2011
Committee for Medicinal Products for Veterinary Use

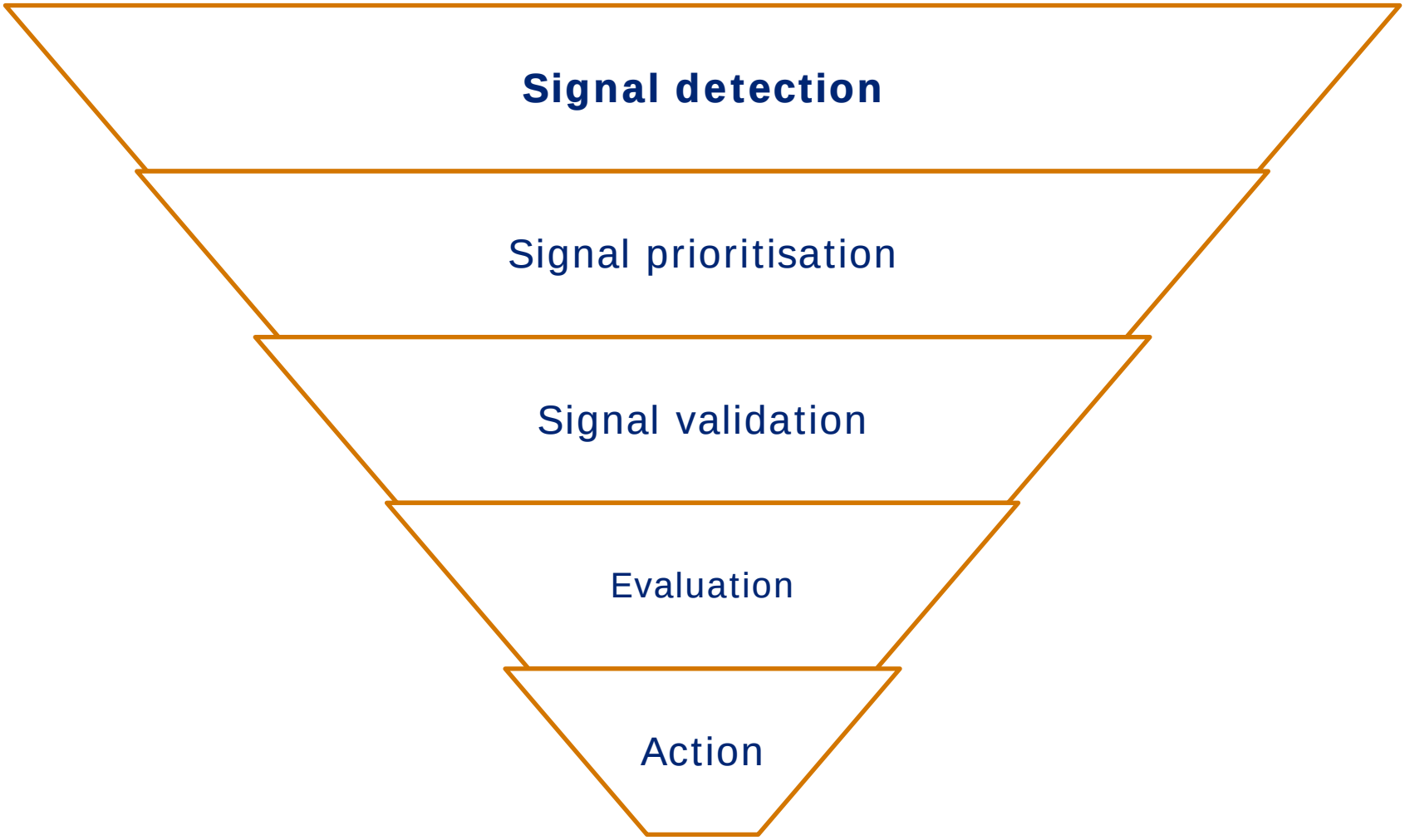
Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products

Draft

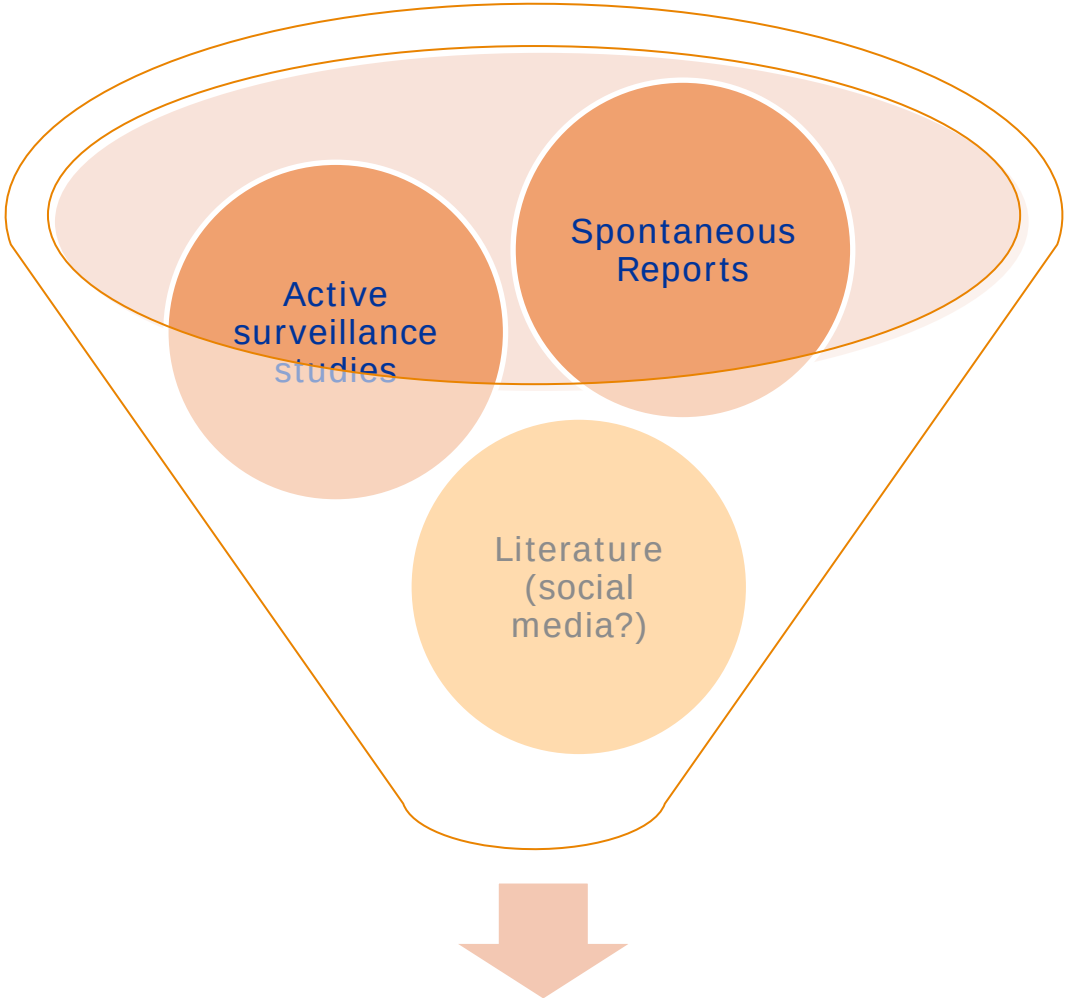
Adopted by CVMP	13 June 2013
Draft agreed by Pharmacovigilance Working Party	24-25 September 2013
Adopted by HMA-V	29 November 2013
Endorsed by CVMP for release for consultation	12 December 2013
Start of public consultation	16 December 2013
End of consultation (deadline for comments)	30 June 2014

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Signal management process



Signal detection (1 of 6)



Signal detection (2 of 6)

Main goal: highlight « higher than expected »
frequencies of drug-event association without exposure data

Several complementary approaches:

- **Observational**: daily experience of each operator
- **Trend analysis**: comparison of reported data over given time periods
- Calculation of **statistical indicator(s)**

Signal detection (3 of 6)

Principle of a statistical test

=> **H_0: drug / event combination occurs with no significantly greater frequency** for drug X than for any other product

Signal of Disproportionate Reporting (SDR)

for drug/event pairs

Signal detection (4 of 6)

Examples of available tools, used on the human side:

- **Multi-item Gamma Poisson Shrinker (MGPS):** Bayesian approach used by the FDA
- **Bayesian Confidence Propagation Neural Network (BCPNN):** Bayesian approach using a particular disproportionality measure (IC), used by the WHO-UMC
- **Proportional Reporting Ratio (PRR):** homogeneous with a Relative Risk (RR), used by the UK-MCA and by the EMA for HMPs and VMPs
- **Reporting Odds-Ratio (ROR)**
- **Chi-square (χ^2)**

Signal detection (5 of 6)

- PRR is **very sensitive** (low number of reports)
  => *high number of **false-positive***

- Further criteria (*time on market dependent?*)
  - **Individual cases ≥ 3** *(interpretability)*
  - **PRR ≥ 2** *(indicator of disproportionality)*
  - **PRR (-) ≥ 1** *(significant disproportionality)*

Signal detection (6 of 6)

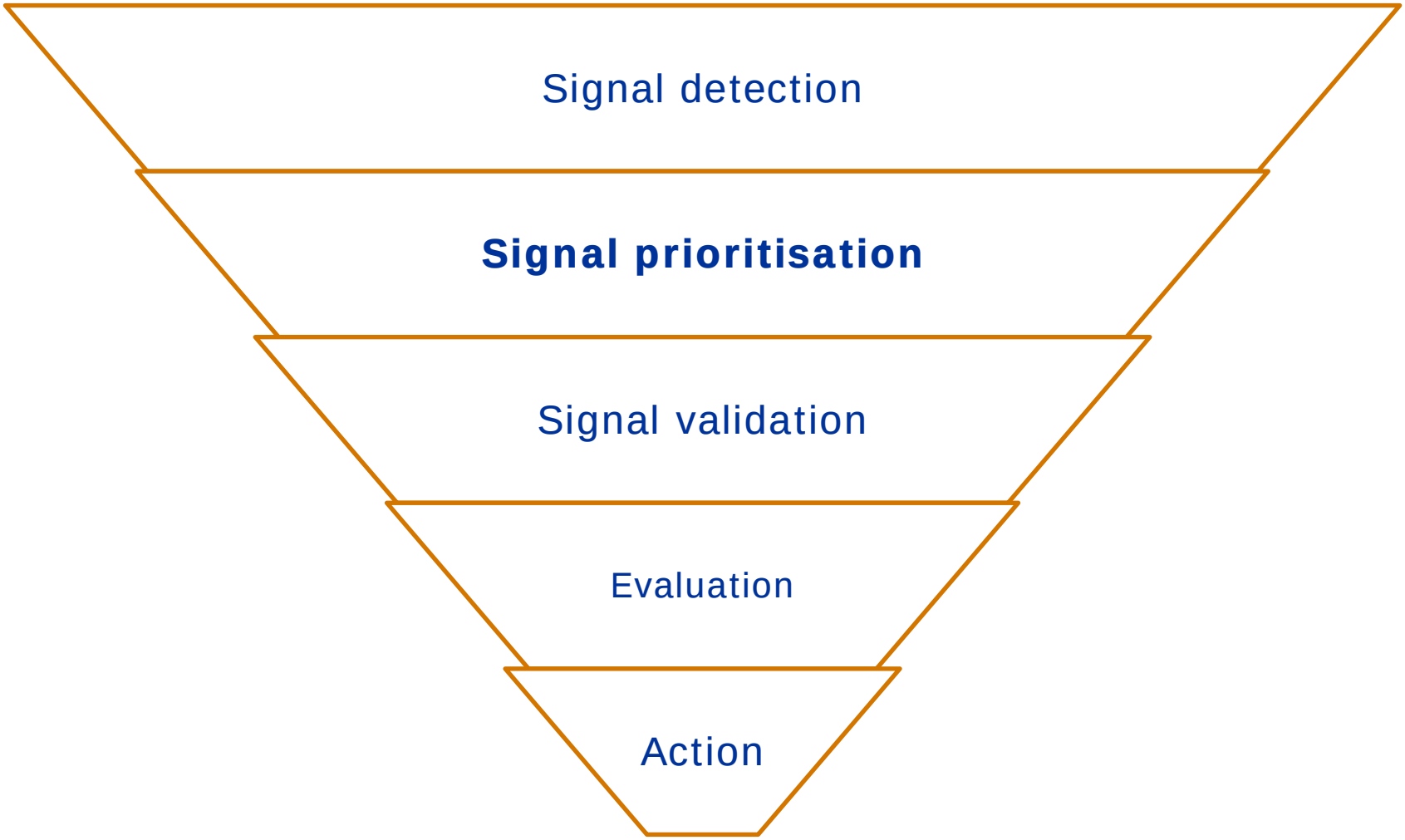
Comparison of 5 disproportionality methods.

4 companies, one Agency and 2 International spontaneous report databases. (500 k – 5 million reports)

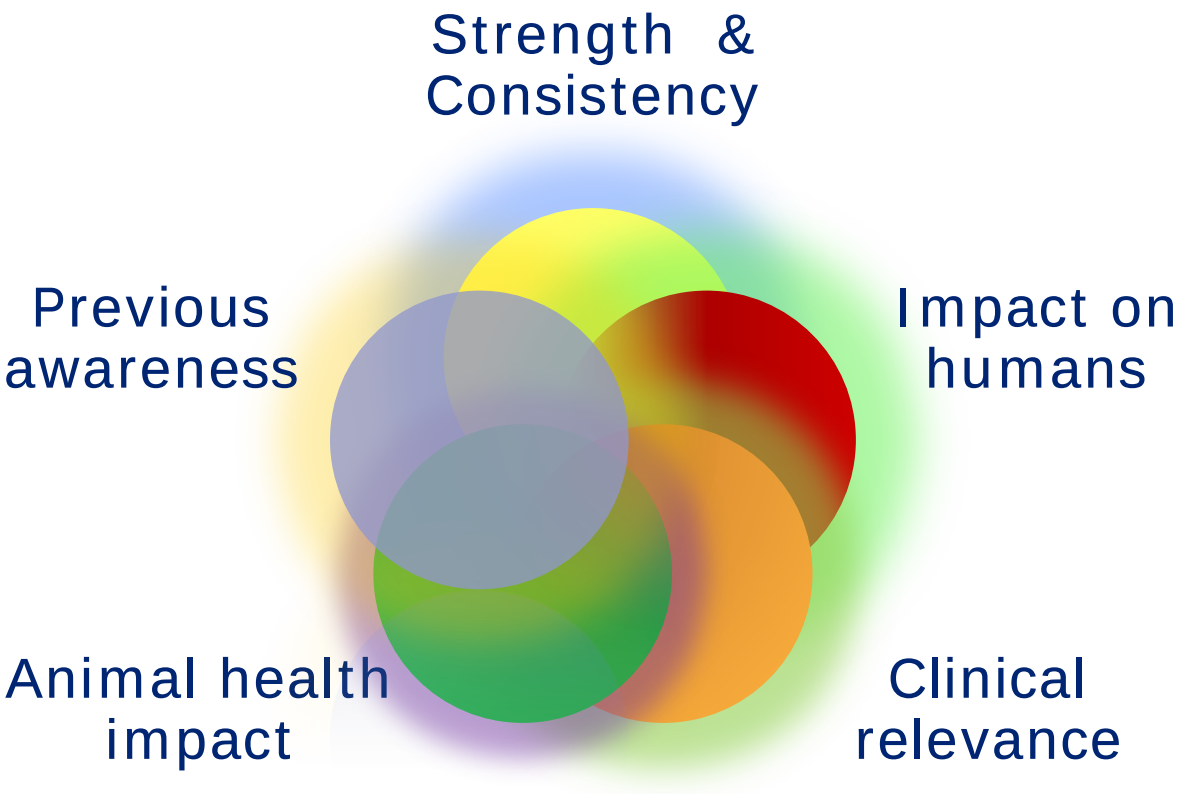
"Choice of a disproportionality statistic for signal detection should be primarily based on ease of implementation, interpretation and optimization of resources."

Product life-time ⇧ ➢ Precision of method ⇩

Signal management process



Signal prioritisation



Signal validation

Review individual cases

Define population

Signal evaluation

…This requires a thorough pharmacological and clinical assessment…

IN PRACTICE FOR CAPs

- All CAPs on “Signal detection schedule” of either 3, 6 months or 1 year as agreed by CVMP
- Performed by Rapporteur and/or its experts
- Using the EMA Data Warehouse
- Recording the analysis outcomes on a separate database
- Discussion by PhVWP-V
- Discussion by CVMP

NUMBER OF CASES AND REACTION OVERVIEW INCLUDING NUMBER OF FATALITIES | Last Modified 29/09/2014 15:57:32 | Owner BI Administrator Role
This query allows the monitoring of new cases received in a specified period of time. It particularly focuses in new fatal cases.
Expand | Open | More

OVERVIEW OF HUMAN / ANIMAL AERs PER PRODUCT/ACTIVE SUBSTANCE/ATCVET CODE | Last Modified 29/09/2014 15:57:32 | Owner BI Administrator Role
This report provides Count of Human /Animal /Serious /Non-serious for a particular product.
Expand | Open | More

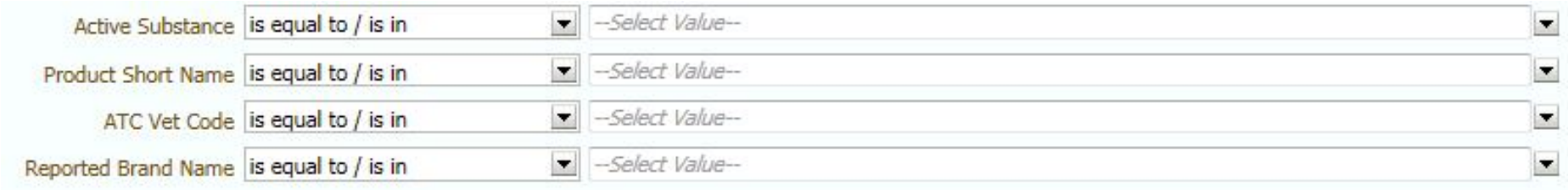
PRR CALCULATION USING NUMBER OF ANIMALS FOR A PARTICULAR VEDDRA TERM | Last Modified 29/09/2014 15:57:32 | Owner BI Administrator Role
This query constructs a PRR table using the number of animals for a particular product or active substance and selecting a particular Veddra term.
Expand | Open | More

REACTION MONITORING - COMPARISON BETWEEN 2 TIME PERIODS | Last Modified 29/09/2014 15:57:32 | Owner BI Administrator Role
This query allows the user to compare the cases received for a particular Product/ substance/ ATC code in two different periods of time stated by the users.
Expand | Open | More

SIGNAL DETECTION QUERY (WITH 2 PRR CALCULATIONS, UNTIL DATE 2 AND UNTIL DATE 1) | Last Modified 29/09/2014 15:57:33 | Owner BI Administrator Role
This query allows to identify new emerging potential signals on the basis of comparing the PRR calculated up to e.g. the previous surveillance assessment to the PRR calculated at present.
Expand | Open | More

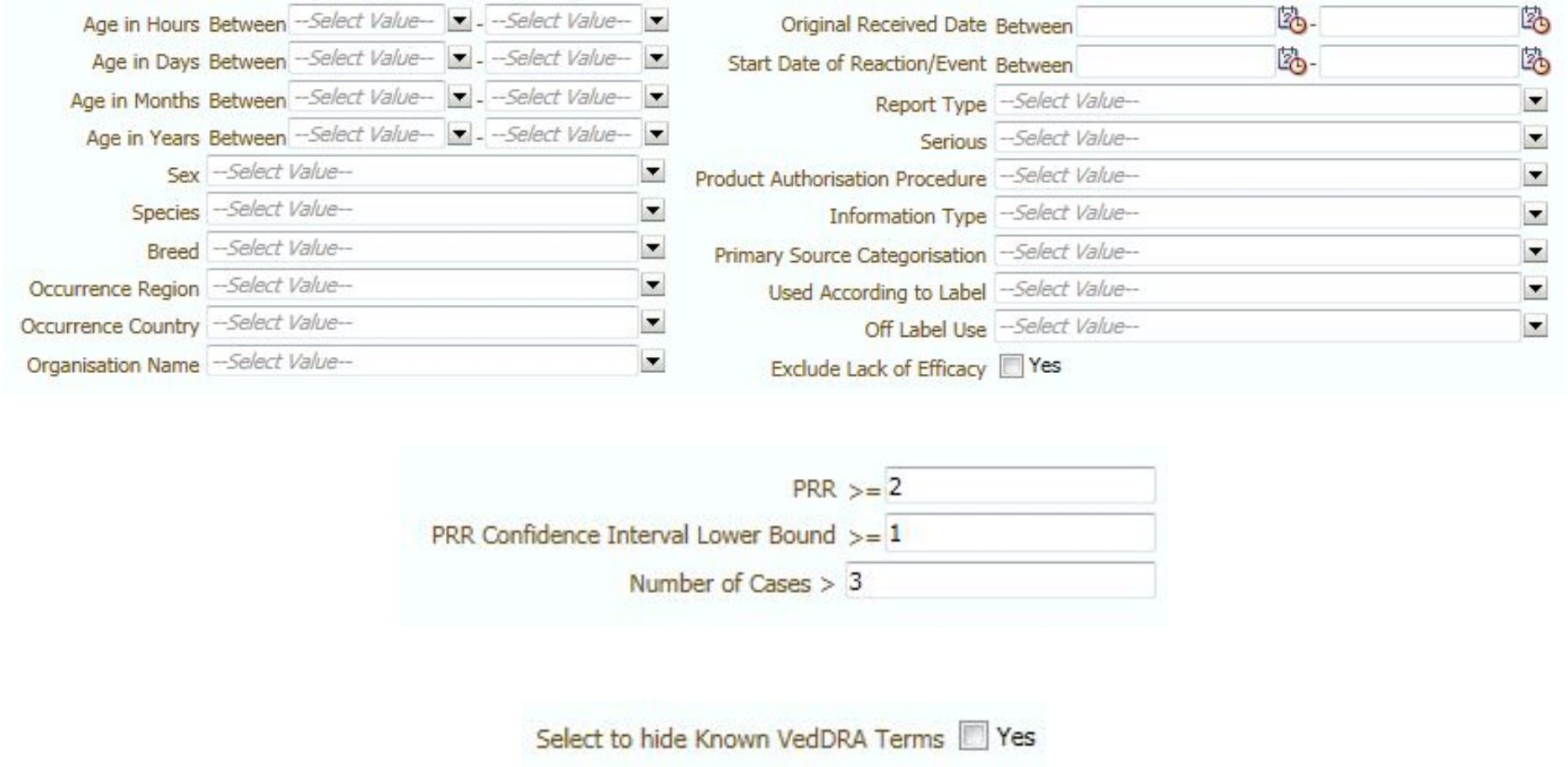
SIGNAL DETECTION QUERY (WITH PRR CALCULATION UNTIL DATE 2) | Last Modified 29/09/2014 15:57:33 | Owner BI Administrator Role
This query allows the user to compare the cases received for a particular Product/ substance/ ATC code in two different periods of time stated by the users alongwith PRR (until Date 2).
Expand | Open | More

SIGNAL DETECTION QUERY (WITHOUT PRR) | Last Modified 29/09/2014 15:57:33 | Owner BI Administrator Role
This query provides the number of events and animals reported up to the specified period and during the specified period for a particular product.
Expand | Open | More


Active Substance
is equal to / is in
--Select Value--
Product Short Name
is equal to / is in
--Select Value--
ATC Vet Code
is equal to / is in
--Select Value--
Reported Brand Name
is equal to / is in
--Select Value--


Enter Date 1
Enter Date 2


Animal
Human


Age in Hours Between --Select Value-- - --Select Value--
Age in Days Between --Select Value-- - --Select Value--
Age in Months Between --Select Value-- - --Select Value--
Age in Years Between --Select Value-- - --Select Value--
Sex --Select Value--
Species --Select Value--
Breed --Select Value--
Occurrence Region --Select Value--
Occurrence Country --Select Value--
Organisation Name --Select Value--
Original Received Date Between -
Start Date of Reaction/Event Between -
Report Type --Select Value--
Serious --Select Value--
Product Authorisation Procedure --Select Value--
Information Type --Select Value--
Primary Source Categorisation --Select Value--
Used According to Label --Select Value--
Off Label Use --Select Value--
Exclude Lack of Efficacy Yes
PRR >= 2
PRR Confidence Interval Lower Bound >= 1
Number of Cases > 3
Select to hide Known VedDRA Terms Yes

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

Product Hierarchy Level
Active Substance OK

Date 1: 03/03/2014
Date 2: 02/03/2015

Click to go to line listing

Species Canine/dog

Number of Rows **507**

Veddra Term PT	# Cases between Date 1 and Date 2	# Reacted between Date 1 and Date 2	PRR(-) until Date 2	PRR until Date 2	PRR (+) until Date 2	# Cases until Date 1	# Reacted until Date 1	PRR(-) until Date 1	PRR until Date 1	PRR (+) until Date 1	Total Cases
Emesis	264	264	1.68	1.75	1.82	1,469	1,481	1.68	1.76	1.84	1731
Lethargy	176	178	1.08	1.13	1.20	980	1,010	1.09	1.16	1.22	1156
Anorexia	175	175	1.84	1.94	2.04	1,017	1,029	1.92	2.04	2.16	1192
Diarrhoea	136	140	1.72	1.84	1.98	638	645	1.68	1.82	1.97	774
Death	131	147	0.87	0.92	0.97	973	1,010	0.84	0.89	0.95	1103
Renal insufficiency	102	102	1.57	1.80	2.06	125	129	1.21	1.46	1.75	227
Haemorrhagic diarrhoea	88	91	2.77	3.04	3.34	402	404	2.54	2.82	3.13	488
Abnormal test result	66	67	1.25	1.36	1.49	439	440	1.50	1.64	1.81	505
Hepatopathy	62	62	1.53	1.69	1.87	344	344	1.64	1.83	2.04	406
Anaemia NOS	43	43	1.80	2.05	2.34	203	204	1.89	2.19	2.54	246
Changes in blood phosphorous	39	39	2.14	2.68	3.35	52	52	1.66	2.22	2.99	91
Urine abnormalities	38	38	1.64	1.90	2.21	150	150	1.74	2.06	2.45	188
Ataxia	35	35	0.51	0.57	0.64	261	265	0.53	0.60	0.68	296
Hyperthermia	35	35	0.44	0.53	0.64	75	82	0.38	0.48	0.60	110
Haematemesis	33	33	3.52	4.05	4.67	207	207	3.40	3.96	4.63	240
Convulsion	31	31	0.41	0.47	0.53	204	204	0.43	0.49	0.57	235
Polydipsia	31	31	1.30	1.51	1.75	158	157	1.33	1.56	1.84	189

PRR until date 2 PRR until date 1

TABLE OF CONTENTS

SAFETY REPORT:	[x] Adverse Drug Reaction Report in Animals
	[ ] Adverse Drug Reaction Report in Humans

SAFETY REPORT DATA

Human Veddra version: 9 — Veddra version: 9
Report ID: FR-ANMV-13 CPVL 01205
Report Version: 1 — Report type: Spontaneous
Information type: Safety issue
Case type: CA — Case number: FR-ANMV-13 CPVL 01205
Original Receive date: 25/06/2013 — Most recent information date: 25/06/2013
Primary source country: France — Occur country: France

SENDER

First name: [redacted] — Middle name:
Last name: [redacted]
Street address: [redacted]
City: [redacted]
State: France
Post code: [redacted]
Country code: France
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]
Organization: [redacted]
Department: Pharmacovigilance Department
Categorization: Pharmacist

PRIMARY SOURCE

First name: E — Middle name:
Last name: [redacted]
State: — Post code: 13
Country: France — Phone number:
Categorization: Veterinarian

ANIMAL TREATED SPECIES

Species (Code): CanDo
Species: Canine/dog

BREED

Bulldog

ANIMAL DATA

Age type: Exact — Min age: Year
Age: 9 Year
Max age: Year

Weight type: Exact — Minimum weight:
Weight: 22.7 Kg
Max weight:

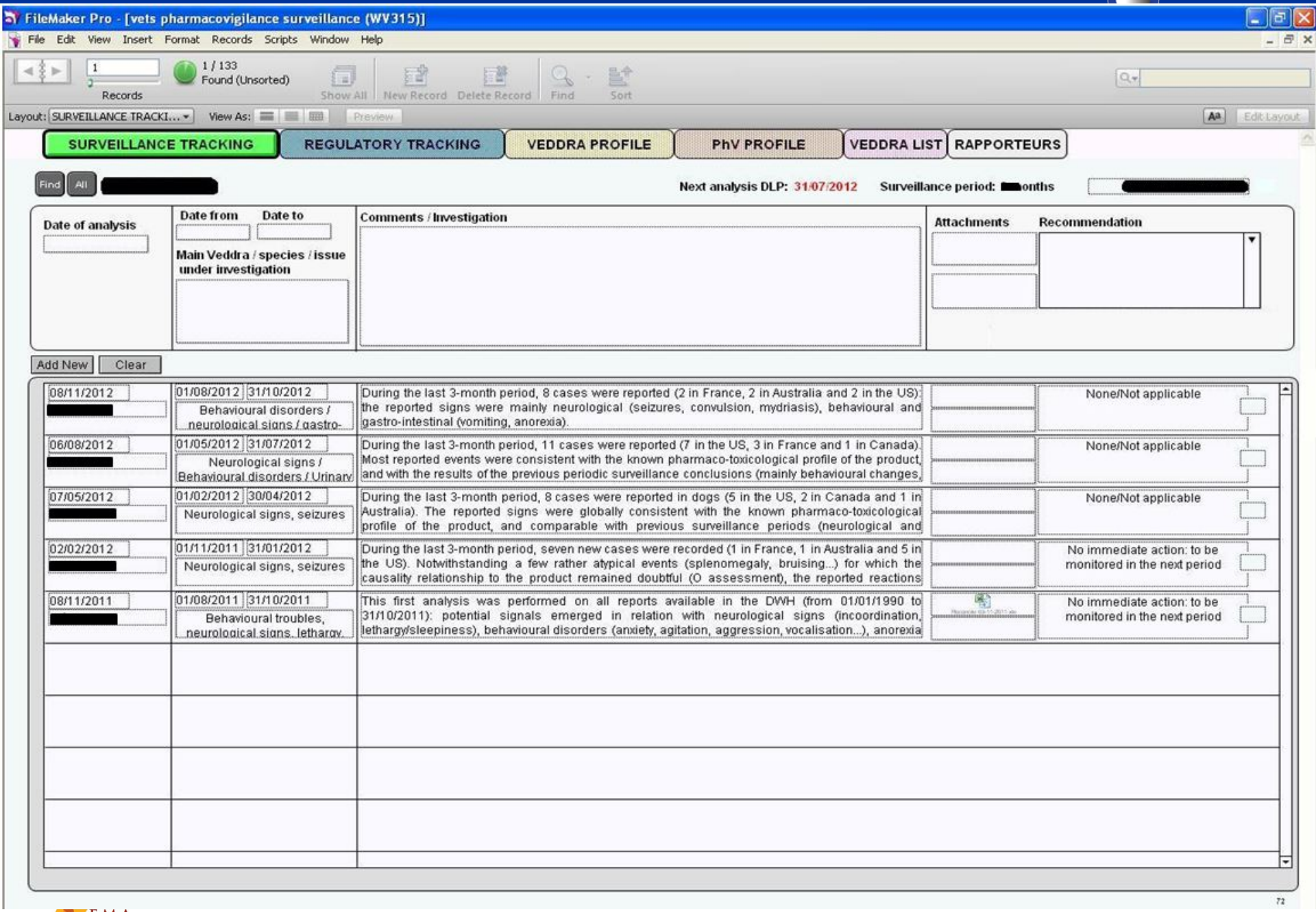
Sex: Male — Animal role:
Exposed number: 1 — Affected number: 1
Production status:
Physiological status:

ANIMAL ADVERSE REACTION

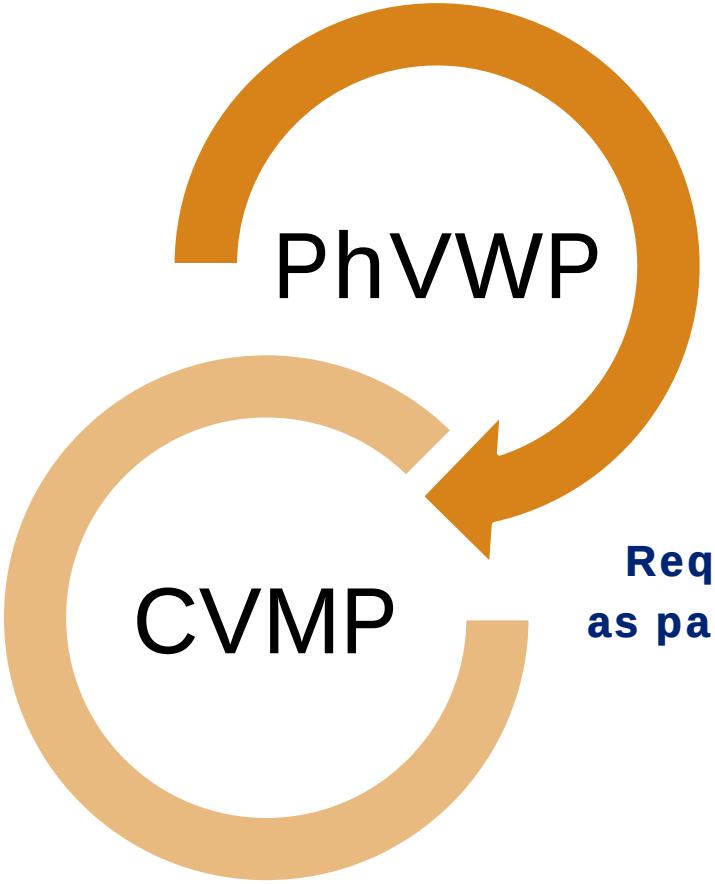
Reaction start date: 18/06/2013
Time to onset of reaction: <= 1 hour
Serious ?: Yes
Results in death ?: No
Outcome died: 0

NARRATIVE INCLUDE CLINICAL

Bulldog with history of cardiopathy, treated with [redacted] (for approximately one month) and [redacted] (for more than one year). It developed epileptic-like seizures (linked to underlying cardiopathy). Prescribed with [redacted] Within one hour after first administration, the dog displayed marked breathing difficulty, panting, drunken gait, abnormal walking behaviour (ambulation) and polydipsia. Spontaneously resolving over a few hours [redacted] stopped. Other drugs continued, without incident. Treatment of SAR[redacted]opped.


FileMaker Pro - [vets pharmacovigilance surveillance (WV315)]
File Edit View Insert Format Records Scripts Window Help
Records
1 / 133
Found (Unsorted)
Show All
New Record
Delete Record
Find
Sort
Layout: SURVEILLANCE TRACKI...
View As:
Preview
Edit Layout
SURVEILLANCE TRACKING
REGULATORY TRACKING
VEDDRA PROFILE
PhV PROFILE
VEDDRA LIST
RAPPORTEURS
Find
All
[redacted]
Next analysis DLP: 31/07/2012
Surveillance period: [redacted]months
[redacted]
Date of analysis
Date from
Date to
Main Veddra / species / issue under investigation
Comments / Investigation
Attachments
Recommendation
Add New
Clear
08/11/2012
[redacted]
01/08/2012
31/10/2012
Behavioural disorders / neurological signs / gastro-
During the last 3-month period, 8 cases were reported (2 in France, 2 in Australia and 2 in the US): the reported signs were mainly neurological (seizures, convulsion, mydriasis), behavioural and gastro-intestinal (vomiting, anorexia).
None/Not applicable
06/08/2012
[redacted]
01/05/2012
31/07/2012
Neurological signs / Behavioural disorders / Urinary
During the last 3-month period, 11 cases were reported (7 in the US, 3 in France and 1 in Canada). Most reported events were consistent with the known pharmaco-toxicological profile of the product, and with the results of the previous periodic surveillance conclusions (mainly behavioural changes,
None/Not applicable
07/05/2012
[redacted]
01/02/2012
30/04/2012
Neurological signs, seizures
During the last 3-month period, 8 cases were reported in dogs (5 in the US, 2 in Canada and 1 in Australia). The reported signs were globally consistent with the known pharmaco-toxicological profile of the product, and comparable with previous surveillance periods (neurological and
None/Not applicable
02/02/2012
[redacted]
01/11/2011
31/01/2012
Neurological signs, seizures
During the last 3-month period, seven new cases were recorded (1 in France, 1 in Australia and 5 in the US). Notwithstanding a few rather atypical events (splenomegaly, bruising...) for which the causality relationship to the product remained doubtful (O assessment), the reported reactions
No immediate action: to be monitored in the next period
08/11/2011
[redacted]
01/08/2011
31/10/2011
Behavioural troubles, neurological signs, lethargy,
This first analysis was performed on all reports available in the DWH (from 01/01/1990 to 31/10/2011): potential signals emerged in relation with neurological signs (incoordination, lethargy/sleepiness), behavioural disorders (anxiety, agitation, aggression, vocalisation...), anorexia
No immediate action: to be monitored in the next period
72

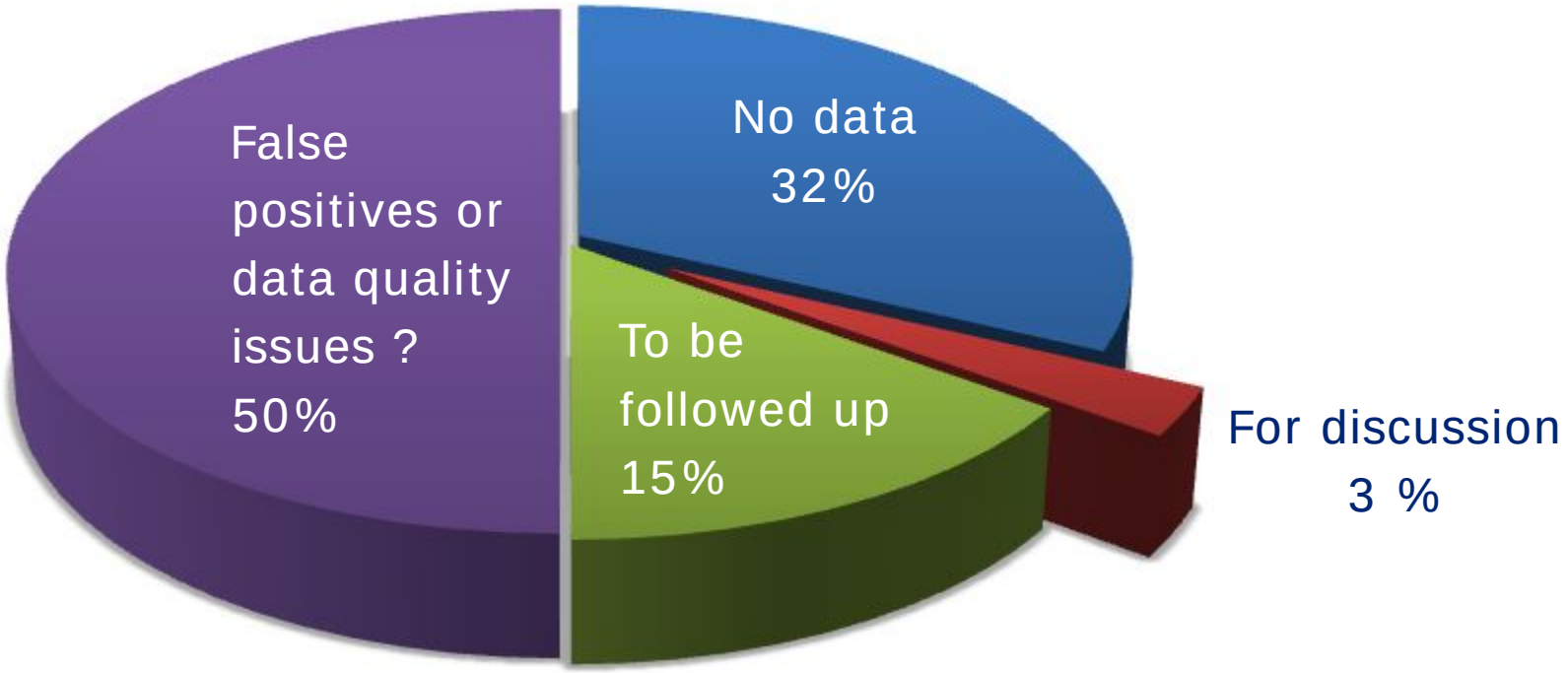
Process

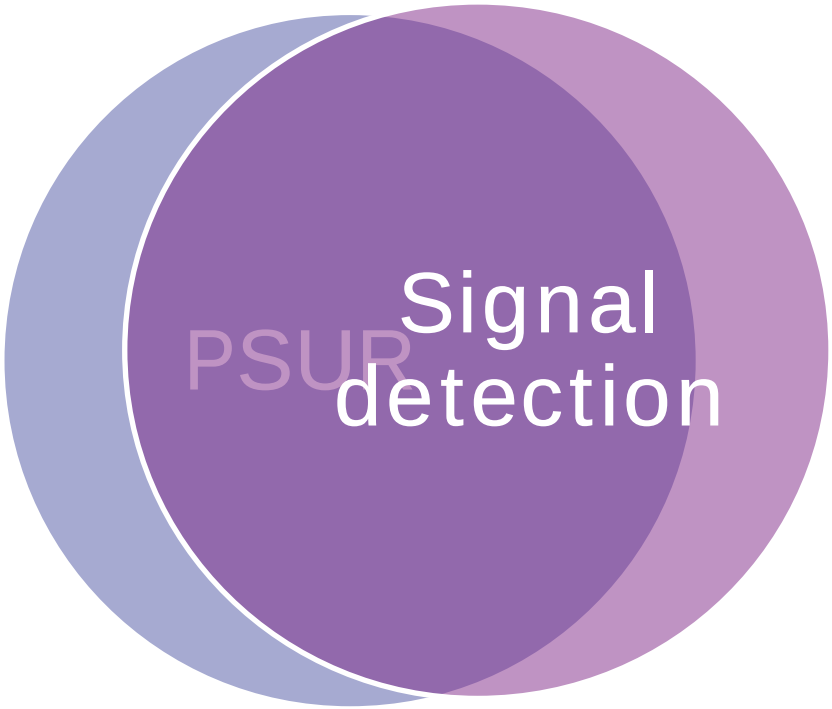


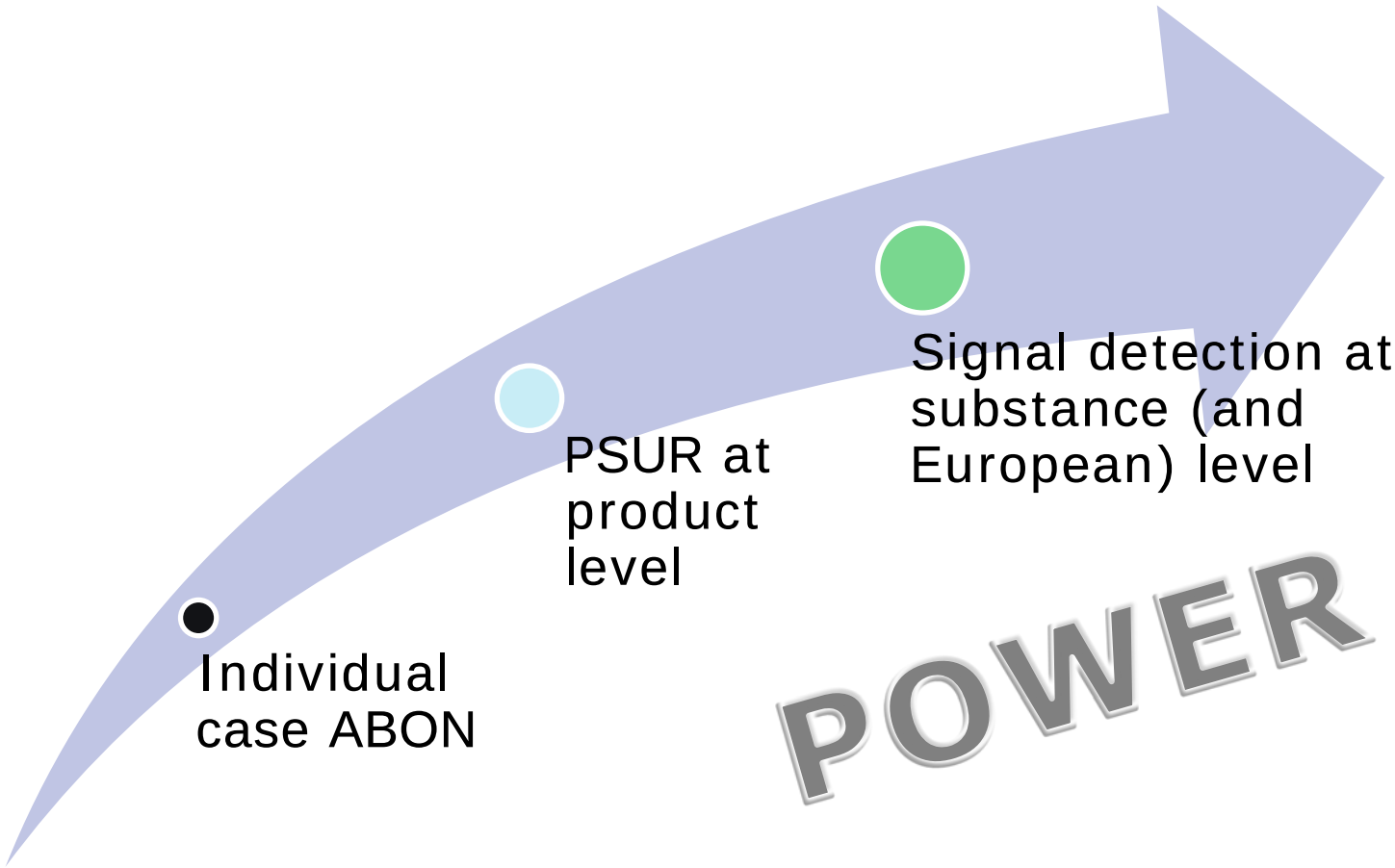
Request to MAH for specific monitoring as part of the next PSUR or targeted PSUR.

OUTPUT

1380 Analyses September 2011 – January 2015

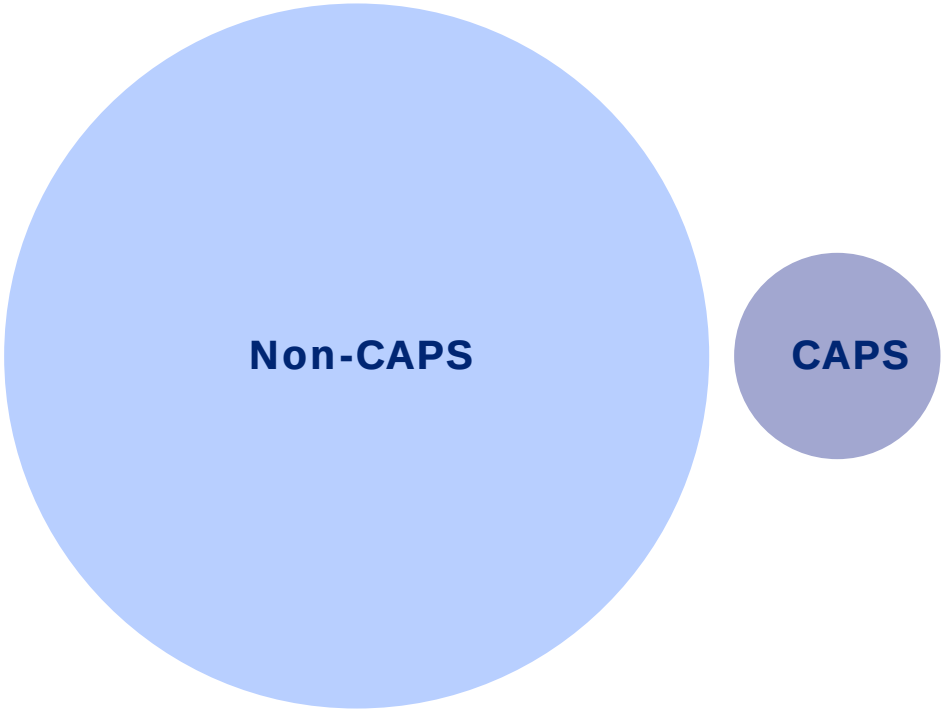



PSUR
Signal detection


Signal detection at substance (and European) level
PSUR at product level
Individual case ABON
POWER

Potential of signal detection/signal management

- Assessing data over a product's life time
- Assessing data at substance level
- Assessing potential "hidden" interactions
- Facilitates comparison between similar compounds
- Allows ad-hoc and continuous assessment


Non-CAPS
CAPS

Next

- How to implement a risk-based approach at EU level as well as product level?
- Are the current procedural tools, including signal detection adequate to monitor e.g. the use of VMPs for food producing animals?
- How can we improve data quality?
- How to lower the rate of false positives?

Next

- How to value sub-group analysis and stratification?
- How to improve query tools, by e.g. ontology?
- How to look for hidden drug-drug interactions?
- Technical and operational hurdles – populating the EU Veterinary Medicinal Product Database.