Introduction to Pharmacovigilance in Veterinary Medicine

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Introduction:

- Definition of Pharmacovigilance
- History of Pharmacovigilance
- Why do we need Pharmacovigilance
- Sources of Pharmacovigilance Information
- Definition of Adverse Event
- Assessment of Pharmacovigilance Information
- Summary of Pharmacovigilance Reports

What is Pharmacovigilance?

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Also applies to medicinal products for veterinary use (VMPs).

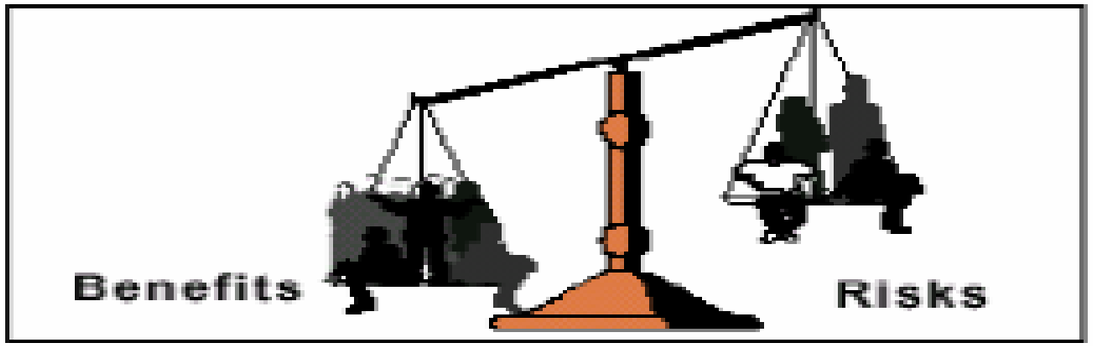
The detection and investigation of the effects of the use of these products, mainly aimed at safety and efficacy in animals and safety in people exposed to the products.

VICH* GL 24, October 2007

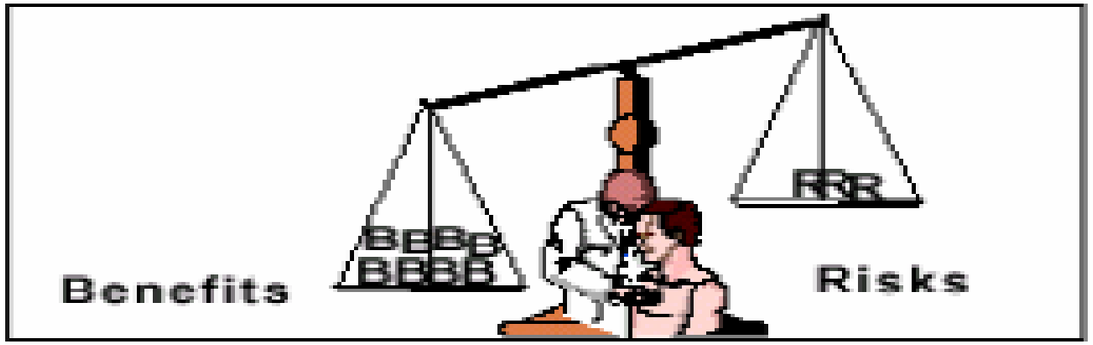
The Cycle of Pharmacovigilance:

Benefit/Risk – Marketed Products:

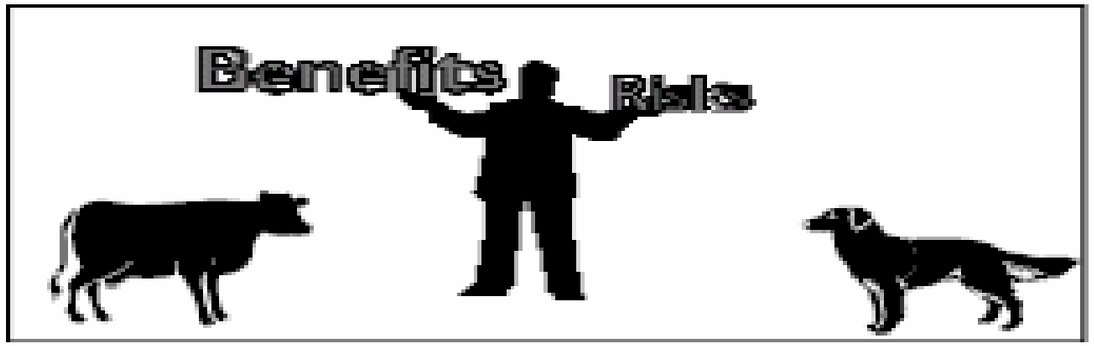
Regulatory Authority evaluates benefits/risks for the population



Veterinarian evaluates benefits/risks for a patient



Owner evaluates benefits/risks in terms of personal values



Pharmacovigilance history:

The occasion in the USA known as Elixir of Sulphanilamide case (diethylene glycol was used as the solvent), caused the deaths of about 100 people in 1937 was the engine behind the passing by Congress of the Food, Drug and Cosmetic Act in 1938.

The Thalidomide tragedy led to the establishment of the regulation of human and veterinary medicines in the UK with the introduction of the Medicines Act 1968.

Pharmacovigilance history:

- **USA**
  - 1962 – Kefauver-Harris amendment to the Federal Food, Drug & Cosmetic Act – this now required both safety and efficacy data

- **UK**
  - 1963 – Committee on Safety of Drugs established
  - 1964 – Yellow card scheme created
  - 1968 – Medicines Act (efficacy, safety and quality requirements)

- **EU**
  - 1965 – EC Directive 65/65 published

- **WHO**
  - 1968 – Programme for International Drug Monitoring

Benefit Risk: The Cycle at Work

Why do we need Pharmacovigilance?

LIMITATIONS OF PRE-MARKETING CLINICAL TRIALS:

- ***Short duration*** - effects that develop with chronic use or those that have a long latency period are impossible to detect.
- ***Narrow population*** - generally do not include special groups (e.g., young, old) to a large degree, and are not always representative of the population that may be exposed to a drug after approval.
- *Narrow set of indications* - those for which efficacy is being studied and do not cover actual evolving use
- *Small size* - effects that occur rarely are very difficult to detect.
- At least 30,000 animals need to be treated with a drug to discover (with a power of 0.95) at least one animal with an adverse reaction which has an incidence of 1 in 10,000
- *Conclusion* - these trials seldom detect or define the frequency of all important adverse reactions

Why do we need Pharmacovigilance?

Table 1. Number of exposed animals needed to detect true frequencies of adverse events (AEs)

	Statistical power			
Frequency of AE	95%	90%	80%	63%
1 in 100	300	231	161	100
1 in 500	1,500	1,152	805	500
1 in 1,000	3,000	2,303	1,610	1,000
1 in 5,000	15,000	11,513	8,048	5,000
1 in 10,000	30,000	23,026	16,095	10,000
1 in 50,000	150,000	115,130	80,472	50,000

O'Rourke, D.J. (2016) Adverse events – vets have a key role. ***Veterinary Practice Today 4(2): 23-26***

Why do we need Pharmacovigilance?

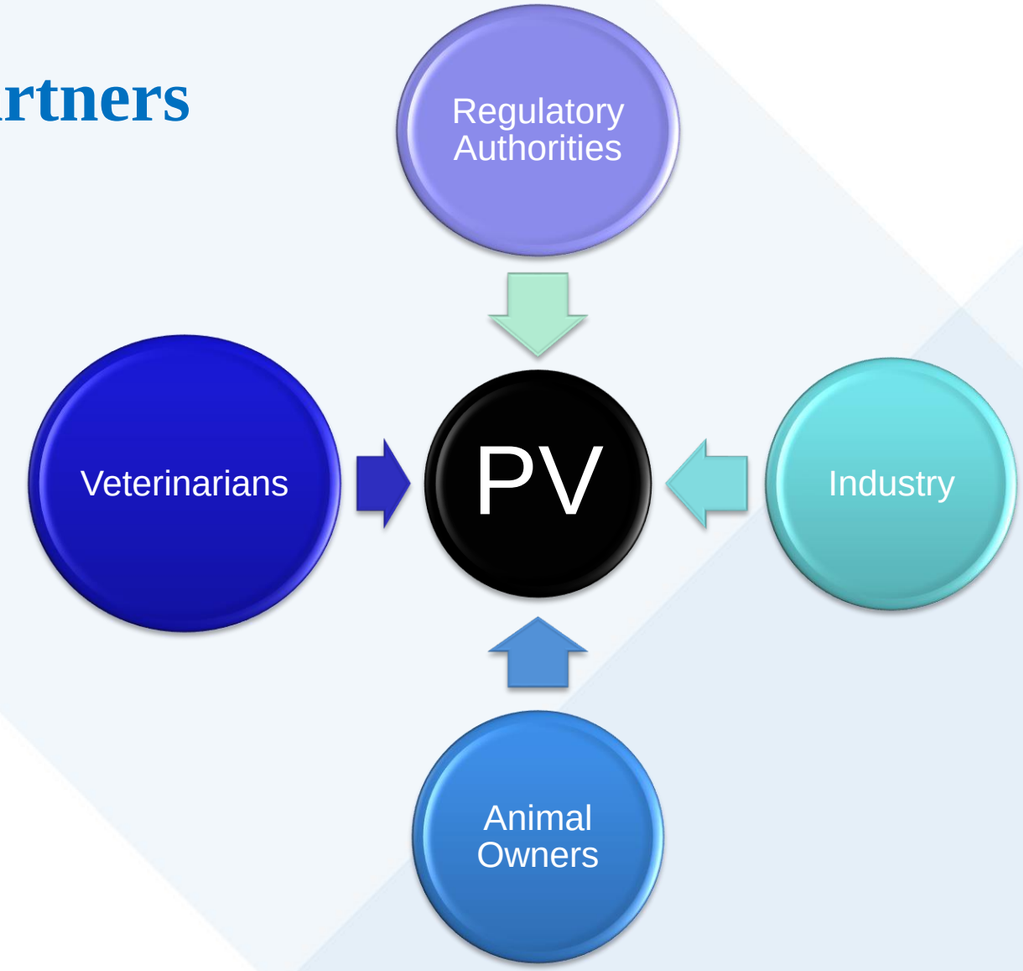
- **But then….Practice….**

- larger number of animals
- combinations with ….
- other environmental conditions
- other (sub)species
- off label use: dosage/time
- age/condition
- sometimes….product failures

The safety profile of a drug evolves over its lifetime on the market

Source of PV Data:

Various partners involved



Sources of PV data:

- Individual reports (from customers, partners)
- Regulatory Authorities
- Health Professionals (veterinarian, doctors and others)
- Farmers/producers
- Post Marketing Clinical Trials
- Peer reviewed scientific literature

Types of PV Information:

- **Adverse events:** An untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine
- **Adverse reaction:** A response to a drug which is noxious and un-intended and which occurs at doses normally used for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function
- **Lack of efficacy:** Evidence of less than the expected effect of a product
- **Residues (MRL) Violation:** Any compound or metabolite of a compound that is present above recommended/approved levels in edible tissues from food animals because of the use of a compound in or on animals.
- **Environmental damage:** Pollution of the environment with pharmaceutical drugs and their metabolites
- **Human exposure:** An undesired clinical signs in human after the veterinary drug handling

Adverse Event Definition?

An adverse event (includes all associated terms) is any observation in animals, whether or not considered to be product-related, that is unfavourable and unintended and that occurs after any exposure to or use of a marketed product (off-label and on-label uses).

Adverse event (AE) can occur in animals treated with veterinary medicines, or in people who are exposed to veterinary medicines.

Adverse Event defintion includes:

- Noxious reaction in humans after being exposed to the product.
- Events related to a suspected lack of expected efficacy (SLEE)
- Cases where substances above the maximum residue limits (MRL) are detected in food products derived from treated animals

- Environmental incidents
- Suspected transmission of an infectious agent via a veterinary medicinal product

What to Report:

The minimum information required for an adverse event is all of the following four items:

- **P**roduct - name of product. If available, formulation and strength
- **E**vent - description of the adverse event
- **A**nimal / Human - Animal: at least species, if available, sex, age, weight. Human: if available name, age, child/adult
- **R**eporter – name and contact details (e.g. phone number, email, address)

Batch/Lot # if possible

Assessment of PV Information:

- VeDDRA Coding for clinical signs
- Causality Assessment
- Seriousness/Non-seriousness classification
- Expected/Unexpected Criteria
- Incidence Calculations (animals treated, animals affected)
- Data mining/signal detection and validation

VeDDRA Dictionary:

VeDDRA dictionary (animal terms):

Veterinary **D**ictionary for **D**rug **R**egulatory **A**ctivities

VeDDRA Dictionary was first published in early 2000. Purpose was to develop an internationally accepted terminology database.

The dictionary is organized in a hierarchy of four related levels:

- SOC (System Organ Class);
- HLT (High Level Term);
- PT (Preferred Term – the level reviewed by regulatory bodies); and
- LLT (Lower Level Term – the level used for internal trending)

VeDDRA Dictionary

A	B	F	G	H	I	J
New line no.	System Organ Class (SOC) Term	Preferred Term (PT)	PT Key	Low Level Term (LLT)NT	LLT Key	LLT Term Type
593	Digestive tract disorders	Diarrhoea	186	Diarrhoea	302	C
594	Digestive tract disorders	Diarrhoea	186	Increased bowel movements (frequenc	2231	C
595	Digestive tract disorders	Diarrhoea	186	Loose bowel	1588	C
596	Digestive tract disorders	Diarrhoea	186	Loose stool	304	C
597	Digestive tract disorders	Diarrhoea	186	Mucous stool	1080	C
598	Digestive tract disorders	Diarrhoea	186	Pasty stool	2438	A
599	Digestive tract disorders	Diarrhoea	186	Scour	303	C
633	Digestive tract disorders	Haemorrhagic diarrhoea	195	Bloody diarrhoea	315	C
634	Digestive tract disorders	Haemorrhagic diarrhoea	195	Haemorrhagic diarrhoea	314	C
635	Digestive tract disorders	Haemorrhagic diarrhoea	195	Intestinal haemorrhage	1083	C

Causality Assessment:

Causal association between the suspect product(s) and reaction(s) is expressed using five categories, the ABON system:

- A: probable
- B: possible
- O: unclassifiable/un-assessable, for cases where reliable data are not available or insufficient information is available to draw any conclusion
- O1: inconclusive, where other factors prevent a conclusion but product association cannot be discounted.
- N: unlikely

- Z: No Assessment for human case reports.

Serious Adverse Events:

Examples of Serious Adverse Events

- Death
- Life threatening
- Requiring prolonged hospitlaisation
- Significant and persistent disability

What is a “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”

The presence of a signal in PV data does not mean a cause-and-effect relationship exists.

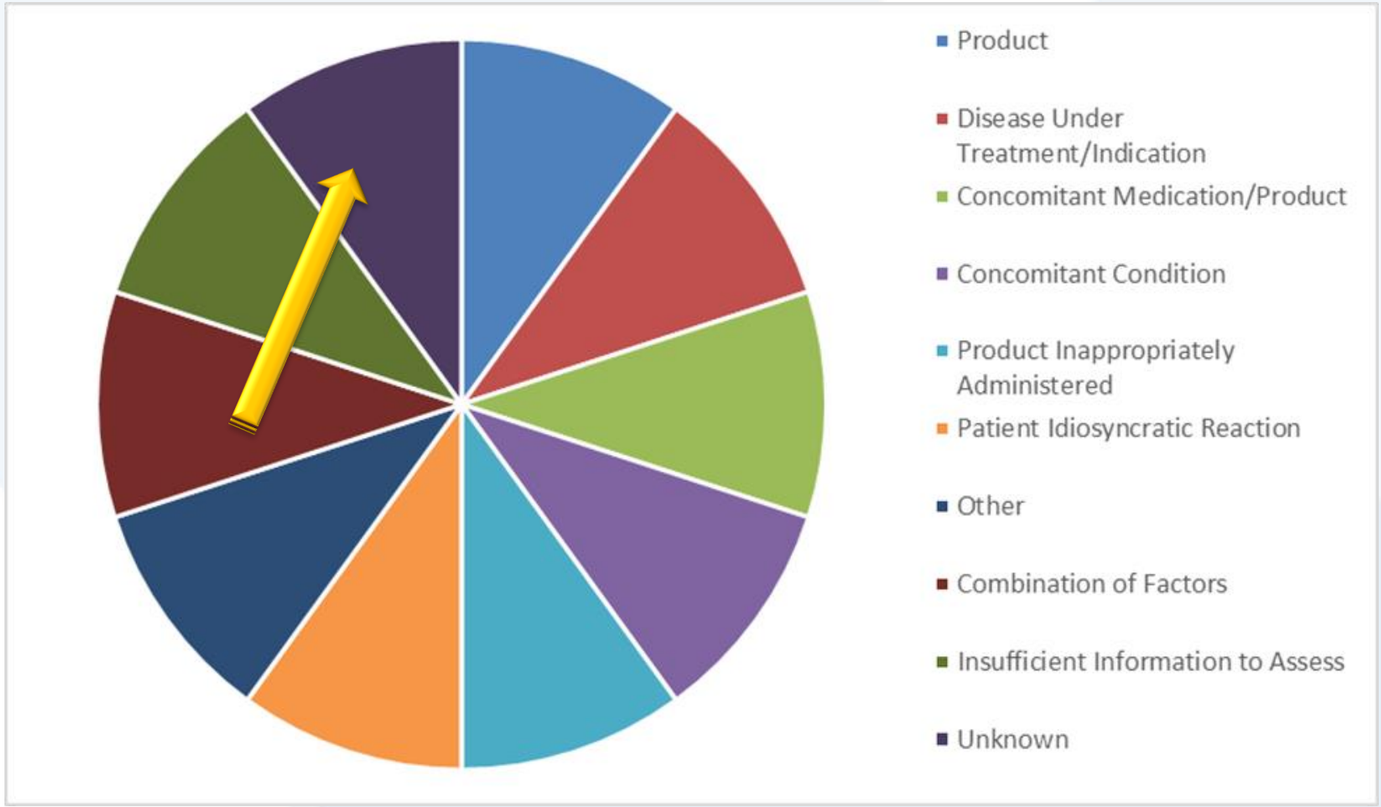
Source: CIOMS Working Group VIII, 2010.

What is a “Signal”??

Finding a valid signal in pharmacovigilance is similar to finding a needle in a haystack

What is a “Signal”??

- Once found, what does the signal mean? Is it a valid signal? Is it a false positive signal? What is the cause? What is the significance of the signal”?



Performing Signal Detection (Signal Detection Tools)

Individual Case Review

- Gold standard: Permits creation of a case series of related events and an assessment of the strength of a signal
- Volume poses a challenge

Literature Review

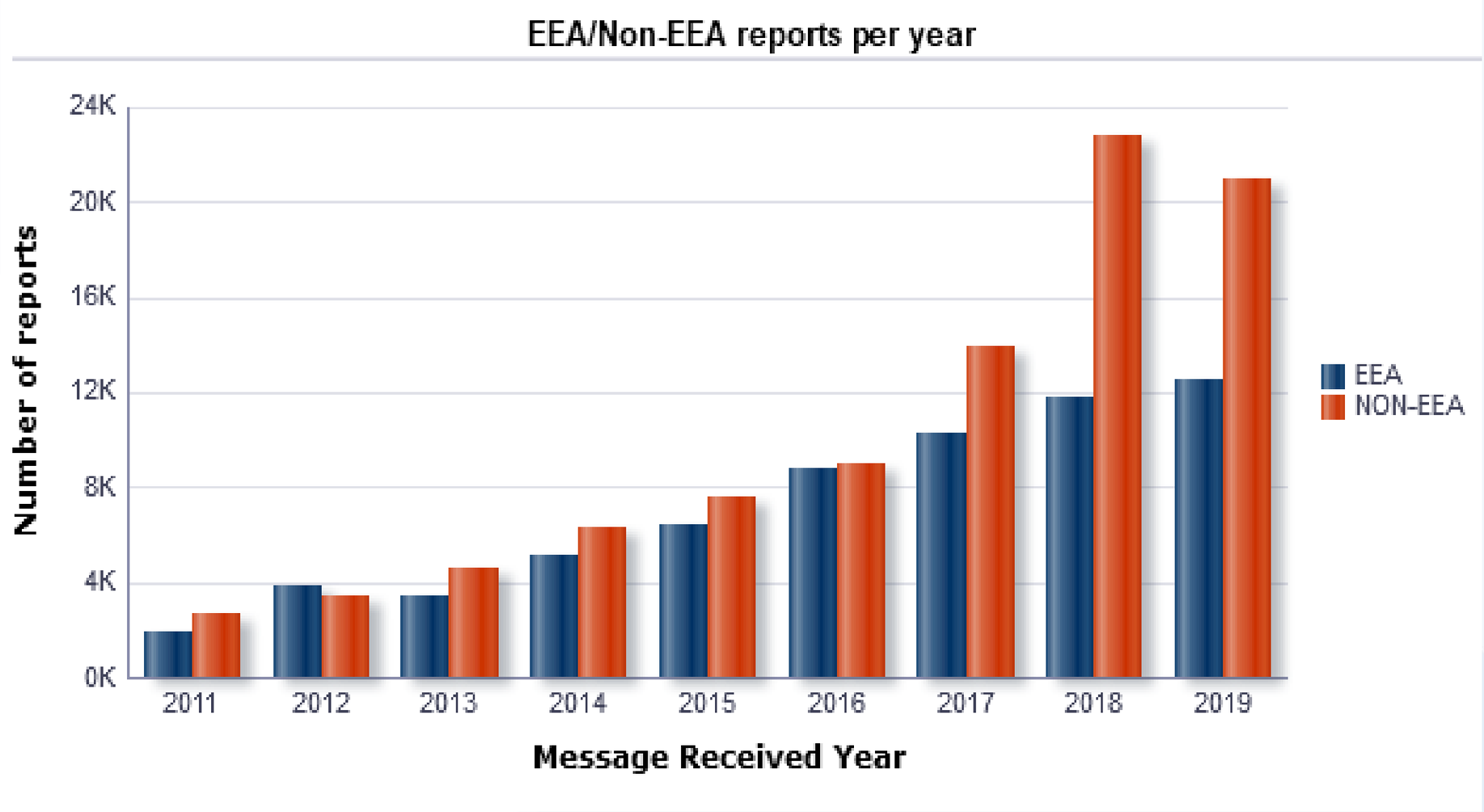
- Part of aggregate reporting process in most geographies

Aggregate report review

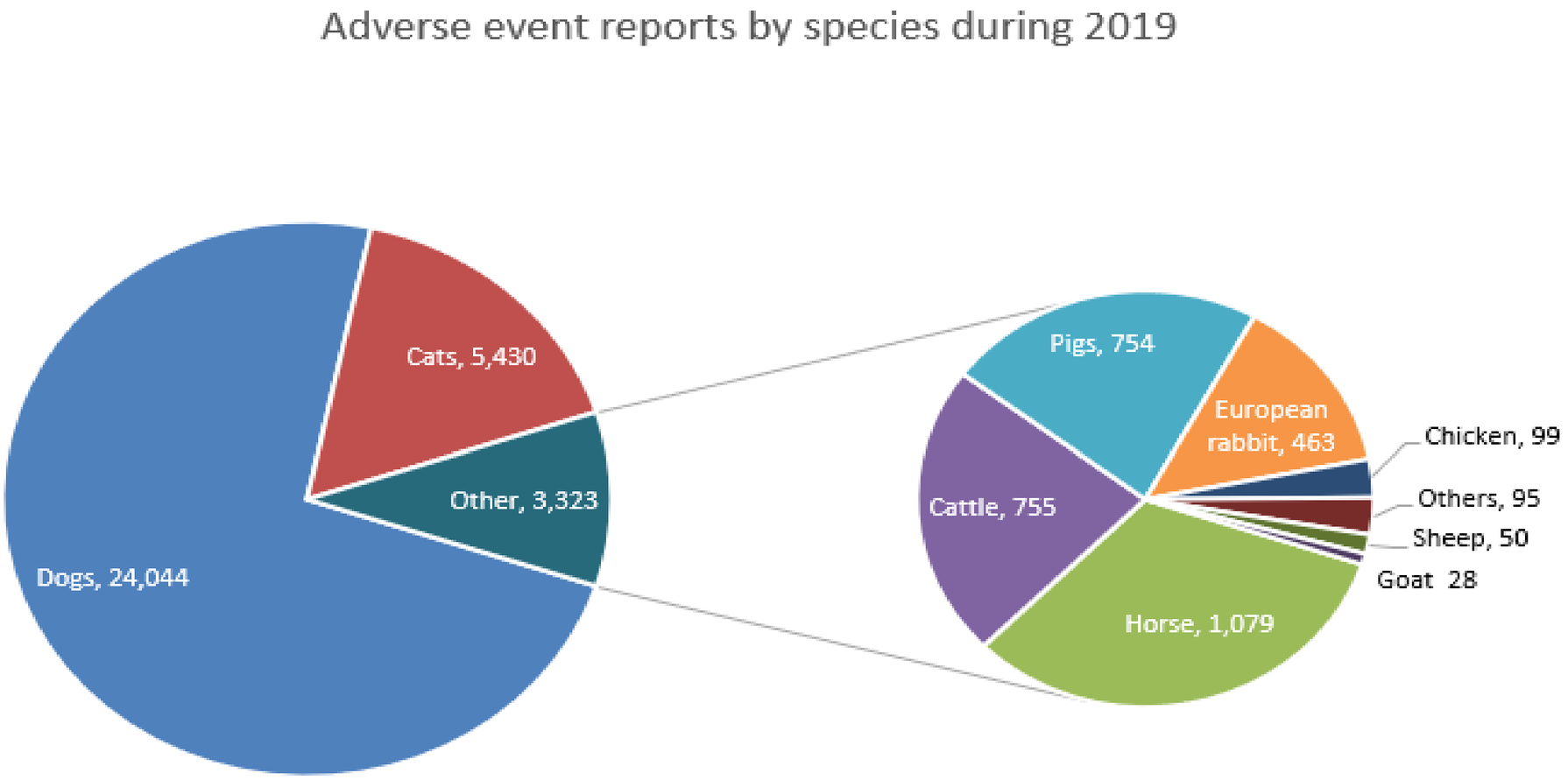
Statistical Methods

- Descriptive statistics
  - Case count, patient demographic data, etc.
- Report rate
- Estimated incidence rate

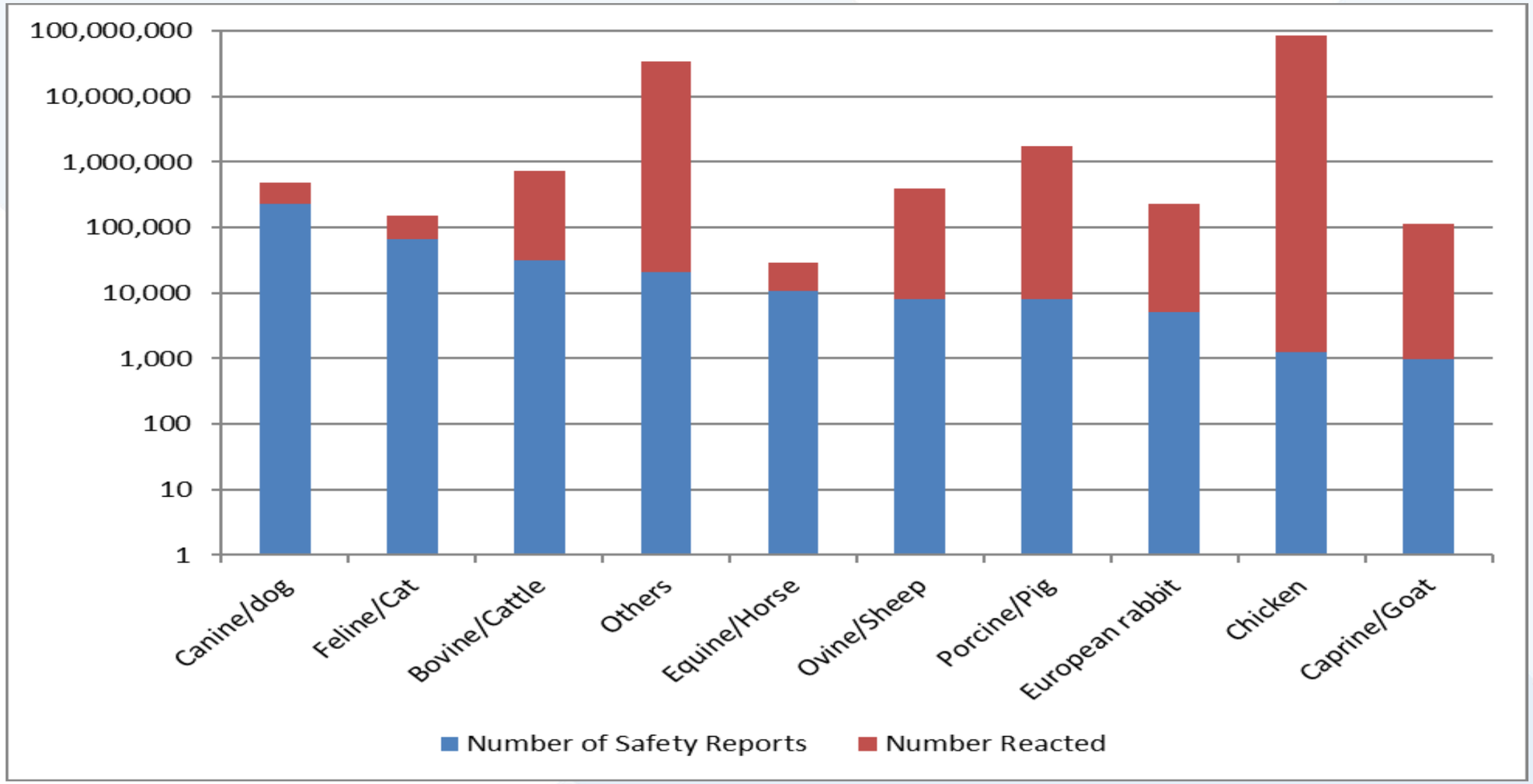
Number of AEs for CAPs reported to EMA EVVet between 2011 and 2019



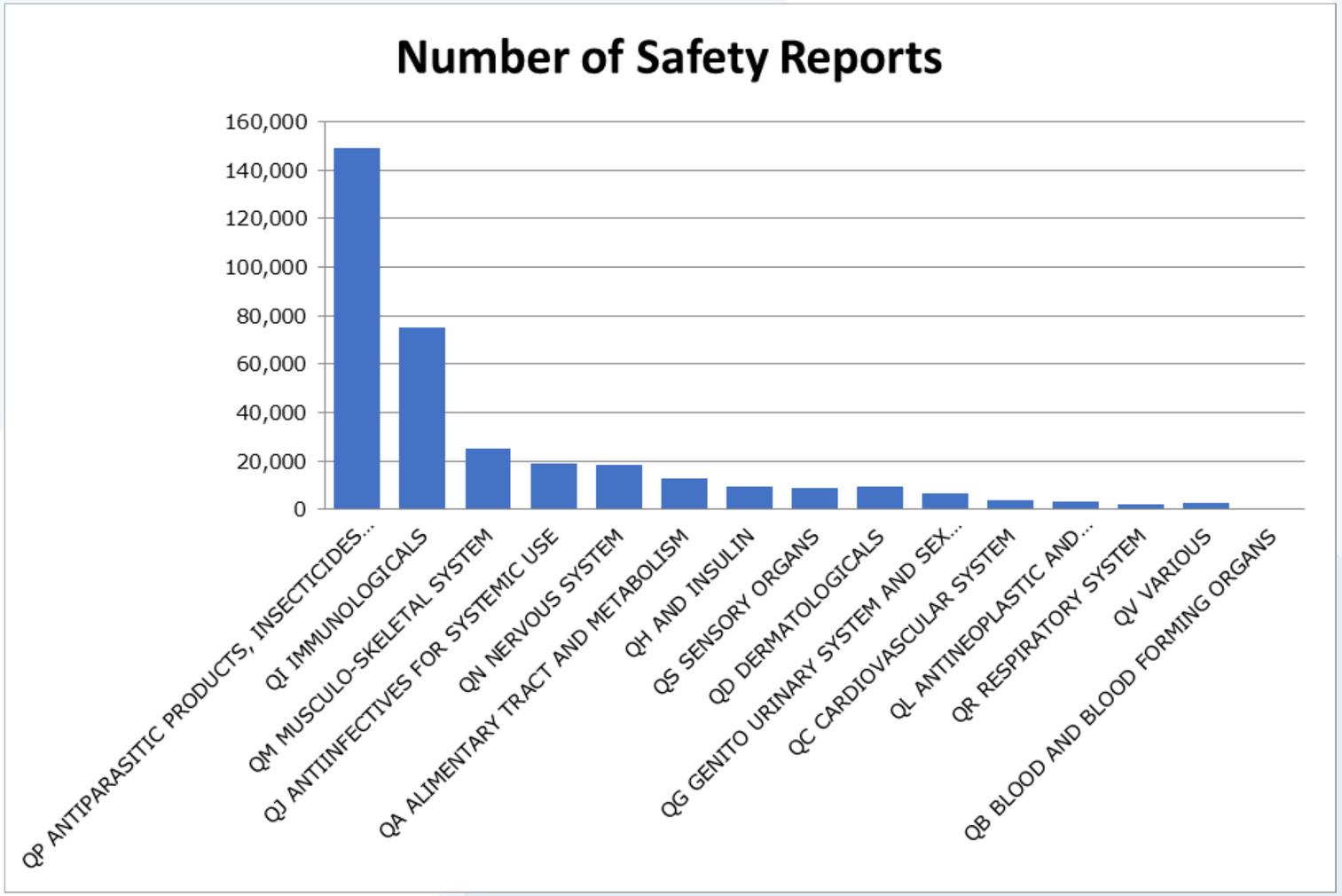
Adverse event reports by species received during 2019



Number of reports and animals affected by species in EMA EVVet between 2005 and 2019



Number of reports by ATCVet group in EMA EVVet between 2005 and 2019



Questions/ أسئلة؟

спасибо
谢谢
GRACIAS
THANK YOU
ありがとうございました
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DANKE
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