BIG DATA & VETERINARY PHARMACOVIGILANCE

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DISCLAIMER

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INTRODUCTION

Big Data refers to large volumes of diverse, dynamic, distributed structured or unstructured data that provide opportunities and challenges with respect to its interpretation due to its complexity, content and size (1).

Within Veterinary Health there are examples of concepts of Big Data. These are more prevalent in production animal than for pet health.

Firstly, lets understand what the applications are in the Human Pharmacovigilance (PV) space and extend the possibilities to Veterinary health.
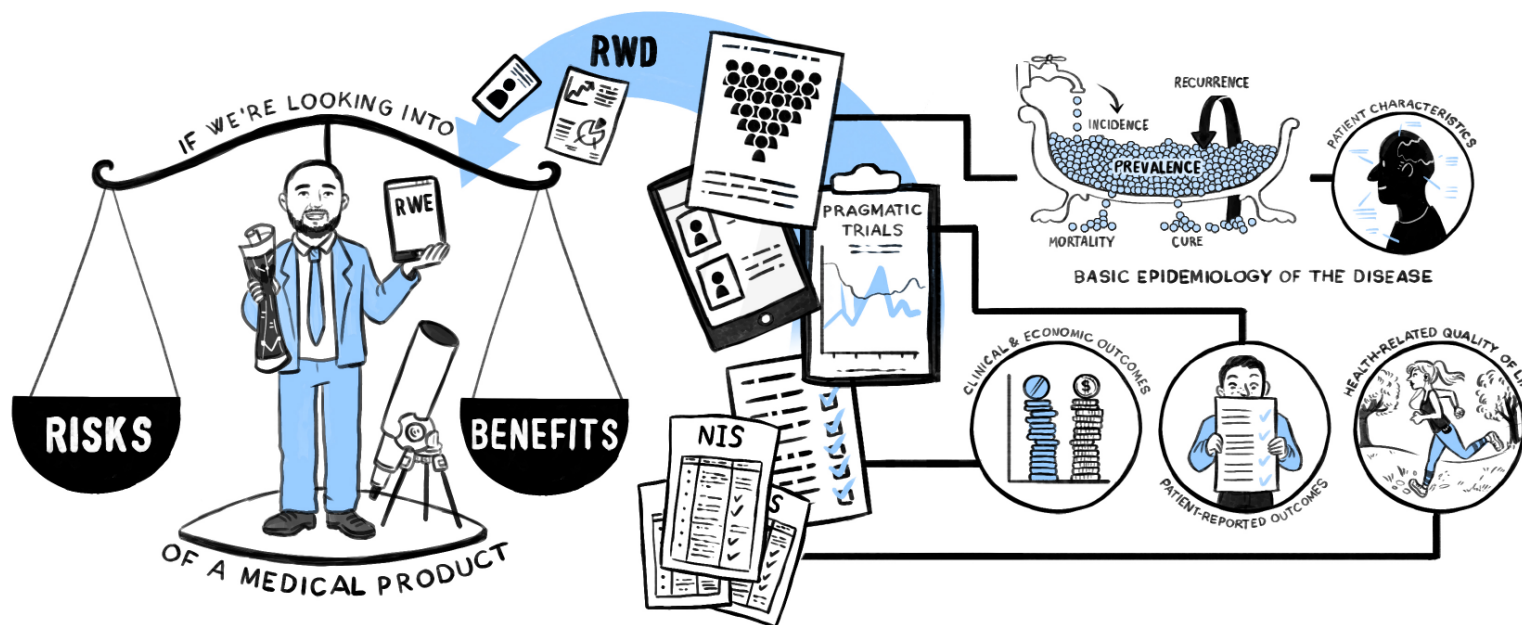
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Big Data = Real World Data = Real World Evidence

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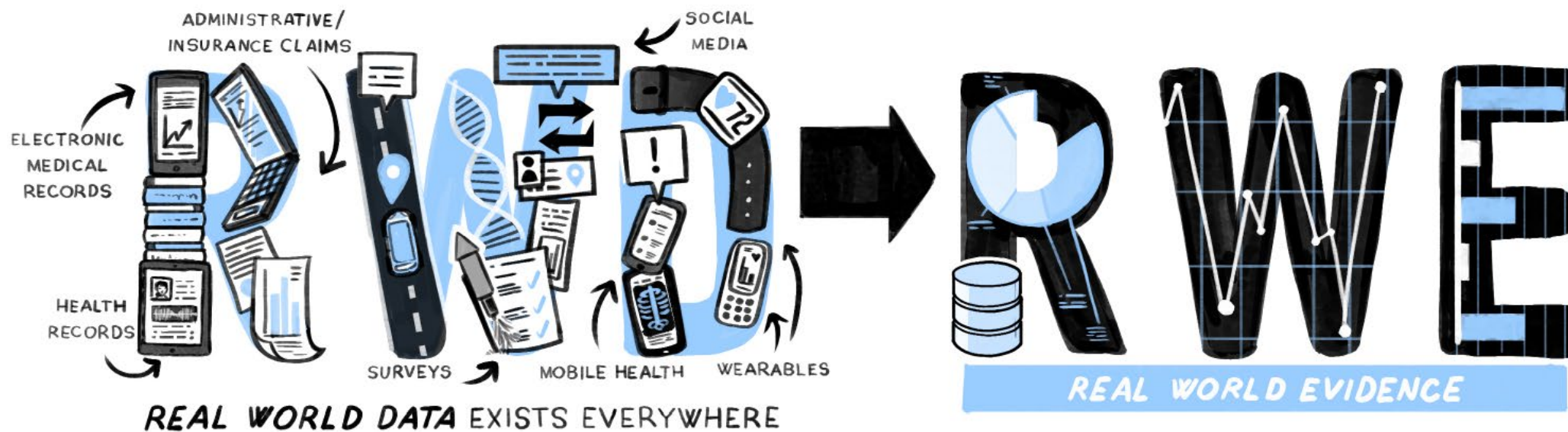
There are nuanced definitions that exist of RWE; however, it is widely agreed that in principle it is clinical evidence derived from the analysis of RWD that is used to make informed healthcare decisions.

What are the opportunities for RWE across the product lifecycle
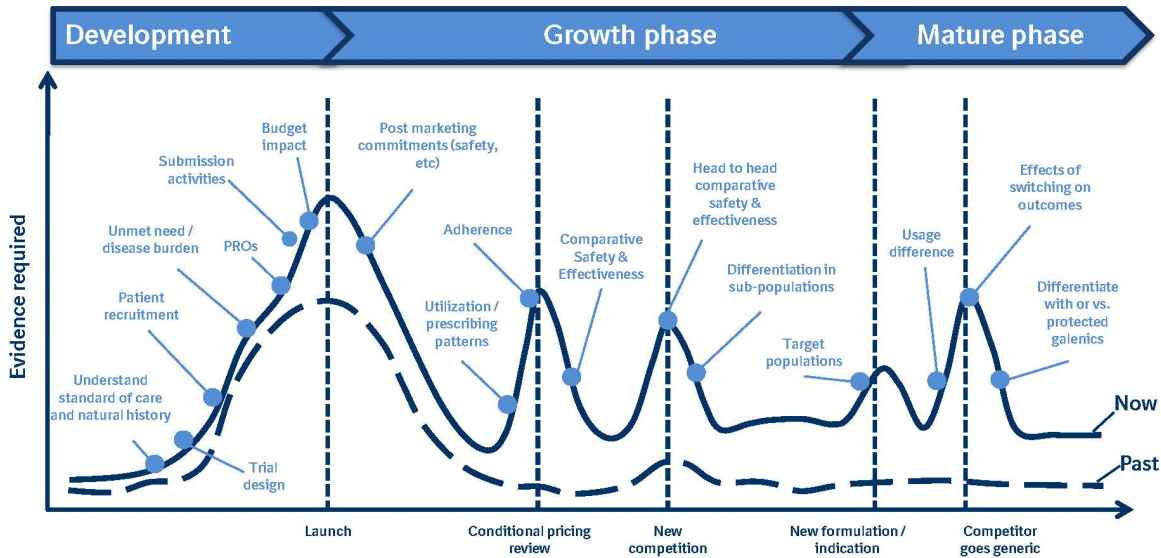
Adapted from IMI GetReal

Characterise treated population

Generate RWE through observational, non-interventional studies

Comparative safety and effectiveness data

Contribute to risk management

Assess effectiveness of risk minimisation activities

Support Regulatory deliverables

Monitor long-term safety and effectiveness

Potential to identify emerging diseases

Predictive Pharmacovigilance profile to better estimate product support costs (i.e. technical services, guarantees, etc.)

BIG DATA AND VETERINARY PHARMACOVIGILANCE

Problem Statement for Veterinary PV:

In animal health, there is a disparity in availability of data between Food Animal and Pet Health. In the latter, availability of data sets are less and generally smaller than Human Health counterparts but the application of the approach is consistent.

The digital revolution and advancement of computing capabilities (including Artificial Intelligence and Machine Learning) are creating the desire and the opportunity to extract value from the data.

It is recognised that a multi-factorial "Big Data" methodology may be able to significantly contribute in some situations to the benefit/risk assessment for veterinary medicines.

Constraints are the availability, volume and accessibility of animal health data. Opportunities exist for disease surveillance and describes the monitoring of population health to ascertain the existence and changes in disease levels. Health surveillance data can be analysed to derive disorder prevalence proportion (proportion of animals affected), incidence risk (proportion of previously healthy animals that become diseased over a specified period) estimates, perform risk factor (attributes associated with disease occurence) studies and examine survival in affected animals (5).

The Big Data approach will help support the move from reactive PV practices to a more proactive PV approach

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What is an adverse event (3) in Veterinary PV?

a) any unfavourable and unintended reaction in an animal to a veterinary medicinal product;

b) any observation of a lack of efficacy of a veterinary medicinal product following its administration to an animal, whether or not in accordance with the summary of product characteristics;

c) any environmental incident observed following the administration of a veterinary medicinal product to an animal;

d) any noxious reaction in humans exposed to a veterinary medicinal product;

e) any finding of a pharmacologically active substance or marker residue in a product of animal origin exceeding the maximum levels of residues established in accordance with Regulation (EC) No 470/2009 after the set withdrawal period has been respected;

f) any suspected transmission of an infectious agent via a veterinary medicinal product;

g) any unfavourable and unintended reaction in an animal to a medicinal product for human use.

So, unlike Human PV, the scope of the benefit/risk evaluation is wider and relates to more than one species. It is important to have different data sources so that all the risks of a given product can be identified. Today, we capture these events into the same data structure which may not always be appropriate.

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Current data sources used in Veterinary PV are either structured (i.e. coded data sets in PV databases) and unstructured (i.e. Social Media)
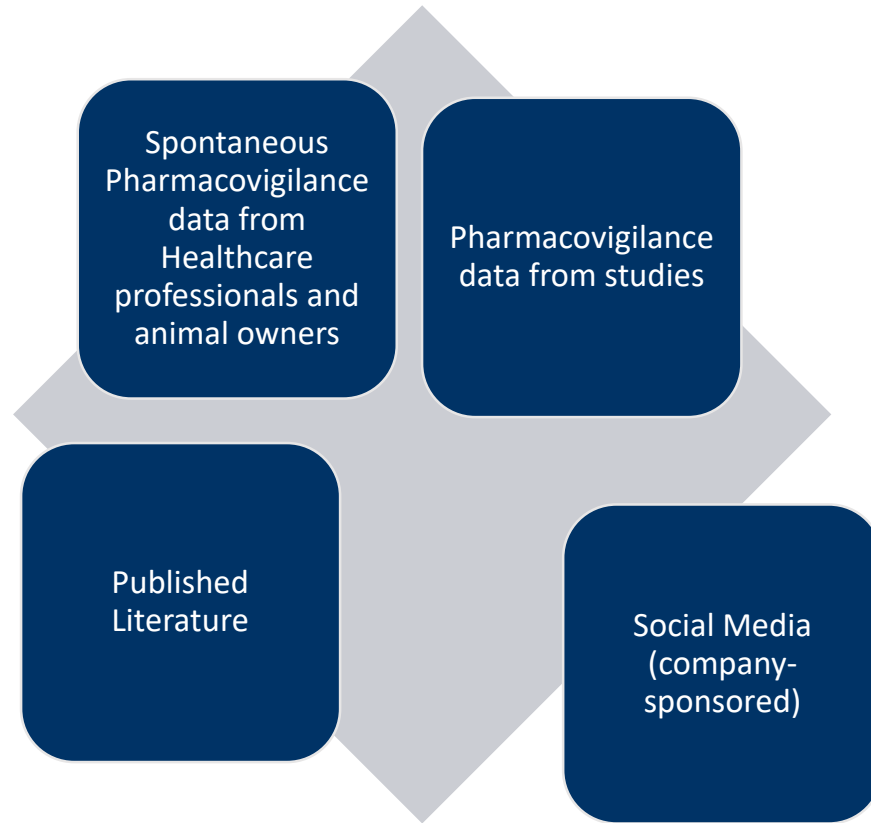
PHARMACOVIGILANCE – SIGNAL MANAGEMENT

Currently within Veterinary PV the methodology for detecting and managing signals is evolving. There are many statistical methods for data mining safety signals. Common approaches often applied are those of Disproportionality Analyses (Bayesian and non-Bayesian).

In a recent paper by Novotny *et al*. (6) different signal detection algorithms were performed on their PV database (table 1) to determine the most appropriate algorithm to detect PV signals. They concluded that the performance (sensitivity, precision, specificity, accuracy and F score) of the algorithm in their pharmacovigilance data was dependent on the statistical methods as well as being species dependent.

Further research is required in this area and we also should understand the application of these statistical algorithms with Big Data approaches.

TABLE 1 Signal detection algorithms assessed in the study and their abbreviations

Statistical method	Alert abbreviation	Signal detection algorithm
IC	T-1	IC (ICf > 0 and $n \geq 1$)
PRR	T-2	PRR (PRR $\geq$ 2 and $n \geq$ 3 and ChiSq $\geq$ 4)
	T-3	PRR-Y (PRR $\geq$ 2 and $n \geq$ 3 and ChiSq-Y $\geq$ 4)
	T-4	PRR025 (PRR025 $\geq$ 1 and $n \geq$ 3)
	T-5	PRR/PRR025 (PRR $\geq$ 2 and PRR025 $\geq$ 1 and $n \geq$ 3)
ROR	T-6	ROR025 (ROR025 $\geq$ 1 and $n \geq$ 3)
O/E	T-7	O/E[a] (O/E > 1.5 and $n \geq$ 3)
EBGM	T-8	EB05 (EB05 $\geq$ 2 and $n \geq$ 1)
	T-9	EB05/EBGM (EB05 $\geq$ 1.8 and EBGM $\geq$ 2.5 and $n \geq$ 3)

Abbreviations: ChiSq, Chi-squared; EB05, lower bound of the EBGM; EBGM, empirical Bayes geometric mean; IC, information component; ICf, lower bound of the IC; *n*, number of cases; O/E, observed-to-expected; PRR, proportional reporting ratio; PRR025, lower bound of the PRR; ROR, reporting odds ratio; ROR025, lower bound of the ROR; Y, Yates correction.

[a] O/E is synonymous with the Relative Reporting Ratio: $A \times (A + B + C + D)/(A + C) \times (A + B)$ (Hauben et al., 2005; Shibata & Hauben, 2011).

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Large sets of PV data are required for these approaches to be effective. The gold standard of signal detection in animal health continues to be individual case review due to relatively low numbers of PV case reports.

Our experience and knowledge is increasing including the ability to identify signals, validate and visualise the signals, and implement appropriate risk mitigations. With the new EU Veterinary Medicines Regulation, the opportunity exists to enhance these skills across different product portfolios and species.

In addition to signal management methodology, other technologies are emerging to evaluate data. These are not commonplace, but the applications need to be assessed and implemented appropriately. Data mining serves as the foundation for Artificial Intelligence. Machine learning may also have its application in identification and triaging of medically severe events.

Text mining technology is also advancing - utilising machine learning to evaluate unstructured "narrative" data. The next slide from SAVSNET demonstrates this data.

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SAVSNET - https://www.liverpool.ac.uk/savsnet/
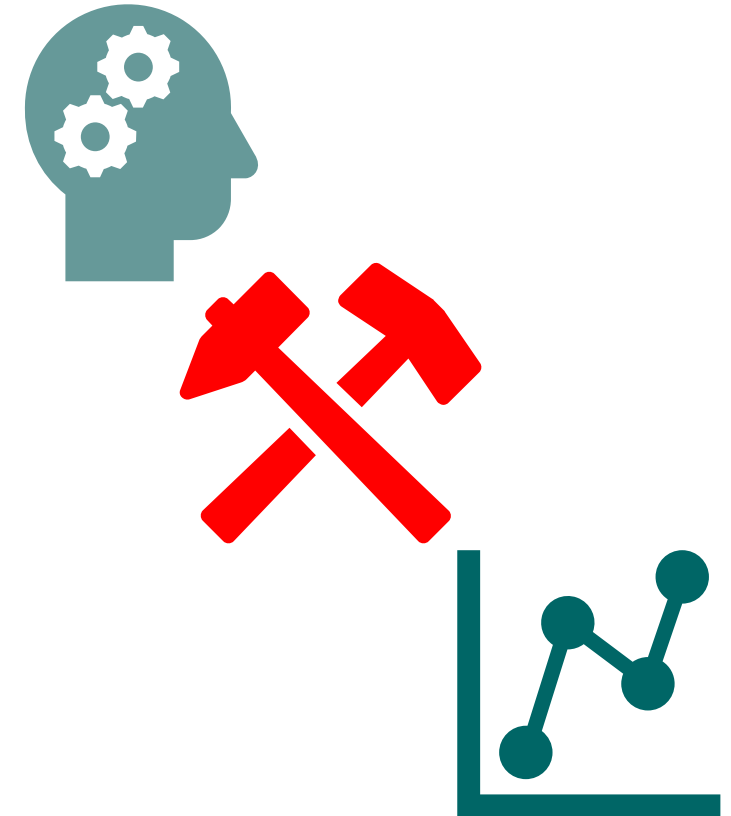
UK wide GP clinical notes
Small animals
~ 10 million narratives
Unstructured data

→ Event definition based on VeDDRA concepts

→ Event and Exposure data

→ Comparison to baseline (internal or external controls)

→ Identify cases and controls for precision medicine and risk mitigation research

1) Simple searches

- Suspect AE and drug mentioned in text

Example
…diarrhoea after [drug-A], potential adr?
…reacted to [drug-B] last time, avoid

2) Investigation of specific drug-event pairs

- Identify drug exposure using SAVSNET drug label & sales data
- Search for specific AE in the consult notes of exposed animals

Example
…o reports <name> vomiting and diarrhoea
…history: v++ this morning

3) Capturing events in unstructured data

- Misspellings & colloquial lexicon limit sensitivity of simple word searches
- High sensitivity search terms using word vectorisation models
- Output is data source specific, example 'seizures' in SAVSNET data

```
printout_similar_words_to(target_word='seizures',
                          word_vectors=word_vectors,
                          match_count=5)

fits              0.867  2203
siezures          0.776  98
seizure           0.742  3591
cluster_seizures  0.720  126
episodes          0.697  6410
```

Funded by Veterinary Medicines Directorate

4) Hypothesis generation using topic modelling

- Gives overview of topics discussed in large volume of data
- Examples – explore drivers for prescription (below), pre / post drug events

Topic	Count	Words	
59	457	'eating', 'food', 'diarrhoea', 'ok', 'drinking', 'vomiting', 'palp', 'panting', 'diet', 'abdo pain'	Related to prior therapy?
80	330	'pain', 'lameness', 'elbow', ███ 'm', 'xrays', 'hip', 'crepitus', 'lh', 'nad'	
37	251	'weeks', 'appointment', 'days', 'week', ███ 'pain', 'appointment weeks', 'lf', 'plan', 'elbow'	Related to indication
73	201	'ear', 'right ear', 'left ear', 'wax', 'ear canal', 'otitis', 'waxy', 'cleaning', 'erythema', 'cleaned'	
75	197	'wound', 'dressing', 'bandage', 'healed', 'stitches', 'sutures', 'healing', 'suture', 'wound healed', 'antibiotics'	

PHARMACOVIGILANCE – FUTURE DATA SOURCES

In addition to current data sources, the opportunity exists to create data sets that include:

Pharmacoepidemiology – large data sets required especially in pet health. Disease state information to provide context/perspective to the risk information (PV data). Specifically, data can be generated from the following sources

- Veterinary clinic data – emerging in some countries (UK – SAVSNET (4), Royal Veterinary College – VetCompass (7), US – CAVSNET (9) Banfield Pet hospitals.)

- Laboratory data – diagnostic labs (e.g. Idexx)

- Insurance data – accessibility to data

- Surveys

- Others?

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PHARMACOVIGILANCE – FUTURE DATA SOURCES

Telemedicine – Technology solutions to manage the healthcare of animals (e.g. mobile apps, "wearables" for animals). This landscape is evolving and we foresee that even through genotype profiling we can find out much more about animals and even consider "personalised" medicine.

Social Media – different approach to monitoring required. Social listening rather than capture in PV data.

Other indirect sources – E.g., Weather/climate/geographical data – can aid in visualising and providing context to (ecto)parasite product reporting patterns.

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APPLICATION OF A BIG DATA APPROACH TO EVALUATING PV

Glickman et al (8) in their paper on the Safety Profile of Moxidectin (ProHeart 6) and two Oral Heartworm Preventatives in Dogs, *presented how Medical records of a nationwide (US) veterinary practice were evaluated to determine the incidence of adverse events and health problems following administration of the sustained-release injectable heartworm preventive moxidectin (ProHeart 6), 2 oral monthly heartworm preventives, and/or vaccines in dogs. Similar information was reviewed for dogs receiving neither heartworm preventives nor vaccines.*

The results determined that the safety profile of these products was comparable. However, ProHeart 6 was associated with a 27% increased risk of mast cell tumor (2.1 per 10,000 exposures), while one of the oral heartworm preventives was associated with a 23% increased risk of death (22.0 per 10,000 exposures). This analysis of medical records for more than 7 million office visits and over 2 million dogs demonstrates the feasibility of using large electronic databases to test hypotheses generated by spontaneous adverse event reports to the United States Food and Drug Administration Center for Veterinary Medicine. In addition, information can be generated on baseline occurrences of certain conditions in a large population of dogs presented to veterinary hospitals across the United States.

This study is important for a couple of factors. It confirmed the hypothesis generated from spontaneous PV data and tells us that evaluating the baseline occurrence of certain conditions can help us provide context to risks observed in PV data.

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CONCLUSION

Big Data and its application can aid Pharmacovigilance departments to understand health problems and make informed decision on the benefit risk profile of veterinary medicinal products.

"Data" can be found in a variety of sources and is frequently fragment, structured and unstructured.

Statistical tools and data mining methodologies are important in understanding how we can evaluate Big Data in Veterinary Pharmacovigilance

It is important to formulate hypotheses in order to draw conclusions from Big Data. If we go into Big Data not knowing what we want to prove it is likely we will be lost continually digging for answers.

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