Pharmacovigilance Unit Industry Information Day

WELCOME!

Veterinary Medicines Directorate

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

FIRE ALARM SOUNDING

- Leave the building by the nearest available safe exit route
- Proceed to the Assembly Point **situated at the far end of the grassy area to the right of the Gatehouse**
- Remain at the assembly point with until you receive instructions from VMD/APHA staff or site security.

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Overview of the day

- Why are we all here, meet the team
- DDPS assessments
- Duplicate detection and nullification
- Data quality and human reports
- Animal adverse events

LUNCH

Questions at end of each session.

- Signal detection
- PSUR assessments
- New developments in Europe

DEPART

Collect feedback forms

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Why are we all here?

- **Customer Survey 2014**
- 70% of respondents scored the Pharmacovigilance team as good or excellent
  - Good, but lower than previously
- Focus group - further feedback
- **Customer Survey Action Plan**
  - Several actions, nearly all completed
  - PhV Industry Information Day

    #Least popular boss ever

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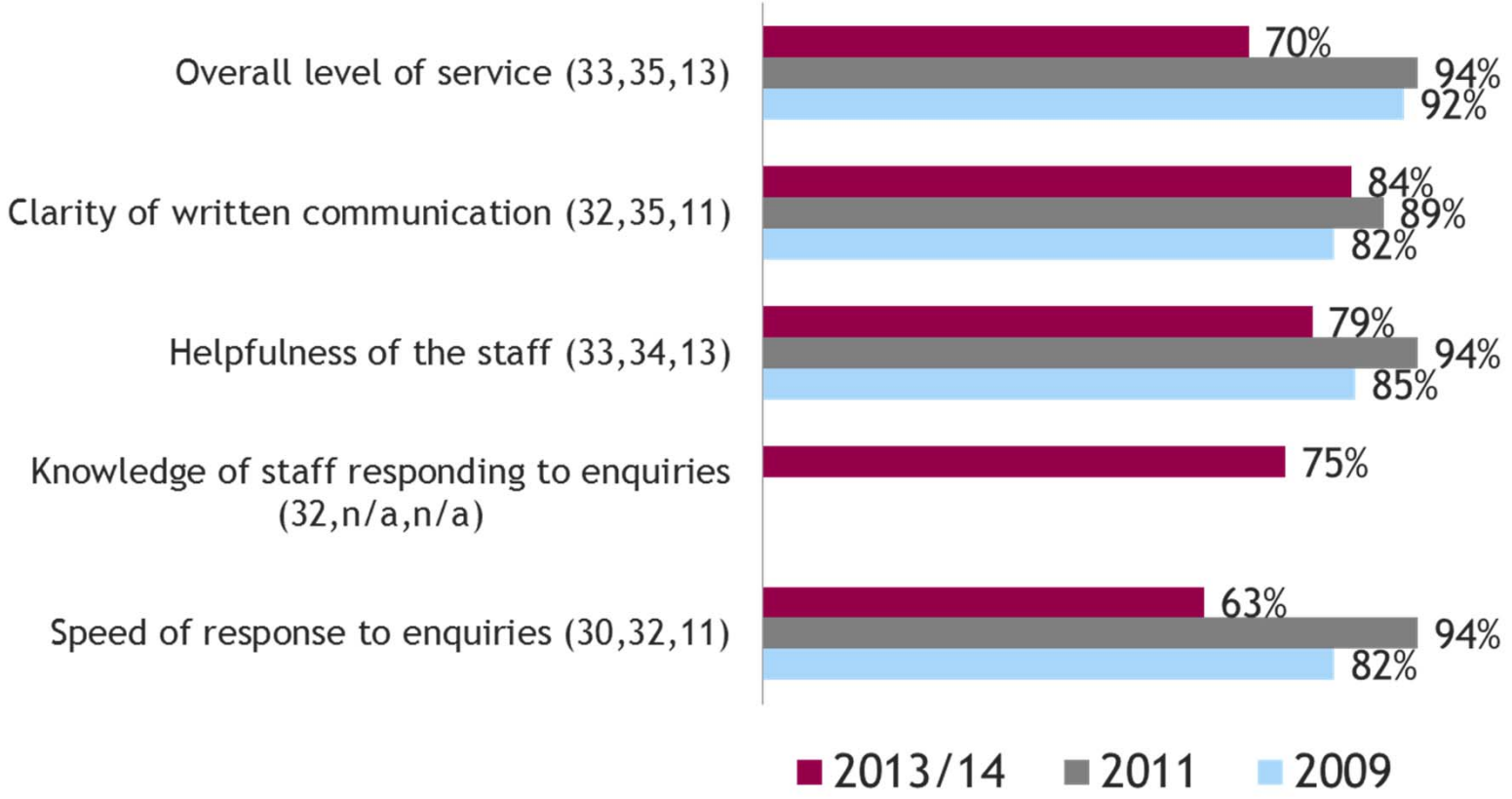
Overall Team Results



Some new questions…affected results?

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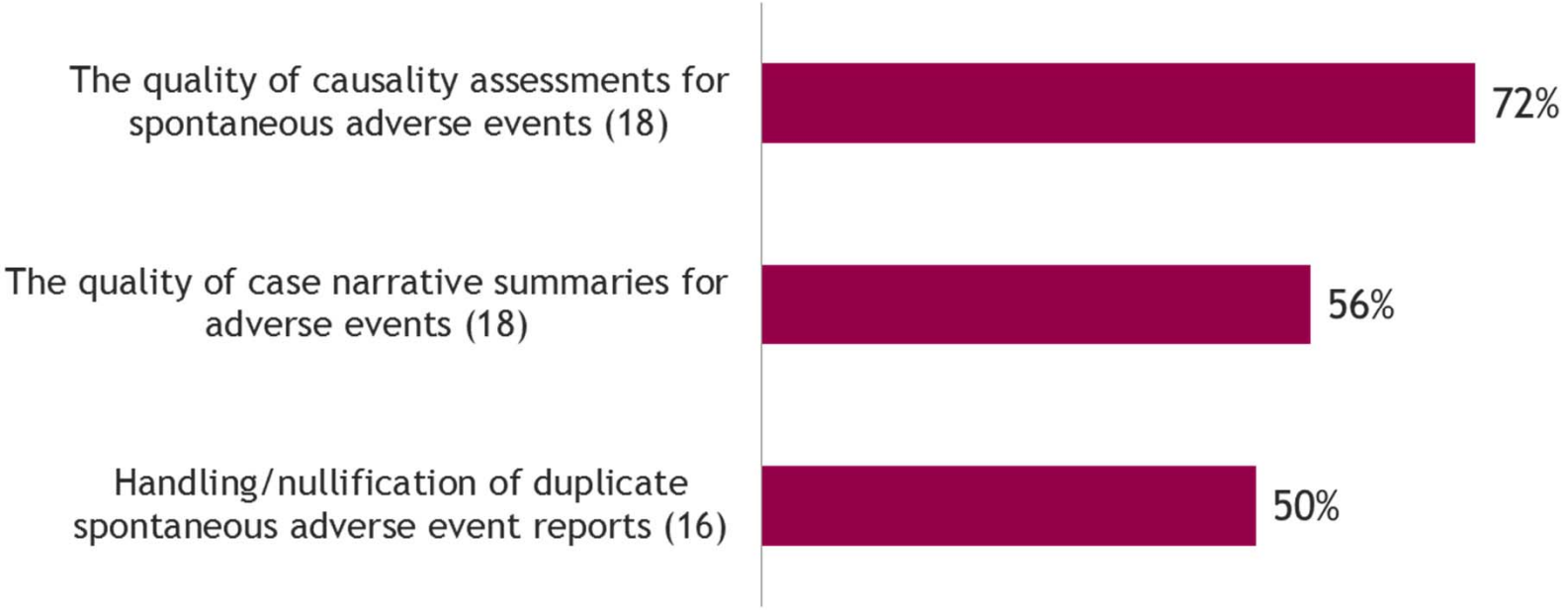
Adverse Event Assessments



Processes had not changed inbetween surveys, but we are trying to improve!

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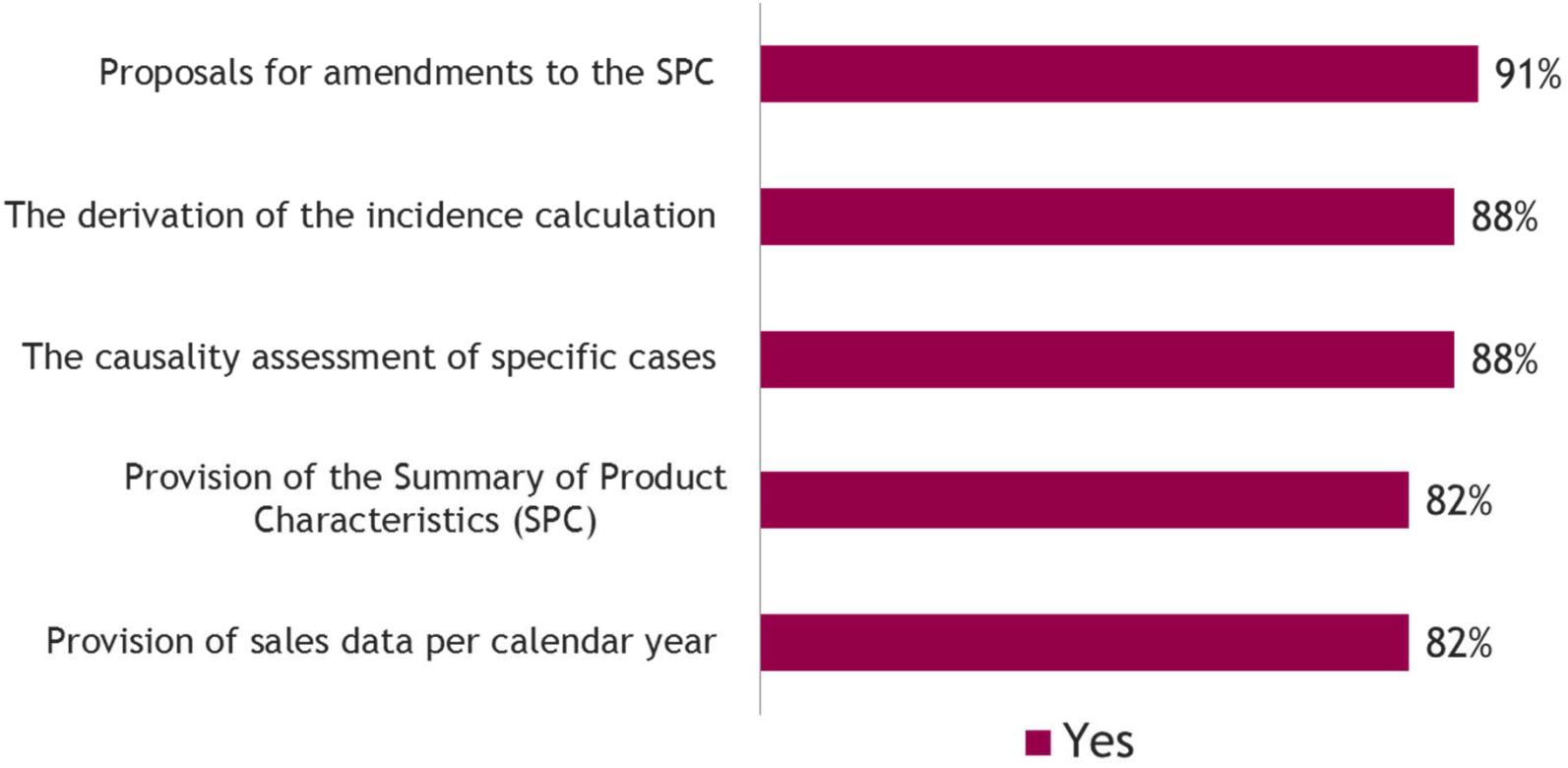
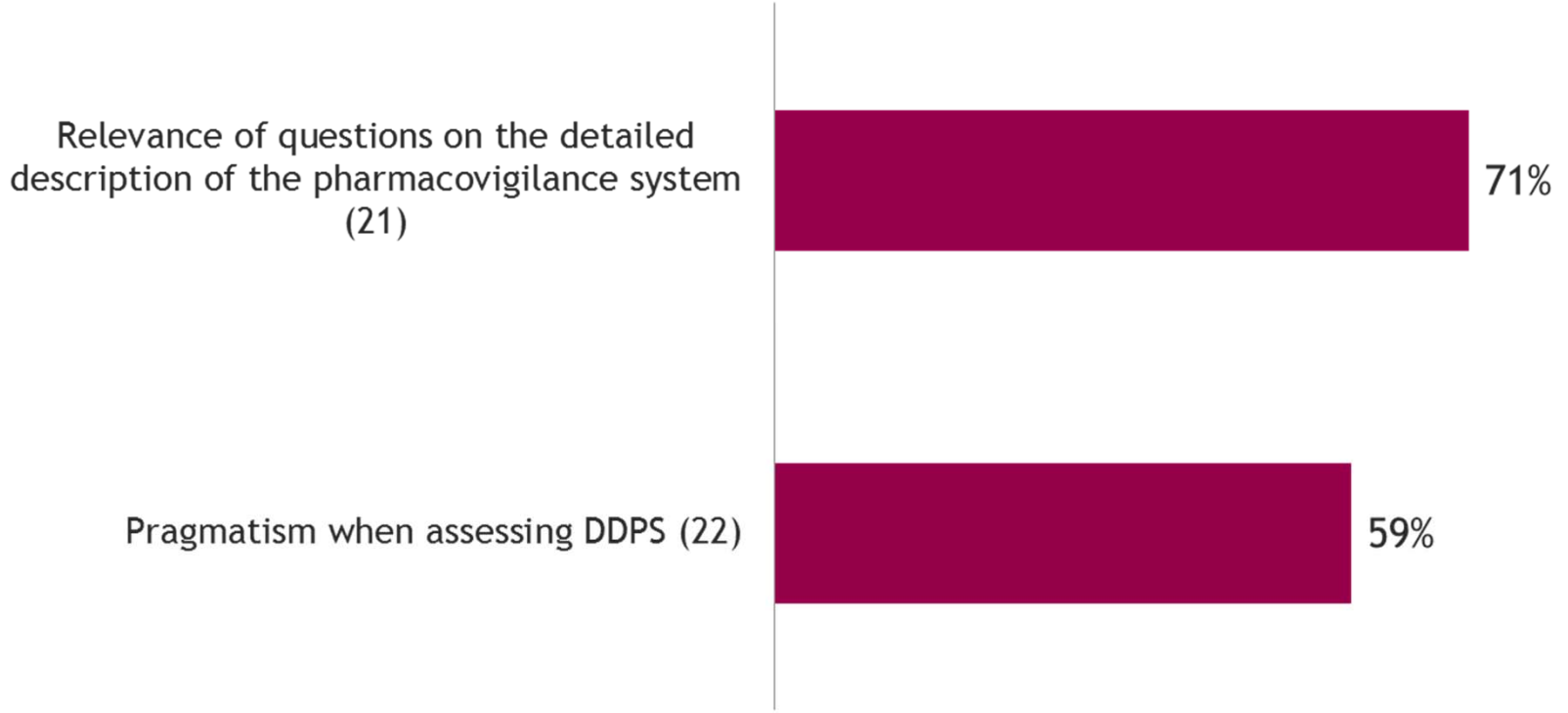
PSUR Assessments



The majority of respondents understand why we ask for these to be provided.

DDPS Assessments



Staff changes? CMS questions?

Comments received

- *"One sentence does not make a coherent narrative, for a full assessment of a case more information is needed."*

- *"Overall very happy with support provided by the VMD. Only frustration is with the handling of duplicate cases, which I appreciate is a difficult problem to solve."*

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Comments received

- *"When receiving adverse event reports, sometimes what an owner describes & what the vet sees differ. While I understand that it is important to have adverse events recorded & reported the quality & reliability of the information is also important. Also, if a client doesn't know the vet has reported the adverse event they may well report it themselves & then we come into the problem of duplicate reports."*

Not all bad though….

- *"I think they are very good; the fact that they do meet the industry and we do have these conversations…they are more approachable than they have perhaps been in the past.“*

- *“The PV department are incredibly helpful and approachable, slightly unfortunate that we do not have responses as quick as I would hope. Previously I worked in RA and responses were quicker then.”*

Customer Service Charter

We will always try to answer your telephone calls promptly, and respond to questions arising from them within five working days. If we cannot provide a complete answer within that time, we will let you know why.

Where the first person you speak to cannot answer your query we will ensure that someone who can deal with it calls you back, within two working days.

If we are away from the office when you call us we will ensure that you are told:

* *when we will be back; and*
* *who you can contact in our absence.*

When you leave a message, we will call you back, or ensure that someone able to deal with your query calls you, within two working days of our return to the office.

We will answer your written enquiries (including faxes and e-mails) within 15 working days of receipt. If we cannot provide a complete answer within that time, we will let you know why, and provide you with the name and telephone number of someone you can talk to about your query.

VETERINARY MEDICINES VMD DIRECTORATE

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Digging deeper

1. **Clinical Summaries** – insufficient information provided by VMD (1 MA holder) *"Abysmal to no information"* leading to *"ambiguous causality."*

➢The MA holder would like more information on the medical event such as:

- ➢What led up to the incident
- ➢Timing of administration of the product
- ➢The outcome / quality of recovery
- ➢Dose used (rather than weight of patient)

Digging deeper

1. Clinical Summaries (contd)

- The additional information surrounding the event was not considered to be available elsewhere but would be required to make a true assessment. Other Member States that were considered to provide more detailed information and *"excellent reports"* were Belgium, Finland and Sweden.

2. PSURs – *"Gold Plating"* (1 MA holder)

- The VMD requests annual sales figures (calendar year). This is believed to be a local requirement and to be above what is specified in Volume 9B.

Digging Deeper

3. Notifying MA holders of all suspected adverse events received by the VMD (1 MA holder)

- Some adverse events may be reported directly to the VMD e.g. by a vet in practice. One MA holder did not have confidence that MA holders were notified of all Suspected Adverse Events received by VMD. MA holders are required to submit Periodic Safety Reports but without such information any reports submitted by an MA holder would be incomplete. Other MS?
- Although serious adverse events were reported on the Eudra Vigilance link. This link a) did not include less serious cases and b) the website is *"the least user-friendly website"* so cases were not easy to pick up.

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Suspected Adverse Reaction Surveillance Scheme (SARSS)

- 30 years old (1984)
- Voluntary, not mandatory
- Over 55,000 reports
- 3877 reports in 2011
- 6000 reports in 2014?
- TIGRESS
  - Totally Integrated Graphical Relational Electronic Surveillance System

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How the team has evolved

1. Change of team name
2. DDPS assessment integrated
3. Stopped deleting duplicates
4. PSUR worksharing rejoined
5. PSUR assessment reports started
6. Microchip adverse event scheme
7. Increased resources (2 vets, 1 admin)
8. Started sending ALL reports to EV Vet
9. More effort to identify products - assumptions
10. Shared mailboxes introduced
11. Tigress tracker introduced
12. Case assessment processes improved
13. PhV inspections restarting

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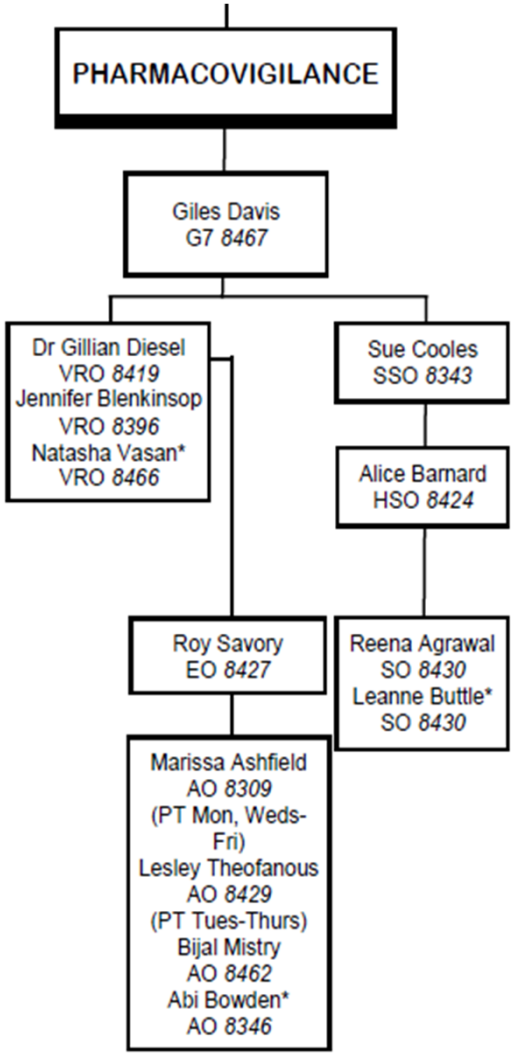
Meet the Team

- Giles: Head of team, PhVWP
- Gillian: Animal reports, PRR
- Natasha: PhV inspections
- Jen: PSURS
- Sue: human reports, articles
- Alice: DDPS, PSURs
- Roy: Head of admin
  - Lesley, Marissa, Bijal, Abi (Carole)
- Leanne: PSURs (covering for Reena)



Vets Scientists Admin

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Looking ahead

- Variety of Practice Management Software (PMS) companies in UK
- VetXML code allows transmission of data between practices, insurance companies, microchip databases etc
- Automated adverse event reporting? Positive feedback.
- Schema now written, currently being shared with PMS providers for comment.

vetxml CONSORTIUM

ENDORSED BY SPVS

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More change is afoot…

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What? Why?

- Government information in one place, simple, clear and fast for users
- So far all 24 Ministerial departments,

  >100 other agencies & public bodies
- VMD was set to transition fully by end of the year but brought forward to **8am tomorrow**!

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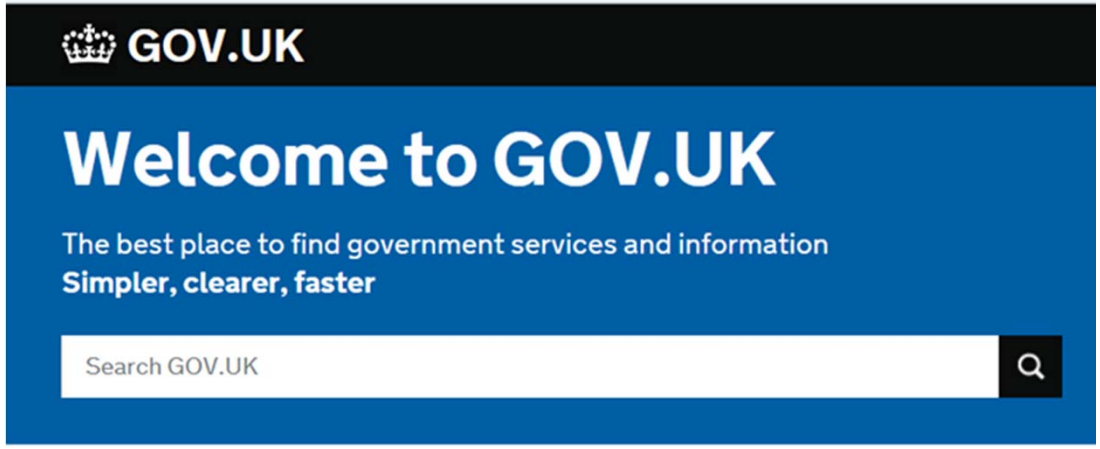
How does GOV.UK work?

- **Search**

  or

- **Navigate**



- 2 types of information:
  - mainstream - aimed at the general public
  - agency – detailed, niche or requiring expert knowledge

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Managing the transition

- Home page at www.gov.uk/government/organisations/veterinary-medicines-directorate
- Page redirects
- VMD site will be extinct except for databases
- Spring cleaning content, then:
  - continuous improvement based on **feedback** and analytics

Is there anything wrong with this page?

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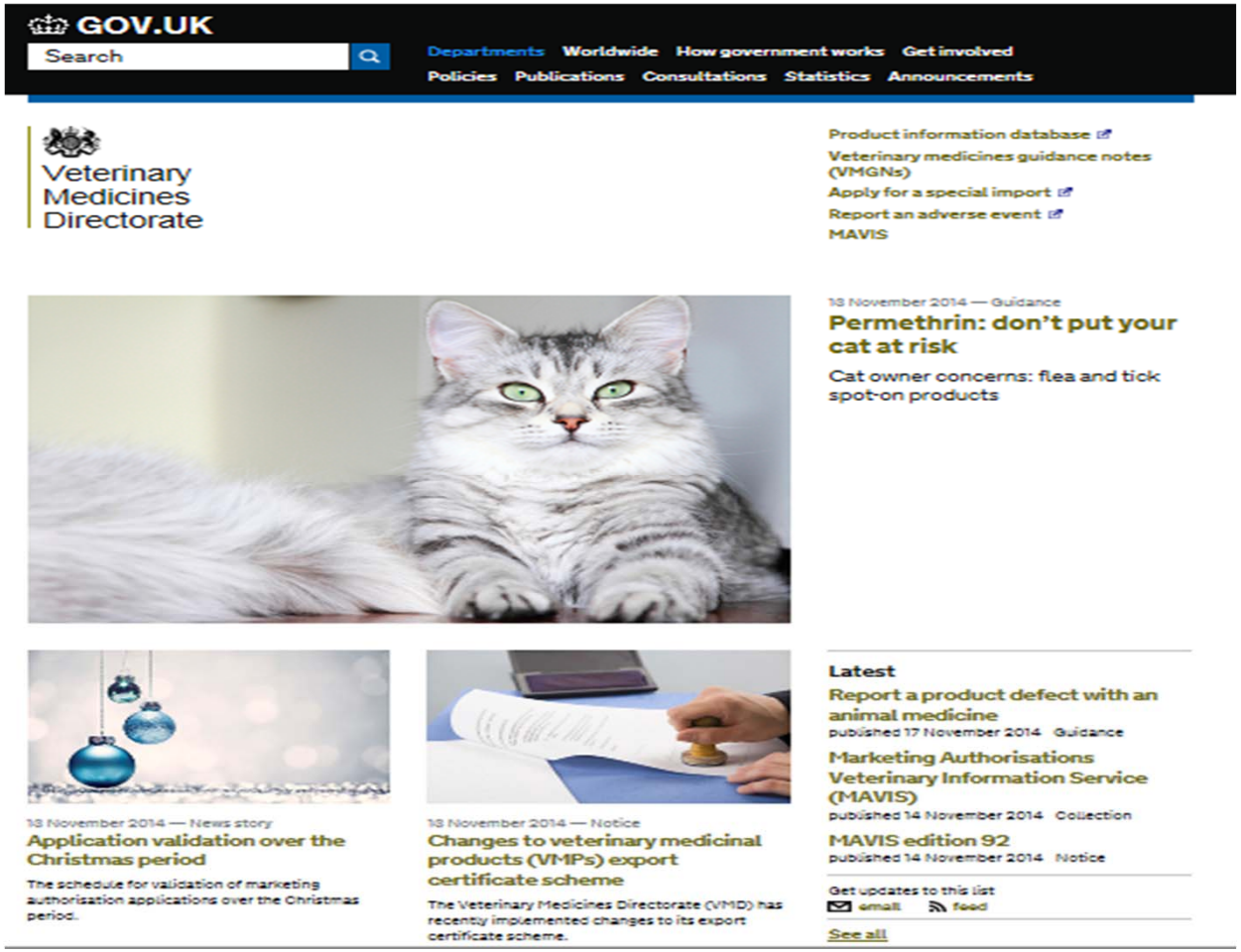
Our New Online Presence



We will send a link for our presentations out to you all once we have uploaded them!

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Any Questions?

Please wait for the microphone and state your name and company.

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DDPS Assessments

Alice Barnard

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Veterinary Medicines Directorate

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Overview

- What the VMD expects
- Product Specific Addendum
- Common CMS Questions
- DDPS Declaration
- Variations

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What the VMD expects

- The DDPS should:
  - Cover all points mentioned in Volume 9B section 2.3
  - Provide confirmation of agreements with distributors to report adverse events
  - More than one person registered with EudraVigilance
  - Be concise and clear
  - Be controlled by a quality management system
    - Do not include SOPs, just refer to them

Product Specific Addendum

- Only required if pharmacovigilance activities are different to those described in the company DDPS
  - It should include:
  - How adverse events are reported and where the data are stored
  - How reports received by the MAH will be communicated to the person responsible for the product (QPPV)
  - If another MAH is responsible for the pharmacovigilance activities only one DDPS should be provided in the application

Common CMS Questions

- Change all references to adverse reaction to adverse event
- Include reference to coding practices

  eg. Reference should be made to the use of VeDDRA terminology and ABON system for the coding and causality assessment of adverse event reports.
- Frequency of Phv training
- Auditing of sub-contractors
- Archiving periods – life of the product should be minimum

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DDPS Declaration

The VMD is taking part in the CMDv pilot scheme for using a DDPS declaration.

- This gives the option for a company to submit a declaration that the DDPS provided has been previously assessed and accepted by a national competent authority or the EMA during a MRP/DCP or centralised procedure
- The declaration should be submitted alongside the DDPS in Annex 5.20

DDPS Declaration

- Further information is available on
- www.hma.eu/150.html?&L=0
- Which includes pilot declaration instructions EMA/CMDv/45777/2014
- DDPS Declaration Form EMA/CMDv/576898/2013

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C.I.9 Phv Variations

- An application for a Type 1A$_{IN}$ variation must be submitted
  - If the QPPV or named deputy changes
  - Changes in safety database, contractual agreements (covered in the DDPS) and change of site where Phv activities are carried out.
  - When the DDPS is updated following the assessment of the same DDPS during another procedure

C.II.7 Phv Variations

- When a change in legal entity occurs or a transfer of MA occurs a variation to introduce a new DDPS is required.
  - An application for a Type 1B variation should be submitted if the DDPS has been assessed by the relevant NCA
  - An application for a Type II variation must be submitted for a DDPS which has not been previously assessed.

Any questions?

Thank you!

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Duplicates and Nullifications

Roy Savory

Pharmacovigilance (PhV) Administration Team

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Duplicate SAEs

- Duplicate adverse events are like taxes. . . . Inevitable and in most instances are unavoidable.

Reasons for duplicate SAEs

- Sources – vets, animal owners
- Destinations - NCAs and MAHs.
- Products – combined use of different MAHs VMPs.

Important aspects of duplicate SAEs

- Detection – identifying duplicates.
- Communication – notifying all parties as soon as possible of duplicates.
- Handling – Reducing burden to all parties involved.

Challenges detecting duplicate SAEs

- Differing/unidentifed products.
- Treatment and reaction date discrepancies.
- Full animal details versus limited animal information.
- Clinical case detail discrepancies.
- Varied primary source reporters – Example: Vet reports to one party and the animal owner reports to an other.

VMD's historic detection and handling of duplicates

- Manual searches only of matching product names, reaction dates, matching veddra terms and post codes.
- Single case assessor recognising previously assessed case details.
- Duplicate cases were deleted from the PhV system and VMDs local case refs recycled.
- MAHs complained about the trend of always retaining our version of the SAE.
- VMD's (infamous) Yellow forms – asking the question to the reporter 'has informed the manufacturer been informed', but ignoring the answer!

Other previous but more recent issues – 2013/early 2014

- Significantly increased numbers of SAEs reported to the VMD lead to…
  - Long turn around of SAEs.
  - Late sending to MAHs.
  - Processing targets likely to have effected manual duplicate searches.

Here and now - Improvements

- Increased staff resources.
- 'Has the manufacturer been informed' question added to the online reporting form, and is now the first section of the report that is looked at. This process has even prevented quadruplicate cases!
- Timely forwarding of SAEs to MAHs.
- Simple automatic duplicate detection emails in place to compliment a more robust manual duplicate detection process.
- No longer delete duplicate SAEs – nullification process adopted.

Additional improvements to be implemented

- Automatic duplicate detection notifications to be incorporated directly in to PhV database, rather than via email.
- To gain EMA's duplicate detection algorithm and improve our own automated checks.

A Big thank you…

- To the majority of MAHs who now transmit reporter initials and first parts of postcodes.
- To those MAHs who do not yet routinely transmit this data, please do so as soon as possible!

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Interesting Facts from the period 01/01/14 – 11/11/14

- 110 SAE records received to the VMD have been nullified due to being duplicates.
- Sounds a high volume of duplicate SAEs, BUT considering the 5,151 SAEs received to the VMD, it is a fraction over 2% of cases.

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Of the 110 duplicates. . .

- 29 Original and duplicate sources were MAHs.
- 24 Original and duplicate sources were both the VMD.
- 57 Original and duplicate sources were MAH and VMD . . .
- . . .Of these 57, 36 MAH cases were retained as the master case and 21 VMD cases were retained as the master case.

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What to do if MAH receives SAE and is notified VMD already informed

- Historically some instances occurred where MAH was notified by reporter that VMD had already been informed of the case (even providing VMD case ref) but MAH didn't contact the VMD to prevent a possible duplicate. Instead, MAH just expedited their version to VMD.
- Best practice - contact the VMD immediately, ideally initially by telephone to check and confirm if we have received the SAE.

Important notes:

- If VMD receive a yellow form and are made aware the reporter has already informed MAH of SAE, and MAH confirms receipt, VMD will request that MAH's case is expedited to the VMD, even if SAE is considered non serious. We will add our data to MAH case and send back as a follow up, rather than inputting our case and creating duplicates for duplicates sake.

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Important notes cont. . .

- If MAH receives a duplicate case from VMD before MAH has sent their case version to VMD, do not expedite MAH case to VMD. Instead, add MAH case details to VMD case and send back to VMD as a follow up.

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Nullifications

- Soon after VMD adopted nullifying SAEs, on more than one occasion two MAHs nullified opposite cases. Decision was made for the VMD to expedite all nullifications to avoid this situation.
- Since then it has become evident this creates an additional burden. Therefore, following confirmation of which case is to be retained/nullified, we are now more flexible and will agree for MAHs to locally nullify SAEs if that is their preference.

Considerations which SAE is to be the master case and which to nullify

- Dates which SAEs were sent and received.
- Quality and quantity of clinical data.
- How many parties have received each case – if many MAHs have a version of one case and only one MAH has the version of the other, generally the master case will be the one which has been received by the many.

Nullifications – important information

- Nullifications are a requirement of Volume 9b.
- Nullification does not mean deletion.
- 'Unique case registration numbers' and 'Report identification numbers' should never be changed.
- Primary source reporters should never be changed and must remain as reported in the master case.
- Master cases and nullified cases should be linked to each other in Eudravigilance systems.

Other News

- Please note we have a new adverse event email address for SAE enquiries - adverse.events@vmd.defra.gsi.gov.uk

- Support using EVVET Eudravigilance system – I am going to be working closely with some MAHs and the EMA to highlight and provide support for user problem areas. Please let me know by email of any issues you are facing using the system.

Thank you!

Any questions?

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Data Quality

Human AE reports

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Data Quality

The devil is in the detail

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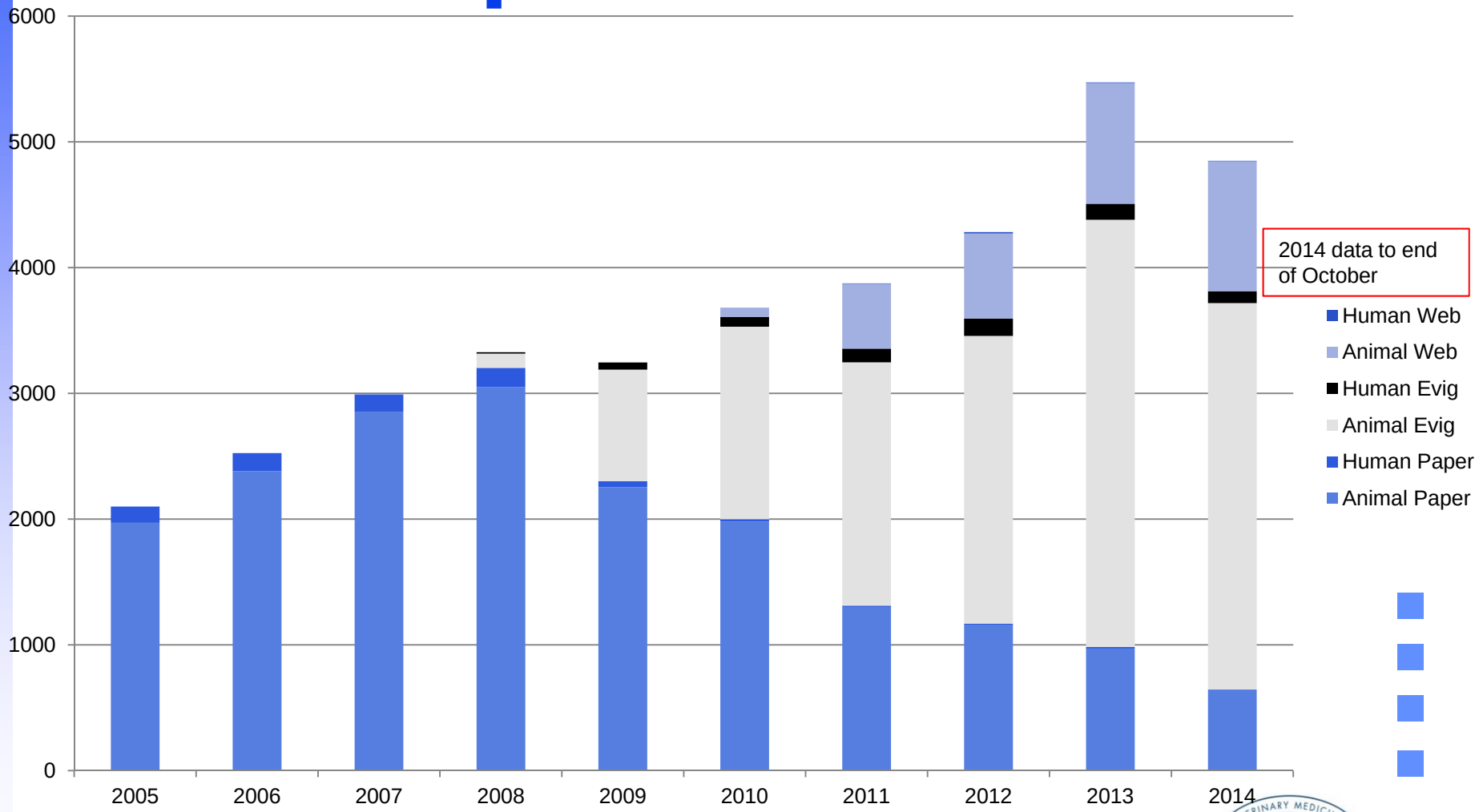
AE reports received



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2013 data

- VMD received 5473 AE reports
- 5329 animal reports (144 human)

Source	# reports
Company	3425

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2013 data

- VMD received 5473 AE reports
- 5329 animal reports (144 human)

Source	# reports
Company	3425
Vet practice	1712

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2013 data

- VMD received 5473 AE reports
- 5329 animal reports (144 human)

Source	# reports
Company	3425
Vet practice	1712
Other	192

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2013 data

- VMD received 5473 AE reports
- 5329 animal reports (144 human)

Source	# reports	proportion
Company	3425	64%
Vet practice	1712	32%
Other	192	<4%

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Incident information

Source	# reports	+ve product ID
Company	3425	99.9%
Vet practice	1712	98.7%
Other	192	94.8%

Incident information

Source	# reports	+ve product ID	Insufficient info (O)
Company	3425	99.9%	23.0%
Vet practice	1712	98.7%	7.2%
Other	192	94.8%	14.6%

Comparison of Evig, paper and online reports (2013)

Time to onset of reaction = unknown

Overall 6.5% of reports

Source	% unknown onset time
Evig	7.1%
Paper	6.7%

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Comparison of Evig, paper and online reports (2013)

Time to onset of reaction = unknown

Overall 6.5% of reports

Source	% unknown onset time
Evig	7.1%
Paper	6.7%
Web	4.0%

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Comparison of Evig, paper and online reports (2013)

Adverse reaction duration = unknown

Overall 64.5% of reports

Source	% unknown reaction duration
Evig	66.4%

Comparison of Evig, paper and online reports (2013)

Adverse reaction duration = unknown

Overall 64.5% of reports

Source	% unknown reaction duration
Evig	66.4%
Paper	92.7%

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Comparison of Evig, paper and online reports (2013)

Adverse reaction duration = unknown

Overall 64.5% of reports

Source	% unknown reaction duration
Evig	66.4%
Paper	92.7%
Web	29.2%

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Case narratives

- These are summaries of cases
- The detail can be found in other Eudravigilance fields, which can be searched to allow comparison of cases with similar features
- It is time-consuming for us to transcribe case details from the narrative to the appropriate fields prior to transmission to the central database

Human Adverse Event reports

Veterinary Medicines Directorate

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Human AE reports

- Patient identification
- Gender
- Age, adult/child
- Occupation
- Dates of exposure and reaction
- Product details
- Type of exposure

Human AEs again

- A brief, but informative, description of the course of events
- Outcome of the incident
- Contact details of any professional help sought
- MAH conclusions on the reaction, including involvement of product
- Animals treated information
- ID/contact details of reporter

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Particular areas of concern

- Case narrative
- Outcome of a case
- Needle stick injuries
- Patient ID
- Categorisation
- Type of exposure

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We are trying to improve the information we transmit

- Overhauling our import and export routines
- Let us know if you do not get what you expect from a report
- We can’t improve if you do not tell us where we are falling short

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Thank you

Do you have any questions?

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Adverse Event Reporting (Animals)

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Veterinary Medicines Directorate

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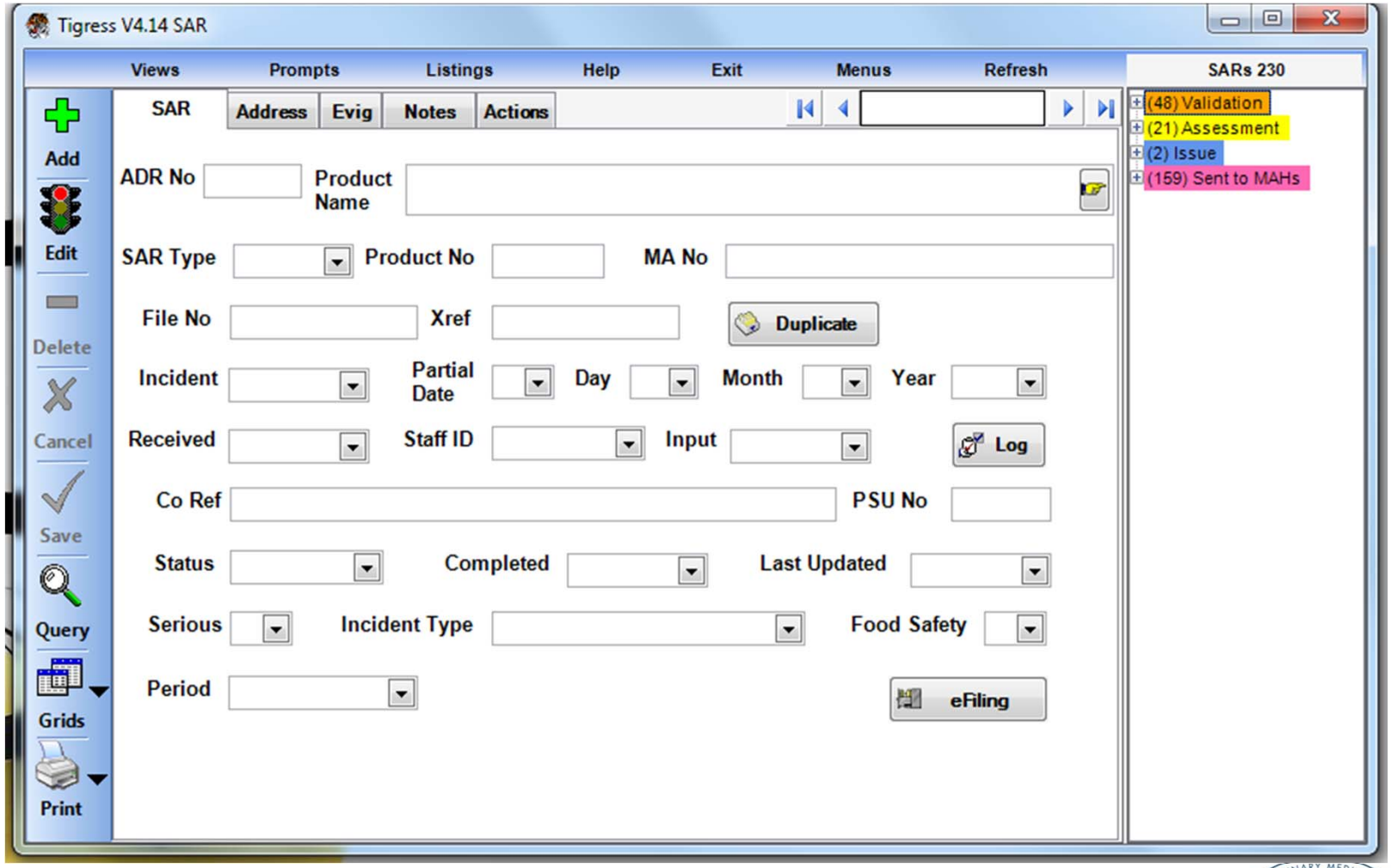
Overview

- Modular system (TIGRESS)
- Overview of Tigress
- Issues relating to data received/sent in adverse event reports
- Solutions to problems
- Questions

Tigress

- Bespoke modular system
- Been used by the VMD since the 1980s
- Supported internally by IT and development team, which means that adjustments can be made relatively quickly and easily (depending on the adjustment of course!)
- Includes a tracking system to monitor work flow and workloads – current processing levels of reports approximately 6000 serious adverse event reports (including SLEEs) per year

Tigress



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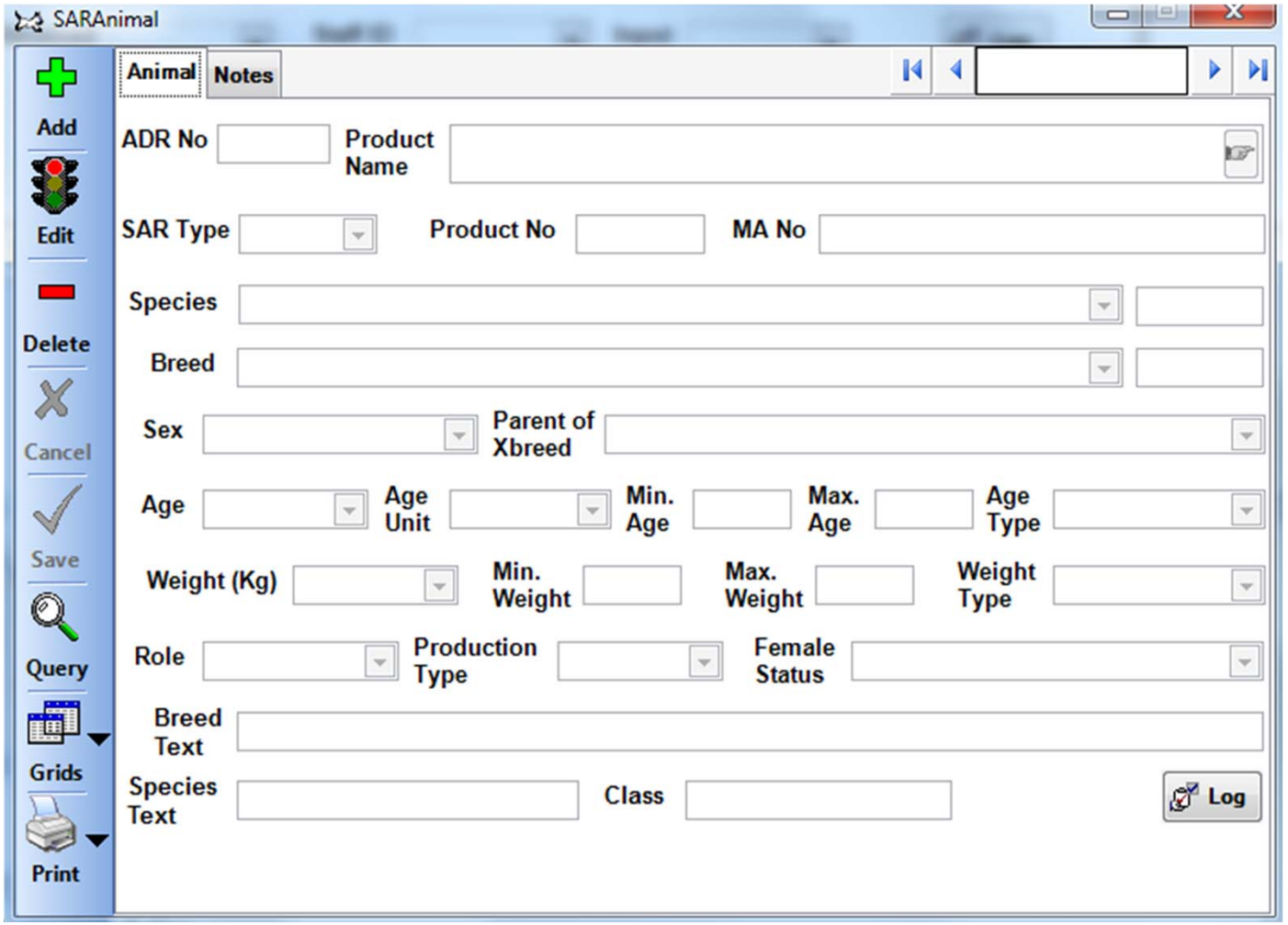
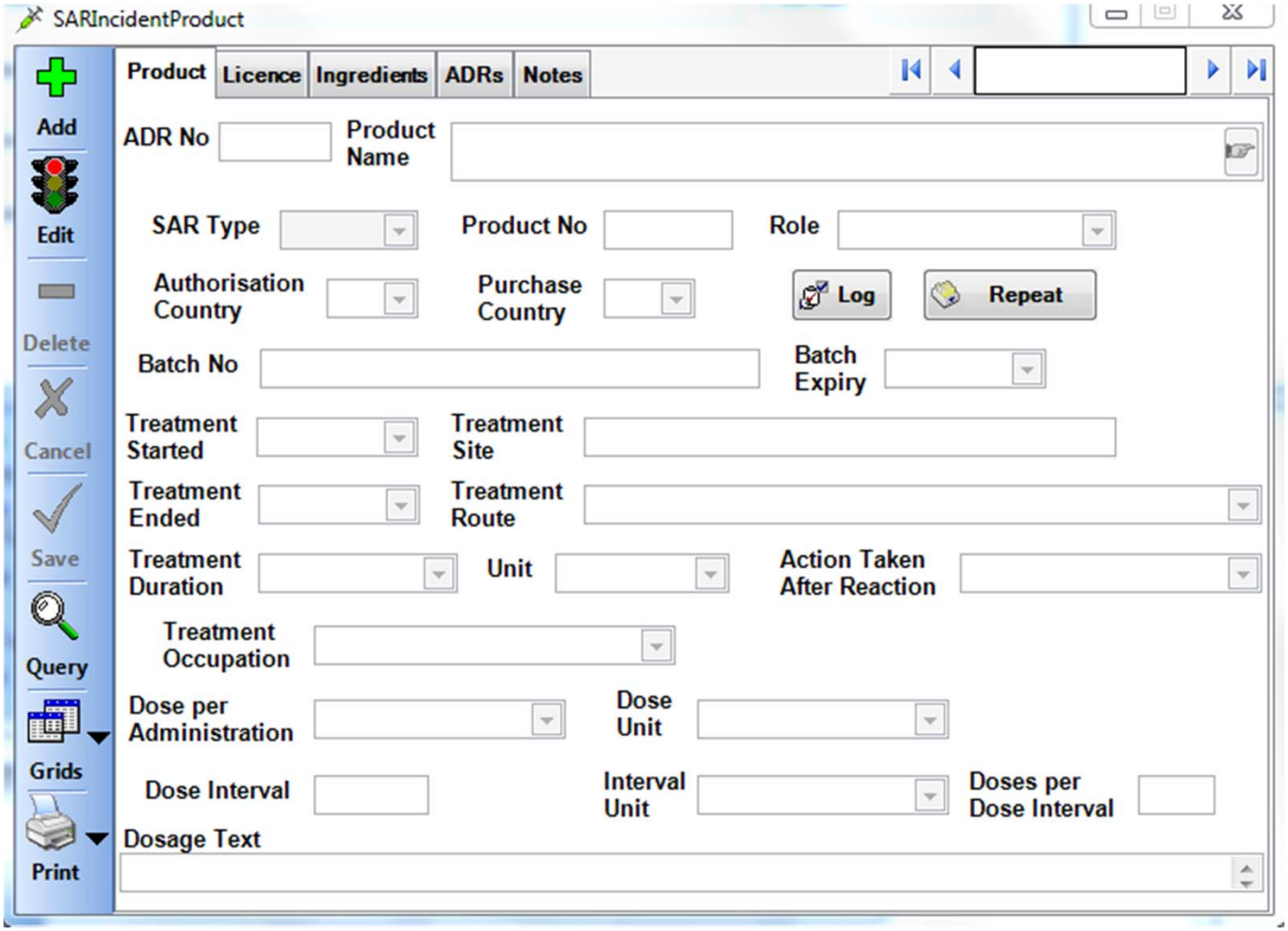
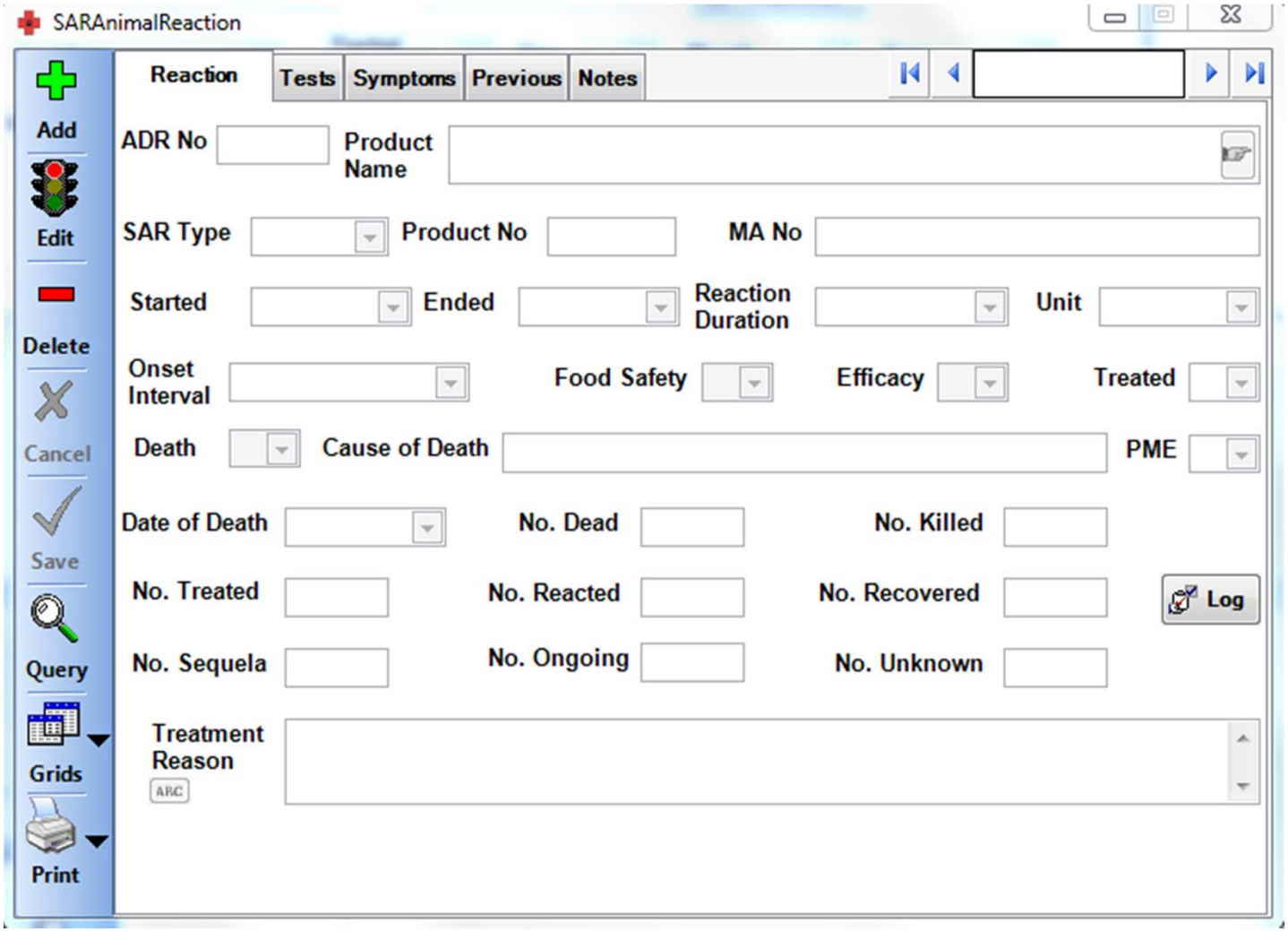


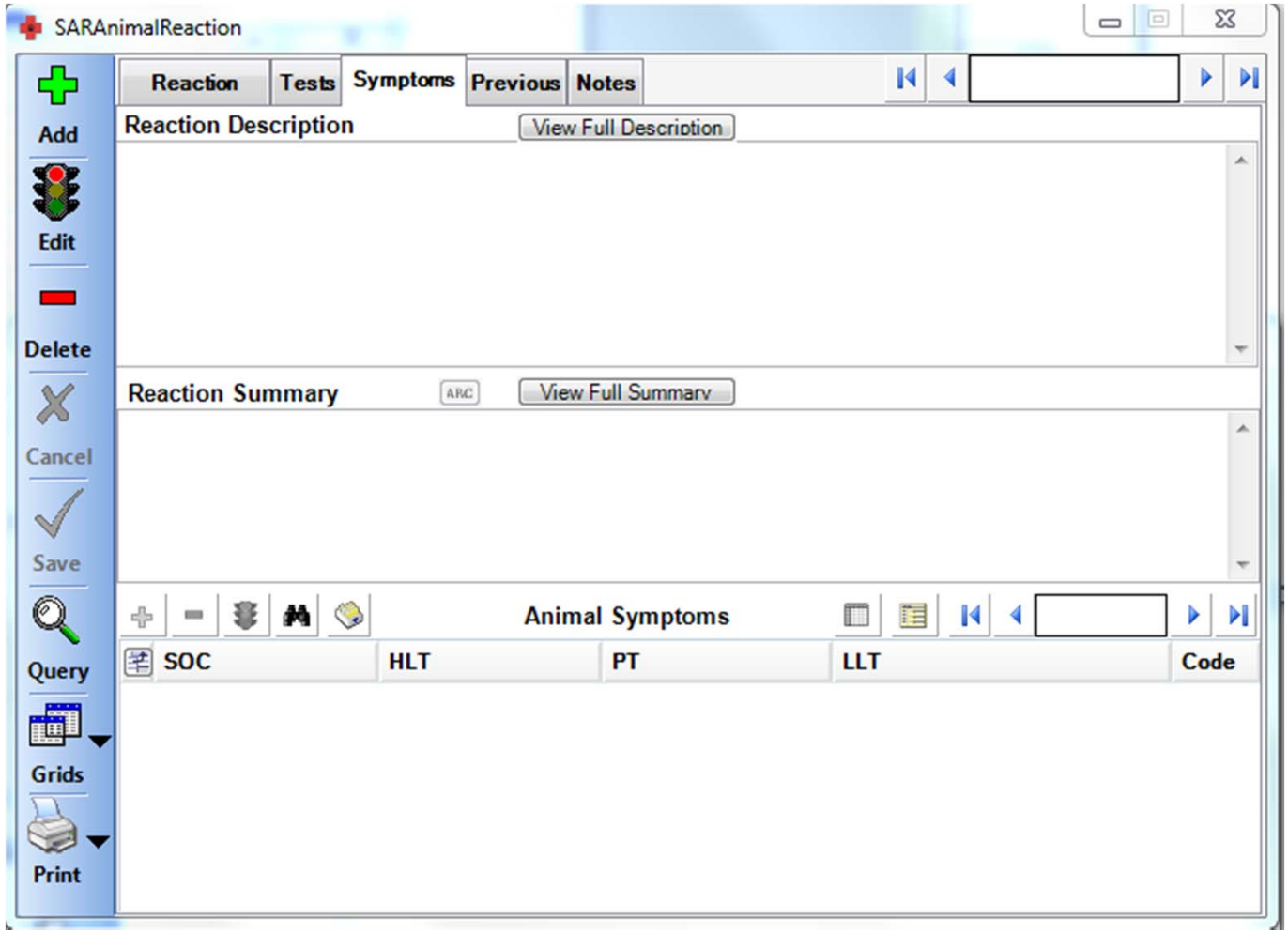
ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES



ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES



ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES



ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

So given our inputs and processes, what difficulties do we run into?

- Dates for Veddra codes
  - Variations between databases
- How does the VMD structure case narratives?
  - Succinct, chronological summary of the case
  - Using PTs vs LLTs in narratives
  - Non native English speakers eg 'put to sleep'
- Reasons for causality assessments
  - The VMD is not required to provide justification
  - Requirement for justification of the causality codes by the MAH

- Assessing products – that aren't products of the MAH
  - Only required to assess your own products
- Are changes to cases made by the MAH permissible to the VMD
  - Yes
  - Any updated information should be communicated via a follow up report, sent through Eudravigilance
- Adverse reaction reporting vs SLEE reporting with respect to vaccinations
  - The VMD treats these reports in the same manner

- Product naming
  - Use local names that are used in the country that it is reported to
- Reporting adverse events associated with ATCs in the UK
  - Serious adverse events from these studies (test or control product) should be expedited within 15 days
  - If there is an ATC assigned, report to the VMD electronically as 'Report from Study'
- Third country reporting
  - Should be reported to the competent authority in the country where the reaction occurred, then submitted in the PSUR for that product

Shared Mailboxes

adverse.events@vmd.defra.gsi.gov.uk

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

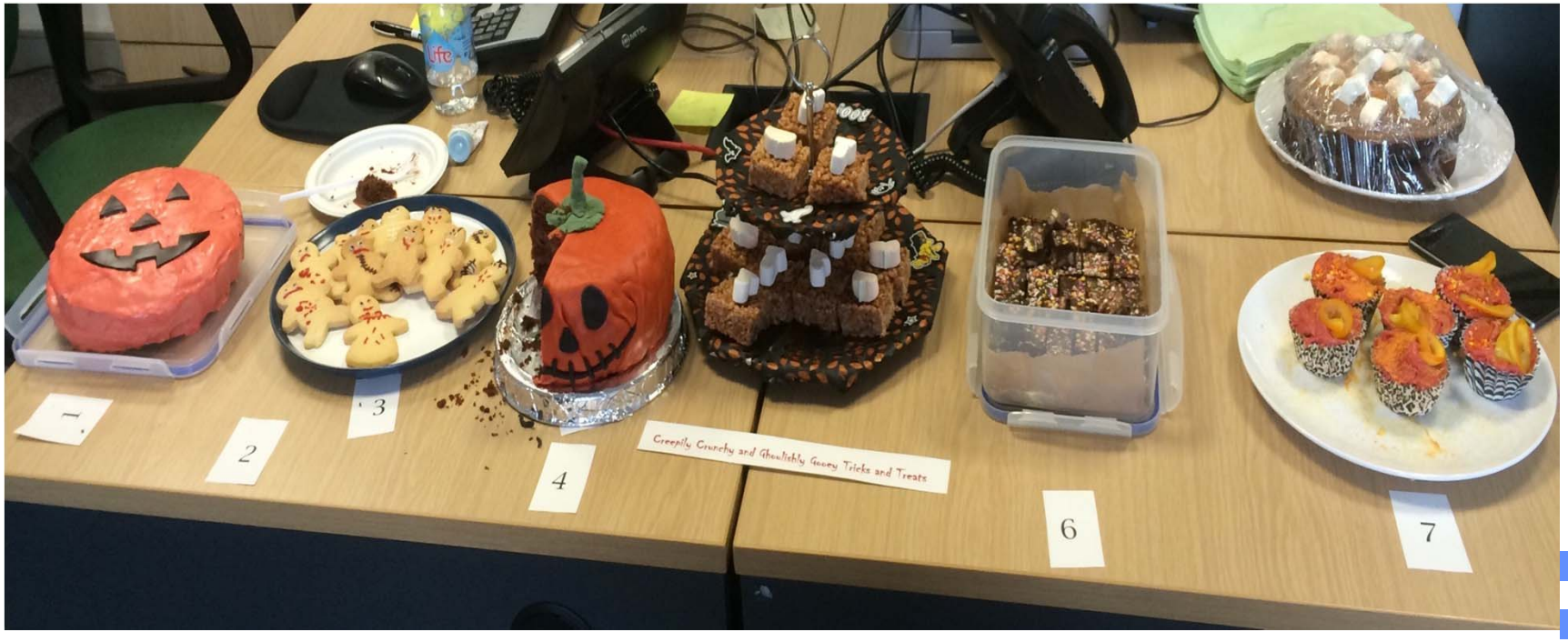
ANY QUESTIONS?

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Lunch is served....

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

...in Room 6



Don’t be scared to talk to us!

VETERINARY MEDICINES VMD DIRECTORATE

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Useful contact details

adverse.events@vmd.defra.gsi.gov.uk

for any queries relating to duplicates and case assessments.

psur.submissions@vmd.defra.gsi.gov.uk

for submitting PSURs (best by Eudralink)

psur.queries@vmd.defra.gsi.gov.uk

for any queries relating to PSURs

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Welcome back!

Veterinary Medicines Directorate

VETERINARY MEDICINES VMD DIRECTORATE

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Please bee seated....

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Signal Detection at the VMD

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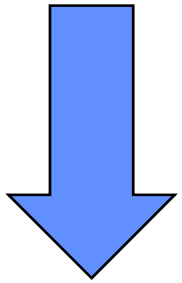
Veterinary Medicines Directorate

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

What is signal detection?

Signal detection is the process of identifying possible new safety or efficacy issues or sudden changes in the frequency of already known adverse events.

What do we do when we detect a signal?



Signal Management

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Signal management

Signal detection

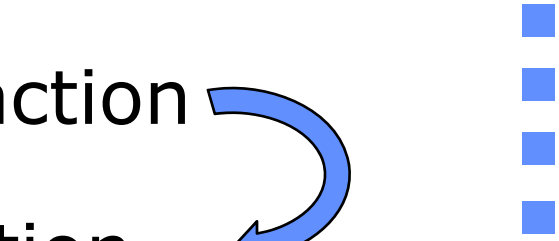
Signal validation

Signal prioritisation

Signal evaluation

Recommendation for action

Exchange of information



ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Methods of signal detection used at the VMD

- Manual assessment of every case, trends detected by assessors
- Automated signal detection
- Individual ADRs of major concern
- Review of PSUR data
- CAPs surveillance using data from EVVet
- Communication with MAHs, other NCAs, vets, other teams in the VMD

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Automated signal detection

Proportional Reporting Ratio (PRR)
= a measure of disproportionality

A signal is a product-VeDDRA term combination which is statistically significant where:

More than 3 cases

PRR>2

LCL>1

Proportional Reporting Ratio (PRR)

	Reports including VeDDRA term ‘y’	Reports not including VeDDRA term ‘y’
Reports involving product ‘x’	A	B
Reports not involving product ‘x’	C	D

$$\text{PRR} = \frac{A/(A+B)}{C/(C+D)}$$

LCL = 95% Lower Confidence Limit

UCL = 95% Upper Confidence Limit

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Proportional Reporting Ratio (PRR)

- Advantages:
  - Simple
  - Easy to understand

- Disadvantages:
  - Based on number of reports, not number of animals
  - Denominator has a big impact on results (background data)
  - High sensitivity, low specificity (lots of false-positives)

Approach to Analysis

- All reports are included in the analysis, including those coded 'N'
- PRR analysis is split by species
  (companion animals / production animals)
- Lack of efficacy reports analysed separately to safety reports (this is done based on the VeDDRA term "lack of efficacy").

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	164	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	261	35	34513	25.78209	11.55494	57.5266	3	3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5	45	137	34629	25.37664	10.86606	59.26474	3	3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	9.122551	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5	273	27	34511	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4	143	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4	4	801	34007	21.72784	10.82932	43.59453	3	3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	164	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	261	35	34513	25.78209	11.55494	57.5266	3	3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5	45	137	34629	25.37664	10.86606	59.26474	3	3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	9.122551	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5	273	27	34511	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4	143	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4	4	801	34007	21.72784	10.82932	43.59453	3	3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	164	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy											248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self tra											36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen											38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism											245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis											138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritu											4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia											34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism											224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision											33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer											115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension											51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phos											149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflamm											14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination											99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy											224	29	33252	15.16679	4.653406	49.43296

Product	PT
Product A	Oral haemorrhage
Product B	Paralysis
Product C	Skin and/or appendage neoplasm NOS
Product D	Bacterial skin infection
Product B	Weight gain
Product E	Hyperaesthesia

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
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Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
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Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	9.122551	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5	273	27	34511	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4	143	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
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Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5	45	137	34629	25.37664	10.86606	59.26474	3	3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	[illegible]	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product [illegible]	Hypothyroidism	5	5	273	27	[illegible]	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
[illegible] Product K	Skin necrosis	4	4	[illegible]	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4	4	801	34007	21.72784	10.82932	43.59453	3	3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

Product J	Hypothyroidism
Product K	Skin necrosis
Product E	Application site pruritus
Product A	Hyperglycaemia
Product L	Hypothyroidism

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	[illegible]	4	17	62	[illegible]	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	164	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	261	35	34513	25.78209	11.55494	57.5266	3	3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5	45	137	34629	25.37664	10.86606	59.26474	3	3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	9.122551	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5	273	27	34511	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4	143	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4	4	801	34007	21.72784	10.82932	43.59453	3	3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.[illegible]								1.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.[illegible]								7.43513	138.051
Product C	Skin and/or append[illegible]ge neoplasm NOS	5	5	61	54	34696	48.7514	20.[illegible]								0.31658	99.81997
Product D	Bacterial [illegible]kin infection	5	4	15	164	34633	44.66881	18.[illegible]								3.32283	106.3666
Product B	W[illegible]ght gain	4	4	254	16	34542	33.48643	11.[illegible]								.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.[illegible]								0.18641	61.47853
Product [illegible]	Proprioception abnormality	4	4	41	106	34665	29.15807	11.[illegible]								.628511	70.04945
Pro[illegible]						34513	25.78209	11.[illegible]								.202546	44.70465
Pro[illegible]						34629	25.37664	10.[illegible]								.689366	60.47751
Pro[illegible]						34644	23.67251	9.1[illegible]								.059719	51.64751
Pro[illegible]						34511	23.00693	8.9[illegible]								.894243	51.77932
Pro[illegible]						34626	21.93893	7.9[illegible]								.839693	47.602
Pro[illegible]						34007	21.72784	10.[illegible]								.028878	44.68572
Pro[illegible]						34599	19.64746	7.6[illegible]								.888399	43.44552
Pro[illegible]						34530	19.13511	6.7[illegible]								.291544	69.72487
Pro[illegible]						34580	17.74286	6.9[illegible]								.054519	44.97566
Pro[illegible]						34568	16.63846	6.0[illegible]								.666102	61.54253
Pro[illegible]						34606	16.12245	6.1[illegible]								.275457	39.50904
Pro[illegible]						34595	14.50262	5.3[illegible]								.50001	45.51705
Pro[illegible]						34386	14.28243	5.8[illegible]								.528261	43.52737
Pro[illegible]						34618	14.2586	5.3[illegible]								.991998	38.74776
Pro[illegible]						34520	14.09955	5.0[illegible]								.653406	49.43296

Reacted	A	B	C	D
5	4	17	62	34733
4	4	14	136	34662
5	5	61	54	34696
5	4	15	164	34633
4	4	254	16	34542
6	4	5	525	34282

	Reports including veddra term ‘y’	**Reports not including veddra term ‘y’**
Reports involving product ‘x’	A	B
Reports not involving product ‘x’	C	D

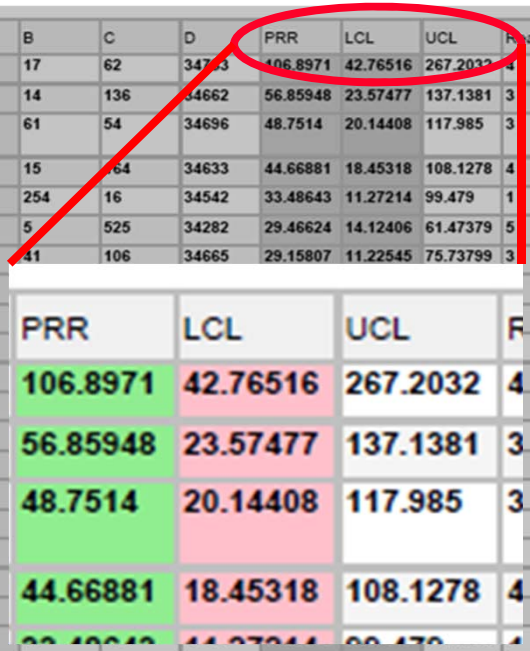
ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	164	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	261	35	34513	25.78209	11.55494	57.5266	3	3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5	45	137	34629	25.37664	10.86606	59.26474	3	3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	9.122551	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5	273	27	34511	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4	143	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4	4	801	34007	21.72784	10.82932	43.59453	3	3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34723	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	64	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7								3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5								3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4								1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5								2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4								2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4								3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4								2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4								3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4								3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4								2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4								3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4								3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4								3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296



VETERINARY MEDICINES DIRECTORATE VMD

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Analysis to detect new signals

- The analysis is run for 2 time periods, which are then compared and only new signals listed
- Time period difference – 4 months
- We also have a signal log, listing all previously detected signals, where it is considered necessary that further monitoring is required

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	[illegible]348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	164	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	261	35	34513	25.78209	11.55494	57.5266	3	3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5	45	137	34629	25.37664	10.86606	59.26474	3	3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	9.122551	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5	273	27	34511	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4	143	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4	4	801	34007	21.72784	10.82932	43.59453	3	3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	[illegible]	4	3	16	58	33431	91.16788	[illegible]	[illegible]
Product B	Paralysis	4	4	14	136	34662	56.85948	[illegible]	137.1381	3	3	13	128	33364	49.06055	17.43513	[illegible]
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	[illegible]	20.14408	117.985	3	3	56	53	33396	32.0905	[illegible]	99.81997
Product D	Bacterial skin infection	5	4	15	164	[illegible]	44.66881	18.45318	108.1278	4	3	14	157	33334	[illegible]	13.32283	106.3666
Product B	Weight gain	4	4	254	[illegible]	34542	33.48643	11.27214	99.479	1	1	226	14	33267	[illegible]	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	[illegible]	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	261	35	34513	25.78209	11.55494	57.5266	3	3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6												33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4												33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5												33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4												33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4												32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4												33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4												33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4												33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4												33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
4	3	16	58	33431	91.16788	31.27774	265.7348
3	3	13	128	33364	49.06055	17.43513	138.051
3	3	56	53	33396	32.0905	10.31658	99.81997
4	3	14	157	33334	37.64444	13.32283	106.3666
1	1	226	14	33267	10.47231	1.382848	79.30679

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

PRR analysis output

Product	PT	Reacted	A	B	C	D	PRR	LCL	UCL	Reacted1	A1	B1	C1	D1	PRR1	LCL1	UCL1
Product A	Oral haemorrhage	5	4	17	62	34733	106.8971	42.76516	267.2032	4	3	16	58	33431	91.16788	31.27774	265.7348
Product B	Paralysis	4	4	14	136	34662	56.85948	23.57477	137.1381	3	3	13	128	33364	49.06055	17.43513	138.051
Product C	Skin and/or appendage neoplasm NOS	5	5	61	54	34696	48.7514	20.14408	117.985	3	3	56	53	33396	32.0905	10.31658	99.81997
Product D	Bacterial skin infection	5	4	15	164	34633	44.66881	18.45318	108.1278	4	3	14	157	33334	37.64444	13.32283	106.3666
Product B	Weight gain	4	4	254	16	34542	33.48643	11.27214	99.479	1	1	226	14	33267	10.47231	1.382848	79.30679
Product E	Hyperaesthesia	6	4	5	525	34282	29.46624	14.12406	61.47379	5	3	5	502	32998	25.0249	10.18641	61.47853
Product F	Proprioception abnormality	4	4	41	106	34665	29.15807	11.22545	75.73799	3	3	40	101	33364	23.11651	7.628511	70.04945
Product G	Lack of efficacy	7	7	261	35	34513	25.78209	11.55494	57.5266	3	3	248	29	33228	13.70669	4.202546	44.70465
Product H	Application site self trauma	6	5	45	137	34629	25.37664	10.86606	59.26474	3	3	36	128	33341	20.11358	6.689366	60.47751
Product I	Fluid in abdomen	4	4	43	125	34644	23.67251	9.122551	61.42884	1	1	38	116	33353	7.398099	1.059719	51.64751
Product J	Hypothyroidism	5	5	273	27	34511	23.00693	8.925104	59.30673	2	2	245	22	33239	12.24181	2.894243	51.77932
Product K	Skin necrosis	4	4	143	43	34626	21.93893	7.977167	60.33681	2	2	138	41	33327	11.62648	2.839693	47.602
Product E	Application site pruritus	4	4	4	801	34007	21.72784	10.82932	43.59453	3	3	4	758	32743	18.94139	8.028878	44.68572
Product A	Hyperglycaemia	4	4	36	177	34599	19.64746	7.665248	50.36009	2	2	34	166	33306	11.20214	2.888399	43.44552
Product L	Hypothyroidism	4	4	254	28	34530	19.13511	6.760146	54.16336	3	3	224	21	33260	20.94462	6.291544	69.72487
Product M	Impaired vision	4	4	36	196	34580	17.74286	6.929934	45.42741	3	3	33	185	33287	15.07748	5.054519	44.97566
Product N	Corneal ulcer	4	4	204	40	34568	16.63846	6.007225	46.08424	2	2	115	38	33353	15.02069	3.666102	61.54253
Product O	Hypotension	4	4	52	154	34606	16.12245	6.189177	41.99805	3	3	51	143	33311	12.99689	4.275457	39.50904
Product P	Changes in blood phosphorous	4	4	158	59	34595	14.50262	5.330717	39.45546	3	3	149	46	33310	14.31178	4.50001	45.51705
Product B	Application site inflammation	4	4	20	406	34386	14.28243	5.807819	35.12296	3	3	14	381	33110	15.51227	5.528261	43.52737
Product E	Inappropriate urination	4	4	103	91	34618	14.2586	5.334532	38.11163	3	3	99	79	33327	12.43708	3.991998	38.74776
Product F	Lack of efficacy	4	4	254	38	34520	14.09955	5.069085	39.2176	3	3	224	29	33252	15.16679	4.653406	49.43296

Signal detection tables presented to the Alert Group

A (yellow) –potential signal suspected if no. of reports (A) is at least 3, PRR (green) – potential signal suspected if PRR is at least 2, LCL (pink) – potential signal suspected if LCL is above 1

Table 1. Statistically Significant New Signals for Dogs, Cats and Rabbits during April to July 2014

		Data up to 31/07/2014				Data up to 31/03/2014		No. new reports received	Comments	Concern
roduct	PT	Reacted	A	PRR	LCL	Reacted1	A1			
oduct A	Oral haemorrhage	5	4	106.90	42.77	4	3	1	2 out of the 4 reports involved convulsions and therefore biting the tongue is a possibility.	N
oduct B	Paralysis	4	4	56.86	23.57	3	3	1	4 reports in an 8 year period.	N
oduct C	Skin and/or appendage neoplasm NOS	5	5	48.75	20.14	3	3	2	The SPC already has warnings regarding the use of Product C in animal with pre-existing disorders	N
oduct D	Bacterial skin infection	5	4	44.67	18.45	4	3	1	4 reports in a 5 year period, SPC already states application site reactions can occur leading to pruritus and erythema.	N
oduct B	Weight gain	4	4	33.49	11.27	1	1	3	Weight gain is an expected effect following the appropriate treatment of hyperthyroidism	N
oduct E	Hyperaesthesia	6	4	29.47	14.12	5	3	1	Neurological signs are expected in dogs following off-label exposure.	N
oduct F	Proprioception abnormality	4	4	29.16	11.23	3	3	1	Only 1 new reports, all 4 reports involved concurrent products where sedation are known side effects	N
oduct G	Application site self trauma	6	5	25.38	10.87	3	3	2	Application site reactions are already listed in the SPC.	N
oduct H	Fluid in abdomen	4	4	23.67	9.12	1	1	3	3 reports involved hepatopathy and clear fluid in the abdomen, 1 reports involved blood in the abdomen due to a haemangiosarcoma of the spleen.	N
oduct I	Hypothyroidism	5	5	23.01	8.93	2	2	3	This is most likely related to an overdose.	N
oduct J	Skin necrosis	4	4	21.94	7.98	2	2	2	All 4 reports involved concurrent products, 1 report involved necrosis at the site of vaccination.	N
oduct K	Application site pruritus	4	4	21.73	10.83	3	3	1	1 new report, sign already listed in the SPC.	N
oduct E	Hyperglycaemia	4	4	19.65	7.67	2	2	2	Hyperglycaemia is commonly found in cats due to stress.	N
oduct A	Hypothyroidism	4	4	19.14	6.76	3	3	1	This is most likely related to an overdose.	N
oduct L	Impaired vision	4	4	17.74	6.93	3	3	1	Reversible neurological signs, including mydriasis, in cats are already listed in the SPC, see "blindness" below.	Monitor
oduct M	Corneal ulcer	4	4	16.64	6.01	2	2	2	1 report involved accidental application of product on the face, 1 report involved an auto-immune reaction	N
oduct N	Hypotension	4	4	16.12	6.19	3	3	1	All 4 reports involved concurrent products and anaesthesia and therefore hypotension could be expected	N
oduct O	Changes in blood phosphorous	4	4	14.50	5.33	3	3	1	3 out of the 4 reports involved renal insufficiency	N
oduct P	Application site inflammation	4	4	14.28	5.81	3	3	1	Application site reactions are already listed in the SPC.	N
oduct B	Inappropriate urination	4	4	14.26	5.33	3	3	1	Neurological signs are already listed as potential adverse effects and these may lead to urination.	N
oduct E	Application site lesion	4	4	13.22	5.32	3	3	1	Application site reactions are already listed in the SPC.	N
oduct F	Application site self trauma	4	4	13.08	4.96	3	3	1	Application site reactions are already listed in the SPC and this might lead to self trauma.	N

Approach to Validation

- All new signals are looked at by the Alert Group
- The Alert Group carries out the validation process and filters the signals
- The Alert Group highlights any validated signals that require the particular review of the VPC

Validated signals

- Further monitoring / further evaluation
- Contact MAH with our concerns

Signal detection for MAHs

- Only requirement is to have a system in place for regular review of the ADRs received – this should be described in the DDPS (this can be manual or automated).

- Measures of disproportionality often not possible for MAHs due to product portfolio.

Thank you!

Any Questions?

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

PSUR Assessments

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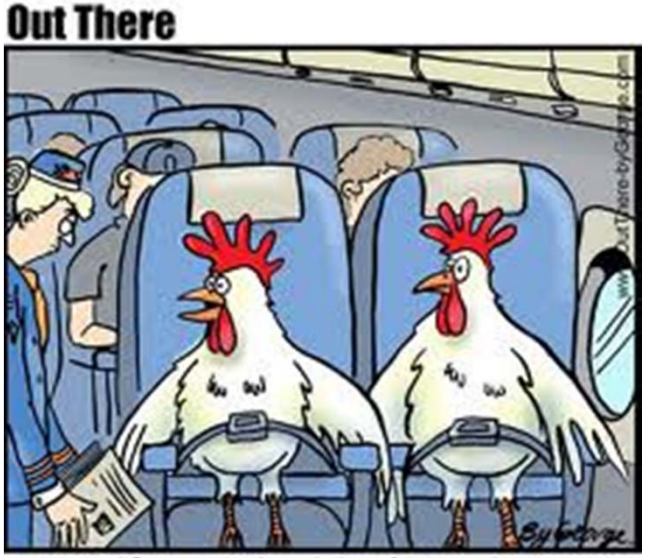
Veterinary Medicines Directorate

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Overview

1. PSUR Submission
2. Common hold-ups
3. Helpful Tips
4. Exposure Calculations
5. Expired Products
6. Reminder Letters - update
7. Work sharing: Overview
8. Work sharing: Variations
9. PSUR Waivers
10. Renewals



"Can you run through the safety procedure again...this is our first time flying"

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

PSUR Submission

Submit via:

CESP (Common European Submissions Platform)

http://cesp.hma.eu/Home

or

Eudralink PSUR Submission

psur.submissions@vmd.defra.gsi.gov.uk

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Common hold-ups

www.thegoodgoodlife.wordpress.com

- **Submit within 60 days of Data Lock Point (DLP)**
  - DLP set according to appropriate Birth Date, or as agreed between MAH & VMD

- **Combined PSURs**
  - According to legislation, each individual MA number (i.e. different dosage forms/strengths) should be provided in *separate* PSURs
  - HOWEVER… combined PSURs will be accepted, providing the sales and adverse events are clearly attributed to each individual MA.

- **Sales figures per calendar year**
  - As per 9B for 3y PSURs, and UK Veterinary Medicines Regulations (VMR)
  - The volume of the product sold in each year (covered by the report), calculated on an annual basis beginning 1st January.
  - This helps to run direct comparisons to other products that may be on different cycles.

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Helpful Tips

www.hailocab.com

- **PSUR format**
  - PDF is fine (Not PDFA's)
- **Line Listings**
  - Please provide in searchable (e.g. excel) format if more than ~20 LL
- **Date of initial placing on EEA market**
  - This is a 9B requirement, and really helps (both parties)
  - Prevents further questions…
- **Literature Searches**
  - Different expectations between MS
  - PhVWP will be producing guidance next year
- **Clarity**
  - Regarding data, calculations, and any assumptions made…

Exposure calculations

For lifelong treatments:

- CVMP guidance recommends 6 mo, therefore be prepared that most other member states will expect this
- Other time frames will be considered, as long as there is consistency between PSURs and justification for using your chosen times lines.
- NB: “dose” does not mean “dose rate” – it means dose rate x bodyweight = INDIVIDUAL DOSE

Expired products

Required to provide:

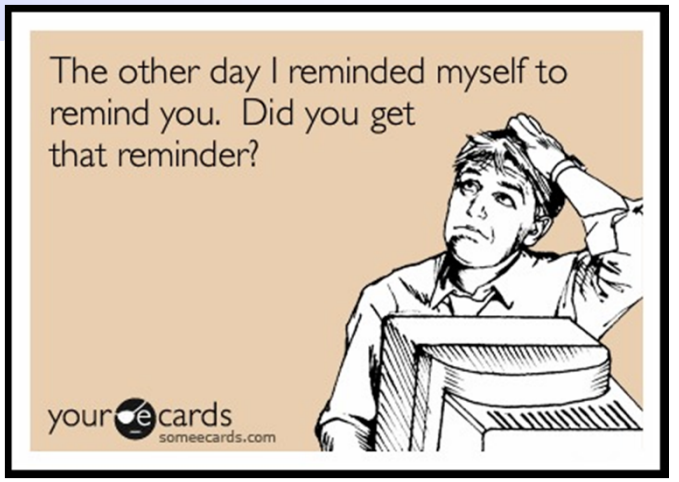
- Still require the full PSUR up until the date the MA was expired
- Sales & line listings until the end of the shelf life of the last manufactured batch

www.foodrepublic.com

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Reminder letters

An update



- Previously, reminders were sent at d30 and d60
- Now only 1 reminder will be sent at the beginning of the month of the DLP (decreasing admin, increasing assessment!)
- If PSUR is not received by 60d, this will be recorded as non-compliance, which may result in an increased frequency of inspections.
- Please let us know ASAP if you disagree with your DLP…

VETERINARY MEDICINES VMD DIRECTORATE

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Work sharing
Overview


www.honan.com.au

- Now for pharmaceutical products only, not vaccines.
- Allows the submission of PSURs for products containing the same active to NCAs at the same time
  - http://www.hma.eu/442.html
- 1 member state then acts as RMS (P-RMS)
- Thereby leading to:
  - More streamlined processes
  - Reduced administrative burden
  - One assessment as opposed to many!

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www.ipwatchdog.com

Work sharing:
Variations

- Note that some other MS have been asking for variations to change DLPs, due to recent regulations legislation
- The UK does not require a variation
- HMA have agreed that for cycles to change to EU DLP (harmonised) this should not require a variation, but if there is, it should be free

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PSUR waiver

For new products / MRP application

"…If a waiver or amendment of PSUR-cycle is applied for, to harmonise with a substance birthdate, please specify…"

- VMD encourages application for a PSUR waiver at time of initial application (as it avoids the discussion about variations). NB *may* not be accepted

- If UK is RMS or it's a national license, the VMD will investigate the possibility of work sharing and, if applicable, it will be suggested in the day 105 list of questions

Renewal Requirements

1. **Bridging Report**

summarising the data from all PSURs to date

2. **Addendum PSUR**

covering period from most recent PSUR to time of renewal application

Note:

- The Addendum PSUR will be requested if it's not present in the application
- Renewal PSURs are not part of the standard cycle

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

psur.queries@vmd.defra.gsi.gov.uk

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

What's new in Europe

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Veterinary Medicines Directorate

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

PhVWP Activities

- Signal detection
  - Recommendation paper (consultation ended)
  - Reflection paper on causality
  - Training in refinements to DataWareHouse
  - Focus Group Meeting 19th November
  - Public Bulletin - potential issues released
- Promotion of PhV reporting
  - Reflection paper (food producing spp)
- Workplan 2015
  - Literature Searches
  - Social Media

VeDDRA Subgroup

- UK developed VeDDRA, remains chair of Subgroup
- Meet annually in April to discuss proposals for new terms
- Proposals must be submitted by 1st March
- Version 11 went live 1st November
- Guidance notes published in July

EMA/CVMP/PhVWP/288284/2007-Rev.7

Lack of efficacy

SOC	HLT	PT	LLT
Systemic disorders	Lack of efficacy	Lack of efficacy	Lack of efficacy
Systemic disorders	Lack of efficacy	Lack of efficacy	Partial lack of efficacy
Systemic disorders	Lack of efficacy	Lack of efficacy	Lack of efficacy (ectoparasites)
Systemic disorders	Lack of efficacy	Lack of efficacy	Lack of efficacy (endoparasites)
Systemic disorders	Lack of efficacy	Lack of efficacy	Lack of efficacy (heartworm)

- Lack of efficacy should always be coded +/- death
- Partial lack of efficacy? consider indications
- Coding all clinical signs? PhVWP debating
- Combined report? Safety signs + lack of efficacy
- New report type foreseen by VICH….

VICH

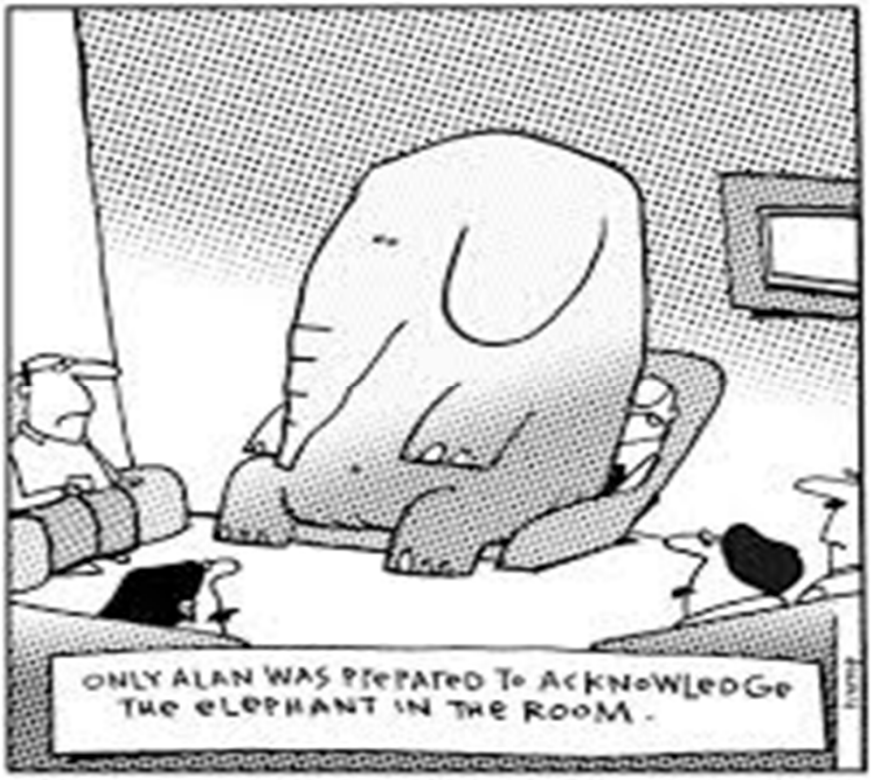
- The following guidelines were agreed years ago and are due to be implemented by the **end of December 2015**:
  - GL24 (Management of adverse event reports)
  - GL30 (Controlled list of terms)
  - GL35 (Electronic Standards for Transfer of Data)
  - GL42 (Data Elements)

- Challenge of introducing Combined Safety/SLEE reports
  - EMA have stated they will not be compliant in time
  - Therefore unlikely that we will be!
  - In meantime code as safety but include Lack of Efficacy VeDDRA code

- GL29 (PSUR management) was implemented in June 2007

BUT.....

The elephant in the room

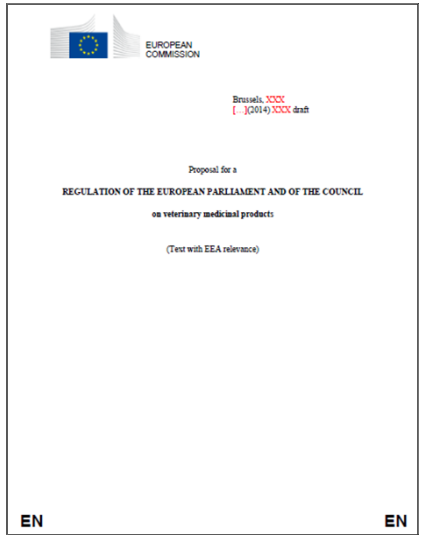


Will we have PSURs in the future?

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

The New Legislative Proposal

- A long time coming
- Published 10th September
- Some expected proposals
- Some surprises too!
- One of the key aims is to reduce administrative burden.
  - "introduces a risk-based approach to pharmacovigilance, whereby certain requirements that do not contribute effectively to public health, animal health or environmental protection (e.g. submitting periodic safety update reports) are relaxed."


EUROPEAN COMMISSION

Brussels, XXX
[...](2014) XXX draft

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on veterinary medicinal products

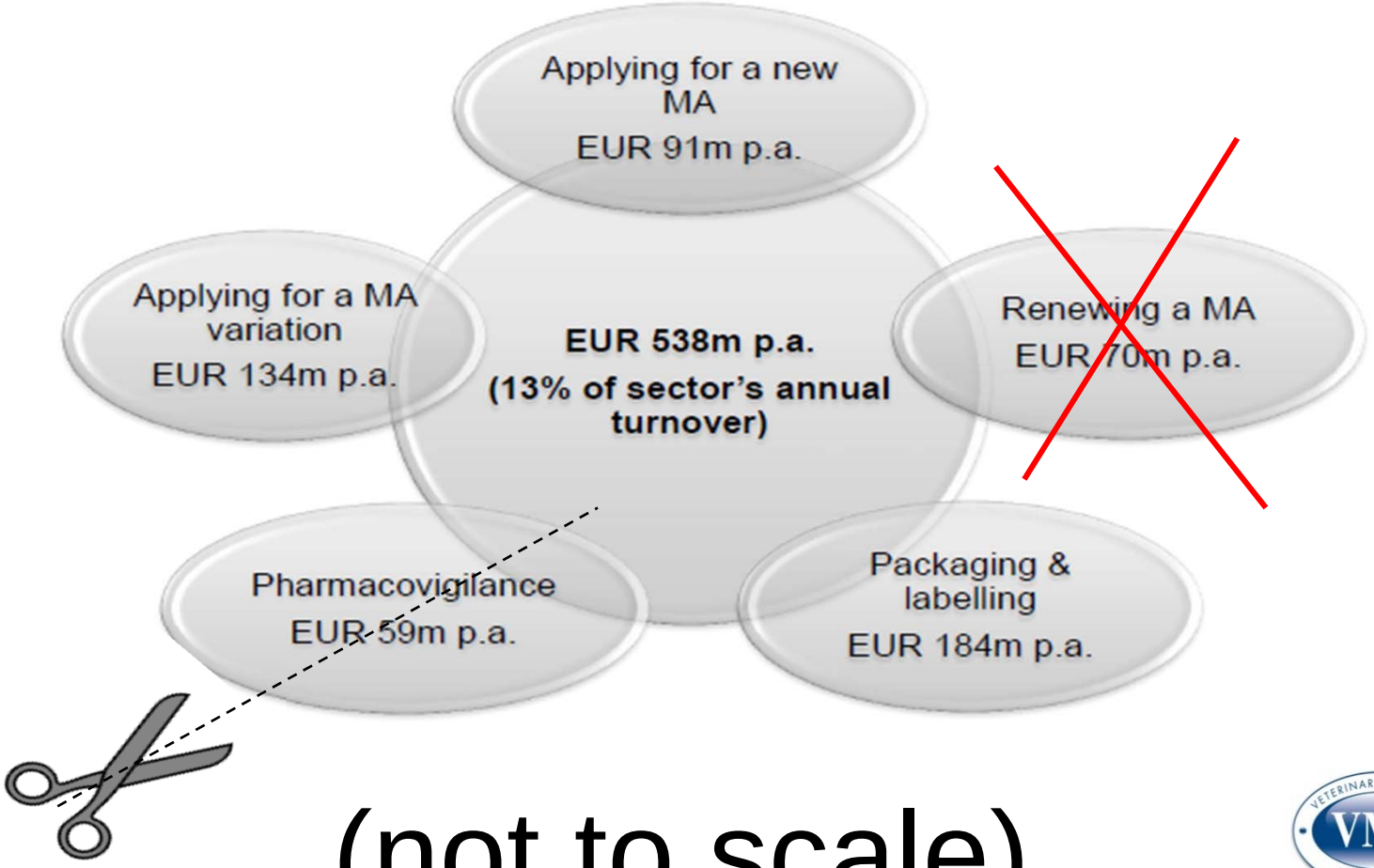
(Text with EEA relevance)

EN EN

VETERINARY MEDICINES DIRECTORATE VMD

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Administrative Burden



(not to scale)

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Major Changes

- No Renewals – rely on PhV
- Central Database
  - **ALL** reports within 30 days
  - 'General Public' have some access
- No PSURs – rely on signal detection
- PhV Masterfile introduced

Positives

- PhV Masterfile
  - if company based (cf product based) reduced burden to MAHs and NCAs
- Central Database
  - all reports available within a month
  - MAH has “blind access” to all data - signal detection possible for all MAH
  - some oversight of data for vets is good

Concerns

- Total removal of PSURS ≠ 'risk based'
  - No exposure data, studies, literature searches
  - No evidence of MAH Benefit:Risk evaluation
  - More requests for info, duplication of work?
- Limitations of statistical signal detection
  - MAH monitoring responsibilities unclear
- Public given access to AE numbers, not incidence – open to misinterpretation
- Fees to NCAs – effect on resources
- Future of PhVWP?

Possible PSUR Solutions

- Maintain status quo (some MS prefer this)
- Fewer PSURs (risk-based frequency)
  - Worksharing/combined PSURs a start on this
- Simpler PSURs – PBRERs?
  - no line listings, just literature and study data
  - exposure data, Benefit:Risk evaluation

OR

- No PSURs, all info entered into database
  - More efficient, available for analysis immediately – no requests for info.

PhV Masterfile

- Art 78(b):"allocating reference numbers to the pharmacovigilance system master file and communicating the reference number of the pharmacovigilance master file of each product to the product database"
- Surely not product based?

PhV Masterfile

No - generally company based but

- MAHs may have more than one masterfile (eg pharmaceuticals & vaccines)
- International subsidiaries may share same masterfile for some products

MAH (as per Part 1A or SPC)	Product Name	Active substance	Target species	QPPV	Masterfile Number
Zoetis Belgium	Geneeskat	Chatine	kat	Mrs. PhViga	Zoetis1
SPRL Vet France	TraiteChat	Chatine	Chat	Mrs. PhViga	Zoetis1
VetBRD	HeilKatz	Chatine	Katze	Mrs. PhViga	Zoetis1
VetMDComp	TreatCat	Chatine	Cat	Mrs. PhViga	Zoetis1
ESVetio	TrataGato	Chatine	Gato	Mrs. PhViga	Zoetis1
Η εταιρεία Vet	θεραπεία Γάτα	Chatine	Γάτα	Mrs. PhViga	Zoetis1

Inspections can be planned more efficiently….

PhV Communication Issues

Current legislation Art 75 states:

8. The holder of a marketing authorisation may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorised veterinary medicinal product without giving prior or simultaneous notification to the competent authority.

In any case, the marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.

New legislation (Art 77) similar but refers to adverse events

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VMD's Opinion

- PhV data should **not** be used for promotional purposes for any audience
- Advertising material should reflect the SPC (content) & distribution category (audience)
- MAHs **can** respond to specific requests from vets, animal owners, researchers etc
- Limitations of the data should be made clear
- Any material for wider dissemination would require our approval
- Meaning of 'general public' is unclear
- If in doubt, ask us!

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What happens next?

- Council working groups
- European Parliament
- Volume 9B?
- VICH?
- National legislation (fees etc)

Adoption end 2017?

- Watch this space.....

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Now it's your turn....

What do you think?

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Thank you for coming

Safe journey home

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