EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance: Signal Management

Update following Implementation of Regulation (EU) 2019/6

EMA Veterinary Medicines Info Day 16-17 February 2023

Presented by Daniel Zondag on 17 February 2023
Pharmacovigilance Officer, EMA

Outline

- Pharmacovigilance principles under Regulation (EU) 2019/6
- First year experience of signal management under Regulation (EU) 2019/6
- Signal Management in 2023
- Update description AEs in product information QRD v9

Regulation (EU) 2019/6 – Pharmacovigilance Principles

Simplify the regulatory environment and **reduce administrative burden** for pharmaceutical companies developing veterinary medicines, for example through streamlined pharmacovigilance rules

↓

PSURs → **Signal Management**

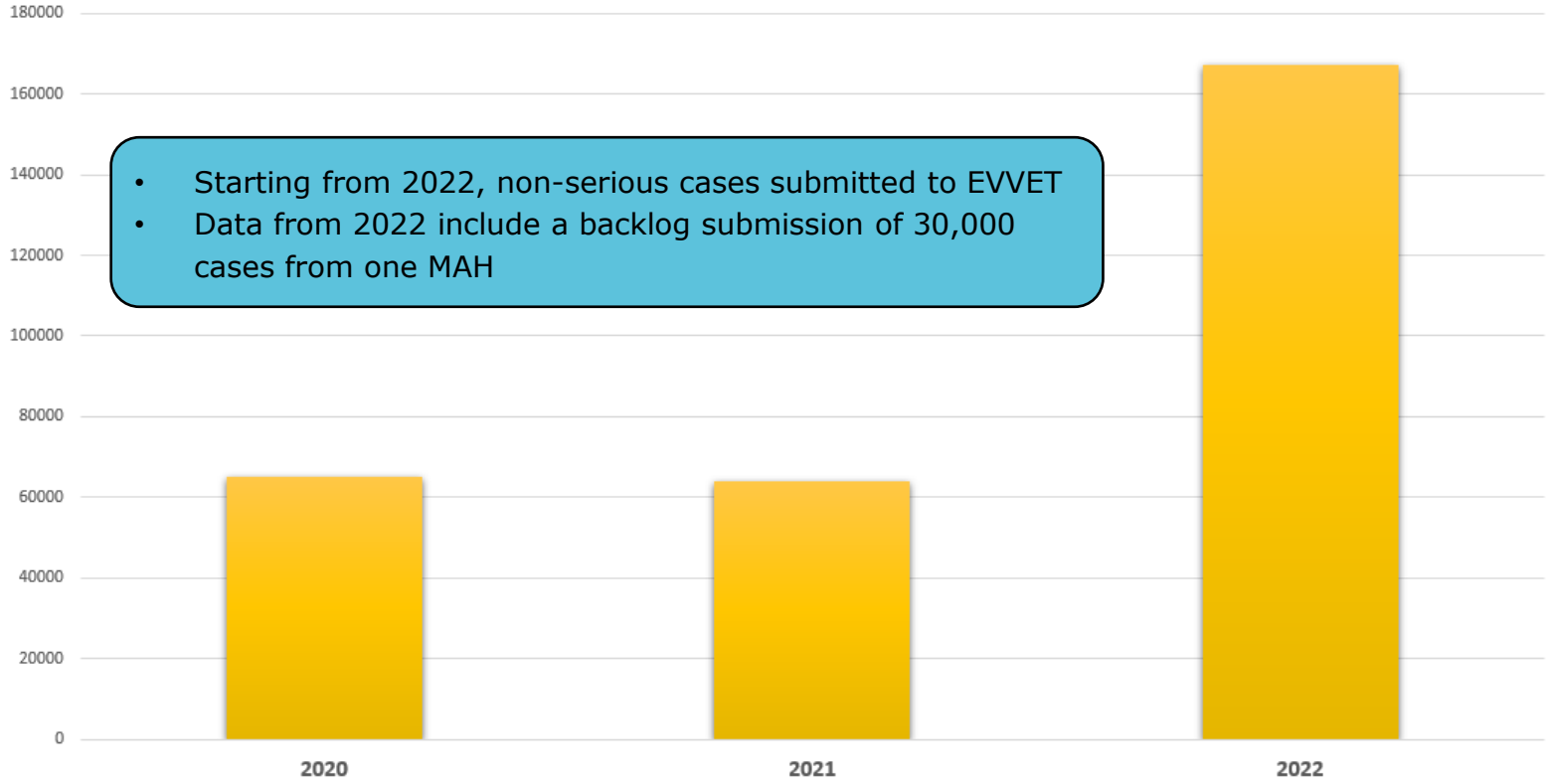
✓ Reinforcing scientific focus of **safety monitoring** activities

✓ **Animal health** and welfare, **public health** and protection of **environment**

Essential PhV Pillars of Regulation (EU) 2019/6

- **Adverse Event reports collection and recording**
  - 30 days + non-serious cases (EU + non EU)
  - Annual sales data (+ estimation of number of animals treated per target species)
- **Continuous Adverse Event analysis by MAH (signal management) (Art. 81)**
  - Using EudraVigilance Veterinary database or own database (+ 1 yearly SD analysis on EVVET)
  - Annual statements by MAH + SM results and outcomes submitted to database
  - If outcome identifies change to B/R or new risk, MAH should submit a VRA
- **Regulators oversight through**
  - PhV Inspections
  - **Evaluation of results and outcome of SM (Art 79)**
  - **Targeted signal management (Art. 81)**
- **Pharmacovigilance Master File (+ Quality Management System)**

Total AERs received in EVVET



- Starting from 2022, non-serious cases submitted to EVVET
- Data from 2022 include a backlog submission of 30,000 cases from one MAH

Pilot Signal Management Expert Group (P-SMEG)

- **Work-sharing operational expert subgroup** from PhVWP-V
- For a period of 2 years

P-SMEG

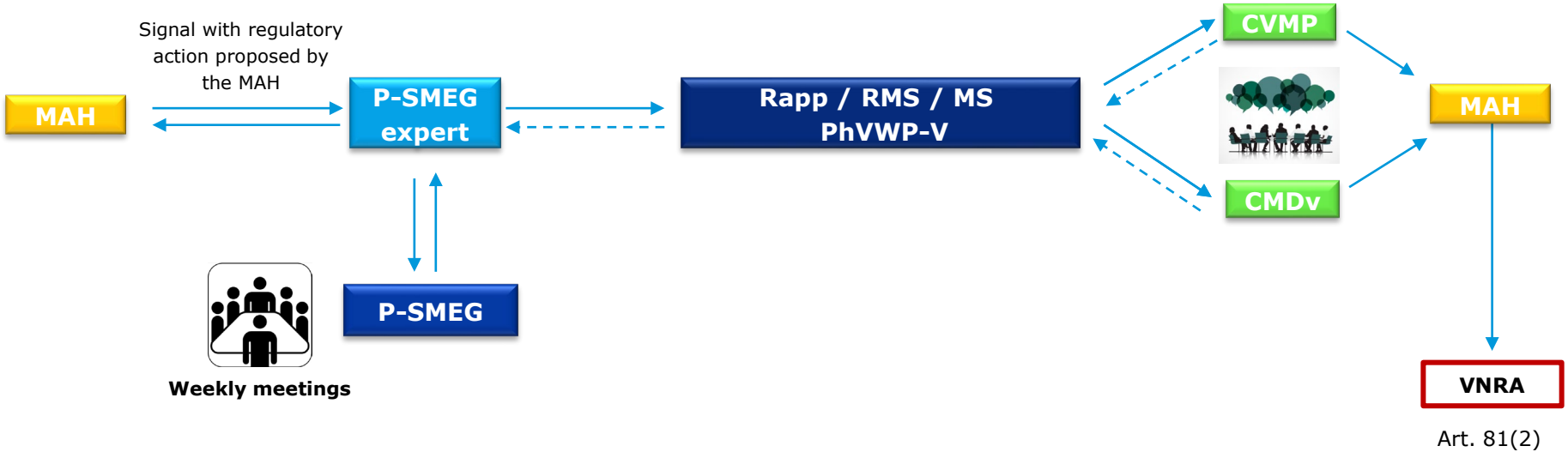
- **12 members**, from NCAs and EMA
- SM for **CAPs** and **non-CAPs**

- **Test new processes**, incl. risk-based approach
- Build **sustainable reg. framework**
- Supports provisions of Reg 2019/6
- Good PhV while managing administrative **burden**

- Pilot evaluation by **2024**
- **Critical review** of procedures, activities and resource efficiency
- **Recommendations** for long-term viability of system and proposals for improvement of approaches used

Signal Management in 2022 – Original setup

How the evaluation of signals with proposed regulatory actions from MAHs has been performed in 2022:



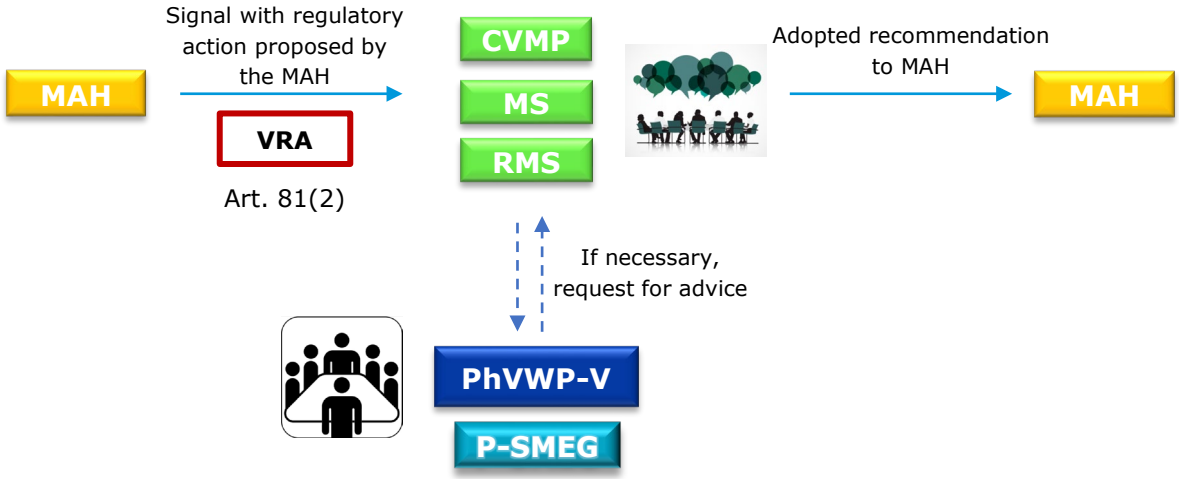
Signal Management in 2023 – what will change

Updated process based on one year evaluation

- Signals where change to B/R or new risk is identified (i.e., with regulatory actions proposed from MAH) will be recorded in IRIS by the MAH and in parallel, MAH will submit a **VRA** (Art. 81(2))
- VRA will be assessed by **CVMP (CAPs), RMS (MRP, DCP, SRP) or MS (NAPs)** with no direct involvement from PhVWP-V, unless their advice is specifically requested
- CVMP, RMS or MS can **request for advice from PhVWP-V** if, for example:
  - Signal is relevant for similar products with **same active substance** and further analyses are necessary
  - Signal is relevant for **other products** and further analyses are necessary

Signal Management in 2023 – what will change

How the evaluation of signals with proposed regulatory actions from MAHs will be performed in 2023:



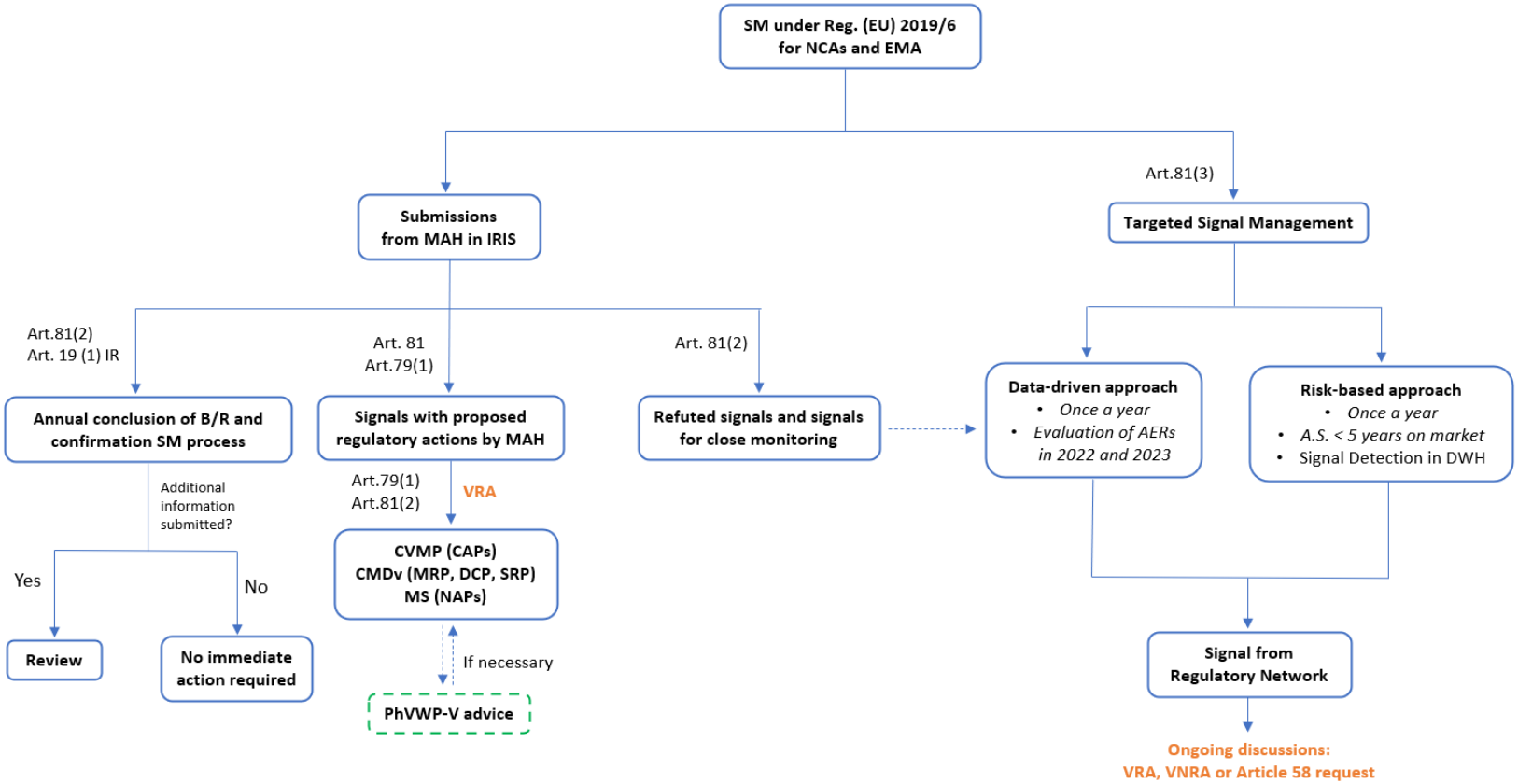
Targeted Signal Management

Risk-based approach

- Work-sharing by P-SMEG during 2023
- New active substances (**< 5 years on the market)**
  - Other criteria may apply exceptionally (e.g., new target species, new combinations, new indication)
  - To be endorsed by PhVWP-V, CVMP, CMDv
- Prioritising potential signals concerning **Medically Important VeDDRA term(s)**
- Analysis performed **at least once a year**, by "**lead authority**", represented by relevant P-SMEG member

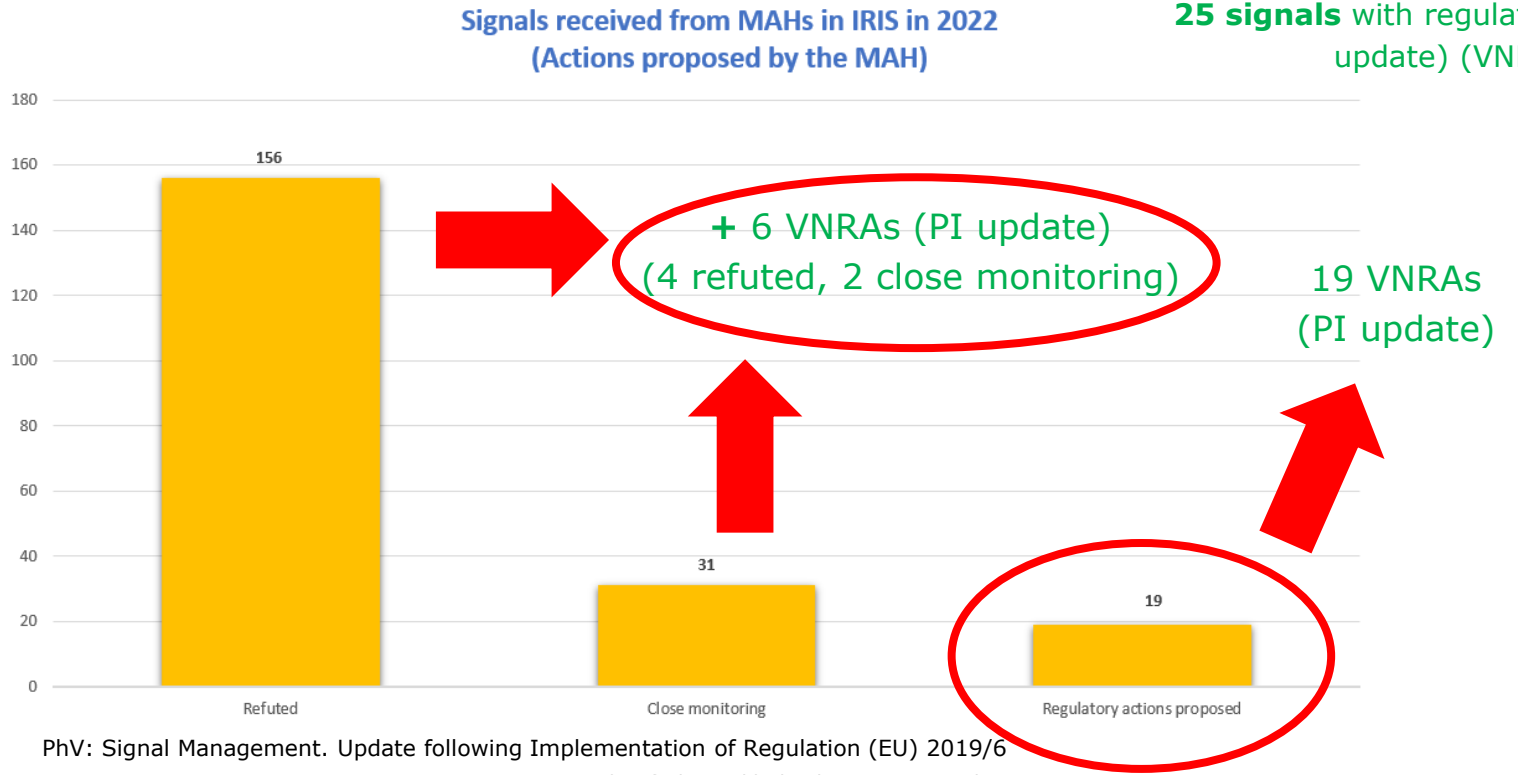
Data-driven approach

- Test effectiveness of risk-based approach by evaluating **data received in 2022-2023** in EVVET
- Using prioritisation criteria



Signal Management in 2022

n=206 signals submitted by MAHs in IRIS
25 signals with regulatory actions (PI update) (VNRAs)



Medically Important (MI) VeDDRA terms list

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

Potential impact on administrative burden

- **Monitoring by regulatory authorities:**
  - Focus on new active substances
  - Check on any other new relevant information received for 2022-2023
  - Streamlined process with well-defined roles and responsibilities
  - Avoid unnecessary regulatory burden
  - Full work-share through P-SMEG, aiming to avoid any duplication

Ongoing actions to manage the administrative burden

- Requirement of **annual statements** for all EU VMPs, including homeopathics
  - + Commission Implementing Regulation (EU) 2021/1281 Art. 17(7) requires **1 yearly signal detection analysis** using the data recorded in the **UPhV** (*MAHs using own database for signal management consider this as a duplication*)

  - Annual statements submission made as a "check-box" exercise in IRIS
  - For products with no AERs or few AERs, not high burden exercise
  - Recommended due dates for submission developed, draft was shared for consultation with industry before publication

Ongoing actions to manage the administrative burden

Signal submission improvement – Ongoing

- Product groupings will be game changer, foreseen by mid 2023
- Recoding ongoing
- Major MAHs that use their own database have to download data from EVVet to align; download facility has been improved recently

Data Warehouse and Signal submission tools - Ongoing

- Improved user tools under development including better integration of systems
- Continuous trainings and additional tools being organised

Signal Management in 2023

- Regulatory Network training for SM experts - *Feb 2023*
- Signal Management process update - *to be finalised second half 2023*
- P-SMEG evaluation report with recommendations for the future - *end of 2023*
  - MAH's feedback will be asked via a survey on the 2-years experience
- Enhance collaboration with PhV inspectors – *Training to PhV inspectors, date tbc*
- System upgrades and improvements – *ongoing throughout the year and 2024*

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Update: describing adverse events in product information QRD v9

EMA Info Day 16-17 February 2023

Background

- QRD template v9 revised 2022
- Q&A describing adverse events (AEs) in the product information (PI; summary of product characteristics (SPC) and package leaflet (PL)) updated
- Experience with variations (G.I.18) → CVMP agreed change in approach

Approach for updating existing PIs to align with QRD v9 (1)

- Apply guidance (QRD v9 and Q&A) pragmatically:
  - New scientific text should not be introduced
  - MAHs and CAs should not re-assess data from MAA dossiers
  - AEs referred to in general terms should be presented as follows:

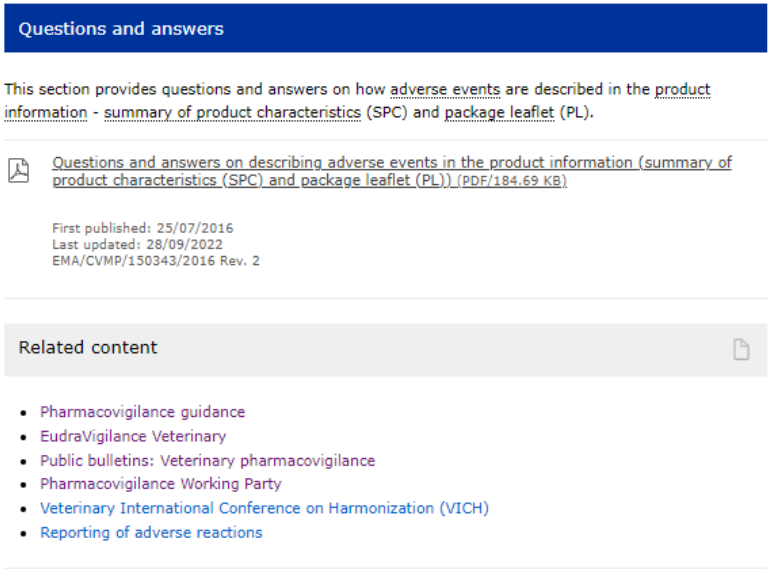
Original text (QRD v8.2)	Aligned text (QRD v9)	
Gastrointestinal signs have been observed commonly	Common (1 to 10 animals / 100 animals treated):	Gastrointestinal signs
Gastrointestinal signs (e.g. vomiting or diarrhoea) have been observed commonly	Common (1 to 10 animals / 100 animals treated):	Gastrointestinal signs (e.g. vomiting or diarrhoea)

Approach for updating existing PIs to align with QRD v9 (2)

- Additional information in footnote under AE table:
  - information for supporting AE management or improving understanding of VMP use
  - current existing imprecise qualifiers now acceptable as footnotes:
    - ✓ e.g., 'transient', 'temporary', 'self-limiting', 'spontaneous resolution'
- Terminology describing AEs in the SPC may differ from PL ('laymen's terms')
- Standard phrase cross-reference from Section 3.6 → PL for contact details for AE reporting to be corrected to remove problematic ref. to PL heading no. 16

Actions

- Change in approach communicated to all MAHs & industry associations
- Q&A describing AEs in the PI to be updated & published (EMA website)
  - Watch this space…



Questions and answers

This section provides questions and answers on how adverse events are described in the product information - summary of product characteristics (SPC) and package leaflet (PL).

Questions and answers on describing adverse events in the product information (summary of product characteristics (SPC) and package leaflet (PL)) (PDF/184.69 KB)

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EMA/CVMP/150343/2016 Rev. 2

Related content

- Pharmacovigilance guidance
- EudraVigilance Veterinary
- Public bulletins: Veterinary pharmacovigilance
- Pharmacovigilance Working Party
- Veterinary International Conference on Harmonization (VICH)
- Reporting of adverse reactions

Thank you for your attention! Any questions?

Further information

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