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The new European Veterinary Pharmacovigilance Legislative Framework:

Regulation (EU) 2019/6

Presented by Antigoni Margariti

Agenda

- Introduction
- New Veterinary PV Legislation –Regulation (EU) 2019/6
- Union Product Database (UPD) and Union Pharmacovigilance Database (EVVet3)
- Veterinary Good Pharmacovigilance Practices (VGVPs)
- MAHs' new obligations
- Q&A session

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Definition of Veterinary Medicinal Product (VMP)

A veterinary medicinal product (**VMP**) is any substance or combination of substances which fulfils at least one of the following conditions:

- it is presented as having properties for treating or preventing disease in animals
- its purpose is to be used in or administered to animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action
- its purpose is to be used in animals with a view to making a medical diagnosis
- Its purpose is to be used for euthanasia of animals

Regulation (EU) 2019/6

Previous legal framework

Directive 2001/82/EC (Article 77)

Regulation (EC) No 726/2004 (Article 51)

Volume 9B – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use (October 2011)

vs

Current legal framework

Regulation (EU) 2019/6

Veterinary Good Pharmacovigilance Practices (**VGVPs)**

Six modules

When did the new regulation come into force?

28 January 2022

Applicability of new Regulation:

Regulation (EU) 2019/6 is applicable to:

- VMPs prepared industrially or by a method involving an industrial process

Regulation (EU) 2019/6 is **not** applicable to:

- VMPs containing autologous or allogeneic cells or tissues that have not been subjected to an industrial process
- VMPs based on radio-active isotopes
- Feed additives
- VMPs intended for research and development
- Medicated feed and intermediate products

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New Veterinary PV Legislation • Regulation 2019/6 • MAH responsibilities • 1

What kind of PV related responsibilities lie with the MAH?

- establishment and maintenance of a pharmacovigilance system for collecting, collating and evaluating information on the suspected adverse events concerning their authorised VMPs
- compliance with good pharmacovigilance practice for veterinary medicinal products VMPs **[VGVPs]**
- one or more pharmacovigilance system master files (PSMF) describing in detail the pharmacovigilance system (*for each VMP, MAH shall not have more than one PSMF*) **[corresponds to GVP-Module II]**
- designation of one or more qualified persons responsible for pharmacovigilance, and back-up (residence and operation in the EU, appropriately qualified and permanently at the disposal of the MAH. One such qualified person shall be designated for each PSMF) **[corresponds to EU-QPPV]**
  - * *Where the qualified person has not completed training as a veterinary surgeon, it shall be ensured that the qualified person responsible for pharmacovigilance is assisted by a person trained as a veterinary surgeon*
- designation of a local or regional representative for the purpose of receiving reports of suspected adverse events who is able to communicate in the languages of the relevant Member States **[corresponds to LCPPV]**

Regulation (EU) 2019/6 – Chapter IV –Section 5 – Article 77

New Veterinary PV Legislation • Regulation 2019/6 • MAH responsibilities • 2

What kind of PV related responsibilities lie with the MAH?

- Continuous evaluation of the benefit-risk balance of the VMPs and, if considered necessary, receipt of appropriate measures
- Full responsibility of the marketing of the VMPs
- Keeping the SmPCs and PLs up to date
- Recording in UPD the date of authorization of the VMPs, information on the availability of the VMPs and the date of suspension or revocation of the relevant MAs
- Compliance with the NCAs or EMA's request to provide data demonstrating that the benefit-risk balance remains positive (within the time limit set in that request)
- Informing the NCA that granted the MA or the Commission, of any prohibition or restriction imposed by a NCA or by an authority of a third country and of any other new information which might influence the assessment of the benefits and risks of the VMP
- Recording in the product database the annual volume of sales for each VMP.

Regulation (EU) 2019/6 – Chapter IV –Section 5 – Article 77

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Union Product Database (UPD) and Union Pharmacovigilance Database (EVVet3) • UPD

Establishment and maintenance of a product database by EMA

What kind of information does the UPD include?

- name of the VMP
- active substance(s) and strength of VMPs
- SmPC
- package leaflet
- assessment report
- list of sites where the VMPs are manufactured
- dates of the placing of the VMPs on the market in a Member State
- respective information for homeopathic VMPs
- VMPs allowed to be used in a Member State in accordance with Article 5(6)
- the annual volume of sales and information on the availability of the VMPs

Regulation (EU) 2019/6 – Chapter IV –Section 1 – Article 55

Establishment and maintenance of a Union PV database for the reporting and recording of suspected AEs by EMA

What kind of information does the EVVet3 include?

- case reports of suspected adverse events
- information on qualified person responsible for pharmacovigilance
- reference numbers of the PSMFs
- results and outcomes of the signal management process
- results of pharmacovigilance inspections

Regulation (EU) 2019/6 – Chapter IV –Section 5 – Article 73 & 74

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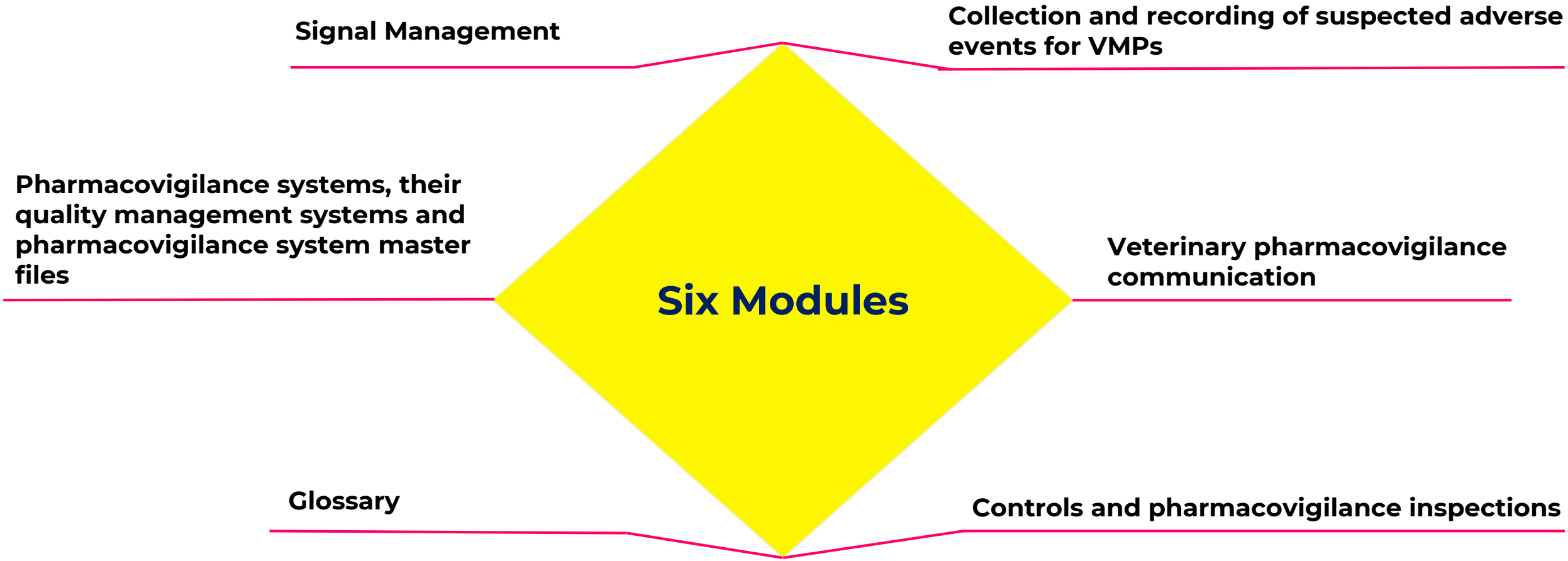
Veterinary Good Pharmacovigilance Practices (VGVPs) • 1

Guideline on Veterinary Good Pharmacovigilance Practices (VGVPs)



EMA website – Veterinary Pharmacovigilance

VGVPs • Collection and recording of suspected adverse events for VMPs • 1

What kind of information should be reported to the EVVet3?

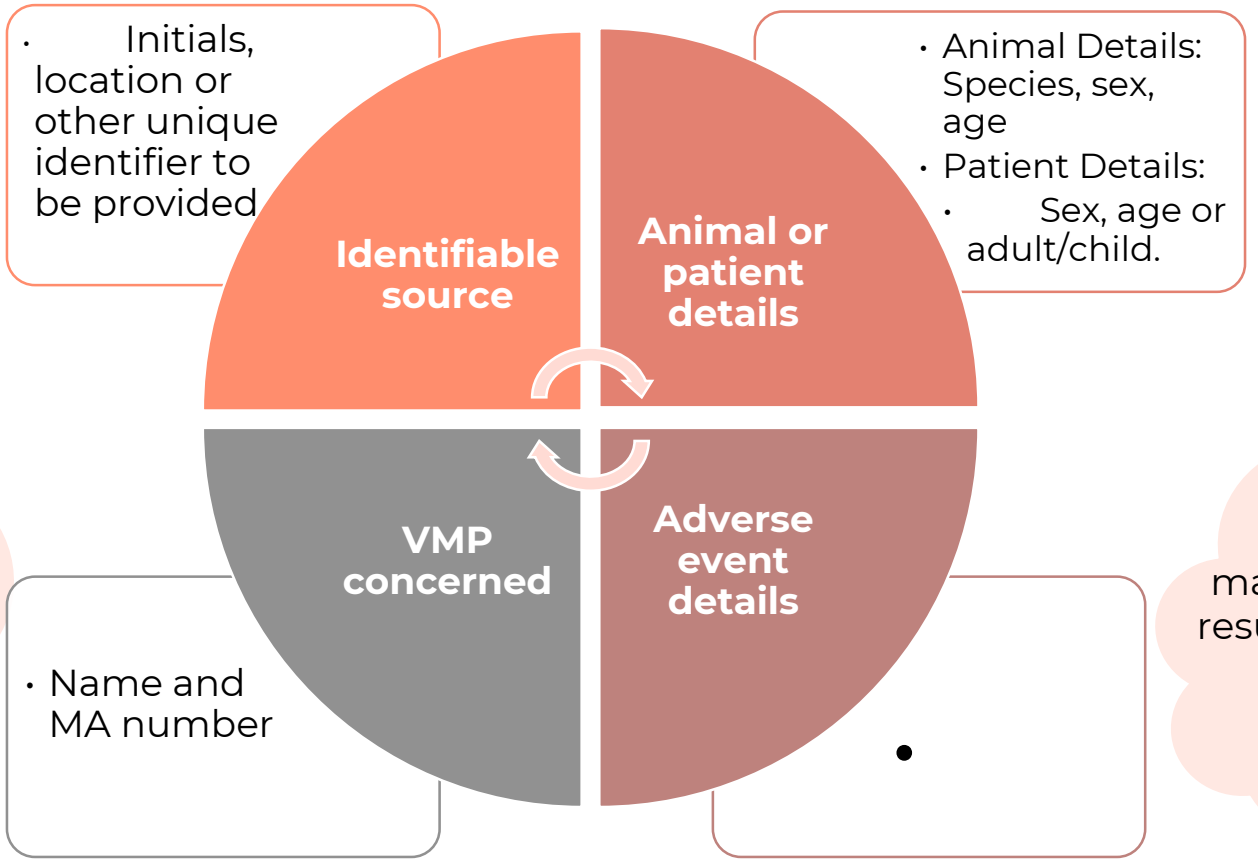
The following suspected adverse events should be reported:

- unfavorable and unintended reactions in any animal to a VMP
- noxious reaction in humans exposed to a VMP
- observations of a lack of efficacy of a VMP following its administration to an animal, whether or not in accordance with the SmPC
- environmental incidents observed following the administration of a veterinary medicinal product to an animal
- findings 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
- suspected transmissions of an infectious agent via a VMP
- **unfavorable and unintended reactions in an animal to a medicinal product for human use**

VGVP - Module 1

VGVPs • Collection and recording of suspected adverse events for VMPs • 2

Minimum information required for reporting in EVVet3



Reasonable efforts to be made in order to obtain the name or at least part of the trade name of the VMP.

Reasonable efforts to be made in order to obtain the results of diagnostic tests, to ensure that AE data are complete.

** Information required despite the AE being serious or non-serious, occurring in animals or humans and occurring in the EEA or outside the EEA.*

VGVP - Module 1

Suspected AE in humans

- Source of AE manifestation: in conjunction with the treatment of animals, following handling of VMPs, following exposure through the environment.

- In addition to the minimum info for a valid AE report:
  - Date of VMP's use / date of exposure to VMP
  - Date of suspected adverse event(s) in humans
  - Nature of exposure including type
  - Outcome of suspected AE(s) in humans
  - MAHs' conclusion/comments on the suspected AE(s) in humans (provided in the case narrative)
  - Animal and treatment data

Off-label use & Special situations

With suspected AEs

Recording in the EVVet3 in the same timelines as classic AEs

Without suspected AEs

- ✓ No submission in the EVVet3.
- ✓ MAHs to keep record of these cases at local site.
- ✓ If there is a potential impact on the VMP's risk-benefit profile, the cases are included in the annual statement of the signal management process.

What is the timeline for reporting?

New

Inside and Outside of the EU

and

in the scientific literature

to the EVVet3

30 days

All suspected Adverse Events

(as previously described)

** CAs may request from MAHs the collection of specific additional PV data and to carry out post-marketing surveillance studies*

VGVPs • Collection and recording of suspected adverse events for VMPs • 6

Before 28 Jan 2022

The **NCA** submits the AE report to EudraVigilance Veterinary

- primary source reports the AE to the MAH and the MAH reports it to the NCA of the MS where the AE occurred in the EU.
- primary source reports the AE to the NCA, who forwards it to the MAH and simultaneously submits it to EudraVigilance Veterinary

for follow-ups, the same route as that of the primary information is followed.

Now

The **body** receiving the AE report from the primary source submits it directly to the EVVet3

- primary source reports the AE to the MAH and the MAH submits it to EVVet3
- primary source reports the AE to the NCA and the NCA submits it to EVVet3

for follow-ups, the same route as that of the primary information is followed.

** For reports of AEs originating in third countries, the reporting route is the same as the current legislation. MAH submits it to EudraVigilance Veterinary (currently) or EVVet3 (in the future)*

VGVPs • Collection and recording of suspected adverse events for VMPs • 7

Literature search is conducted **at least once a year*** by MAHs in order to identify AEs related to their VMPs

* *Where necessary more frequently based on risk-based approach*

MAHs to record in EVVet3 the suspected AE reports identified in scientific literature **no later than 30 days**

AEs in scientific literature

Risk-based approach, taking into account the type of product, length of time on the market and stability of the PV profile

Literature references for AEs identified in publications shall be **recorded in EVVet3**

VGVP - Module 1

VGVPs • Signal Management • 1

What activities should the MAHs undertake ?

- Continuous monitoring of the safety of the VMP(s) in order to promptly detect any new safety issues that may impact their benefit-risk balance
- Signal detection either by using EVVet3 or their own specific data analytical tools for the purpose of signal detection and assessment
- Continuous submission of signals throughout the year
- Conduction of at least one signal detection analysis per year for each of their active substances or products in the EVVet3
- An annual statement on the benefit-risk balance of the VMP(s) together with the validated signals assessed throughout the year which did not require urgent attention or did not lead to any proposals for further regulatory action [by a due date].
- Confirmation that the signal management procedure has been conducted and all assessed signals have been submitted is also required [by a due date].

VGVP - Module 2

Signal reporting

Emerging Safety Issues

Have an impact on:

- ✓ the benefit-risk balance of the VMP
- ✓ the animal health and welfare
- ✓ public health
- ✓ protection of the environment

notification to CAs

3 working days

Non ESI signals

Medically Important VeDDRA terms

- ✓ Signals involving MI VeDDRA terms (**Appendix I**) should always be prioritized against other type of signals
- ✓ Identifying a new risk or change to the benefit-risk balance

notification to CAs

30 calendar days

Other type of signals

Signal detection

- MAHs are required to perform signal detection for each of their active substances or products in the EVVet3.

- If a MAH is responsible for the same or similar veterinary medicinal products in different Member States, signal detection and the signal management process shall be performed by grouping all products considered the same or similar.

- MAHs can use their own analytical tools for signal detection and assessment or EVVet3's dashboards:
    - Signal detection dashboard
    - Signal evaluation dashboard
    - Incidence calculation queries
    - Tailored made queries

- MAHs should conduct at least one signal detection analysis per year for each of their active substances or products in EVVet3 which needs to be performed within 2 months before the annual due date.

VGVP - Module 2

Annual submission & annual statement

MAHs are required to:

- ❖ record a conclusion (annual statement) on the benefit-risk balance for each of their products in the EVVet3
- ❖ confirm that the signal management process has been conducted and all assessed signals have been submitted

What happens if no signals are detected/validated?

Annual submission of a conclusion on the benefit-risk balance for each VMP should be done regardless.

A standard statement confirming that:

- the signal management process has been conducted in line with the guidance
- the benefit-risk balance of the concerned VMP(s) is unchanged

When should the annual submission take place?

The annual submission should take place at the latest by the due date set for each active substance (EMA will publish the relevant list of due dates set for each active substance).

VGVP - Module 2

VGVPs • Veterinary pharmacovigilance communication • 1

Aim of “Veterinary PV communication” VGVP

Active dissemination of veterinary pharmacovigilance information including specific safety information on VMPs for an intended audience.

Shared by:

- MAHs
- CAs
- Agency

Target audience:

- Veterinarians
- Animal healthcare professionals who handle, dispense or administer the VMPs
- Animal owners, carers or keepers
- Media

The module doesn’t support:

- Routine communication
- Responses to individual requests for information on PV issues
- communication with individuals about the treatment or management of adverse events
- promotion of veterinary medicinal products

VGVP - Module 3

VGVPs • Veterinary pharmacovigilance communication • 2

When should PV communication be shared?

- When there is new important information to be conveyed on adverse events relating to the VMPs or medicinal products for human use administered to animals, affecting exposed animals or humans or the environment which needs to be communicated more urgently than through a routine update to the product information.

- Following the request of a CA/Agency, in any situation considered necessary for safe and effective use of the veterinary medicinal product(s).

What kind of information regarding the PV communication does the present VGVP contain?

The present VGVP, contains information on the:

- Content of communication (reason of communication, description of risks, recommendations on how to deal with information, contact points etc)
- Presentation of information

VGVP - Module 3

Communication tools and channels

- Direct animal healthcare professional communication

  *When important and potentially new veterinary PV information needs to be communicated that may require certain actions or adaptation of practices in relation to the administration of a VMP (**Appendix I**: template for use)*

- Bulletins and newspapers

- Websites

  with public-oriented type of information, including links to facilitate AE reporting and should mention regulatory authority websites as authoritative reference points

- Digital communication – social media

  language used to be audience appropriate

- Press communication

- 'Lines to take' documents

  Documents prepared by regulatory authorities to assist regulators that are not to be published

Responsibility of MAHs

✓ MAHs should have an overarching communication plan as part of their pharmacovigilance system that identifies the relevant stakeholders in the Union

✓ In cases of urgent safety concerns, it shall outline the approach to be taken to communicate, in a timely manner, concerns arising from pharmacovigilance data or in relation to other relevant pharmacovigilance information.

Components of overarching communication plan (**Appendix III** : template for use) :

- Objectives
- Target audience
- Additional stakeholders involved
- Communication tools
- Dissemination means
- Follow up and measuring effectiveness of communication
- Timetable
- Topic-specific communication plans (**Appendix II** : template for use)
- Procedures in place for preparing and managing veterinary pharmacovigilance communication

VGVP - Module 3

VGVPs • Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files • 1

Pharmacovigilance system

Pharmacovigilance system - a system of collecting, collating and evaluating information on the suspected adverse events concerning the authorised VMPs which needs to be established by each MAH

Key points:

- To be described clearly and unambiguously in the pharmacovigilance system master file (PSMF)
- Each MAH may have established more than one pharmacovigilance system described in different PSMFs
- Each VMP should correspond to one pharmacovigilance system and be described in one PSMF

Contains:

- all procedures and processes for monitoring the benefit-risk balance and performing signal management (***VGVP Module 2***)
- pharmacovigilance communication (***VGVP Module 3***)
- documentation of risk management measures and their outcome

VGVPs • Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files • 2

What are the responsibilities of the EU-QPPV?

- maintenance of the PSMF
- allocation of reference numbers to the PSMF and their communication to the EVVet3 for each VMP
- notification of the NCAs and the Agency of the place of operation
- establishment and maintenance of a system which ensures that all suspected AEs which are brought to the attention of the MAH are collected and recorded in order to be accessible at least at one site in the Union
- compilation of the suspected AE reports, evaluation, where necessary, and recording in EVVet3
- ensuring that any request from the CAs or the Agency for the provision of additional information necessary for the evaluation of the benefit-risk balance of a VMPs is answered fully and promptly

Regulation 2019/6

VGVPs • Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files • 3

What are the responsibilities of the EU-QPPV?

- provision of information relevant to the detection of a change to the benefit-risk balance of a VMP, including appropriate information on post-marketing surveillance studies
- signal management process
- monitoring of the PV system and preparation and implementation of appropriate preventive or corrective action plans, if necessary
- receipt of continuous training of all MAH personnel involved in the performance of PV activities
- communication of any regulatory measure that is taken in a third country and is related to PV data to the NCAs and to the Agency within 21 days of receipt of information
- being the contact point for the MAH regarding PV inspections

Regulation 2019/6

Local or regional representative

New

MAH(s) shall designate a local or regional representative who:

- operates as a receipt point of reports concerning suspected adverse events
- is able to communicate in the languages of the relevant Member States
- reports to the QPPV in relation to the pharmacovigilance tasks and responsibilities.

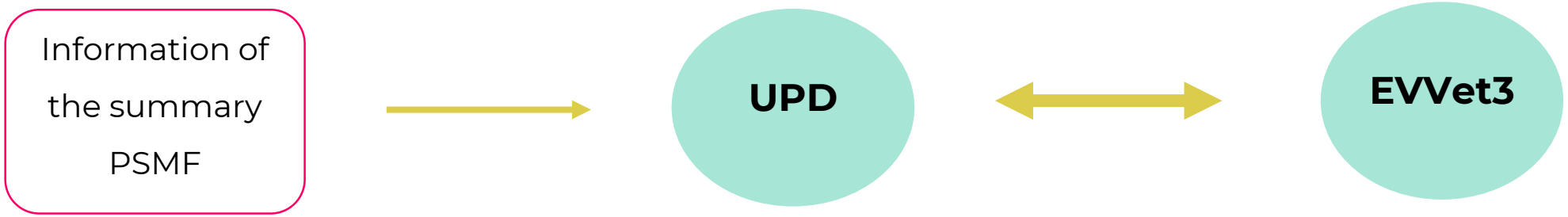
Can the EU-QPPV serve as a local/regional representative?

Yes, as long as he/she is able to communicate in the languages of the relevant Member States.

Pharmacovigilance system master file (PSMF)

MAHs are required to include a PSMF summary in the Marketing Authorisation application, including:

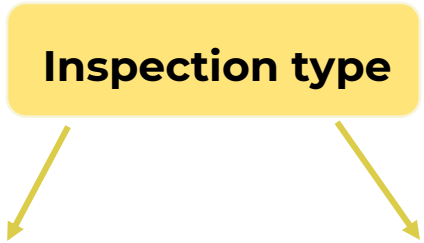
- The pharmacovigilance system master file reference number
- The pharmacovigilance system master file location
- Name, contact details and place of operation of the QPPV
- A signed statement from the MAH and the QPPV that the QPPV has the necessary means to fulfil the tasks and responsibilities requested by Regulation (EU) 2019/6.
- The type of record management system used for adverse events reports



VGVPs • Controls and pharmacovigilance inspections • 1

The CAs of the Member States can perform PV inspections of:

- MAHs of a veterinary medicinal product;
- its qualified person responsible for pharmacovigilance (QPPV)
- the representative(s) responsible for the reporting of suspected adverse events
- any third party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorisation holder



Routine inspection

✓ Scheduled in advance as part of inspection programmes.

✓ No specific trigger to initiate them

Targeted inspection

✓ when a trigger is recognized

✓ focus on specific PV processes or include an examination of identified compliance issues

VGVP - Module 5

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MAHs' new obligations

Reporting of Adverse Events to EVVet3:
- **New timeline of 30 days**
- **No causality assessment**
- **Irrespective of seriousness classification**

Signal Management process via EVVet3:
- **Signal detection**
- **Signal submission to EVVet3**
- **Annual statement on B/R profile**
- **Annual statement of confirmation**

Literature search conducted at least once a year

Regulation 2019/6

Pharmacovigilance System Master File (PSMF)

Local / regional representative

New Databases:
- **Union Product Database (UPD)**
- **Union Pharmacovigilance Database (EVVet3)**

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References and Useful Links

Previous Legal Framework

Directive 2001/82/EC

Regulation (EC) No 726/2004

Directive 90/167/EEC

Current Legal Framework- 28 Jan 2022

Regulation (EU) 2019/6

Commission Implementing Regulation (EU) 2021/1281

Guideline on veterinary good pharmacovigilance practices (VGVP guideline)

EMA pages and documents

- Implementation of the new Veterinary Medicines Regulation
- Post-authorization (Pharmacovigilance)
- Veterinary post-authorisation Q&A
- Union Product Database and UPD: release notes

Thank you!