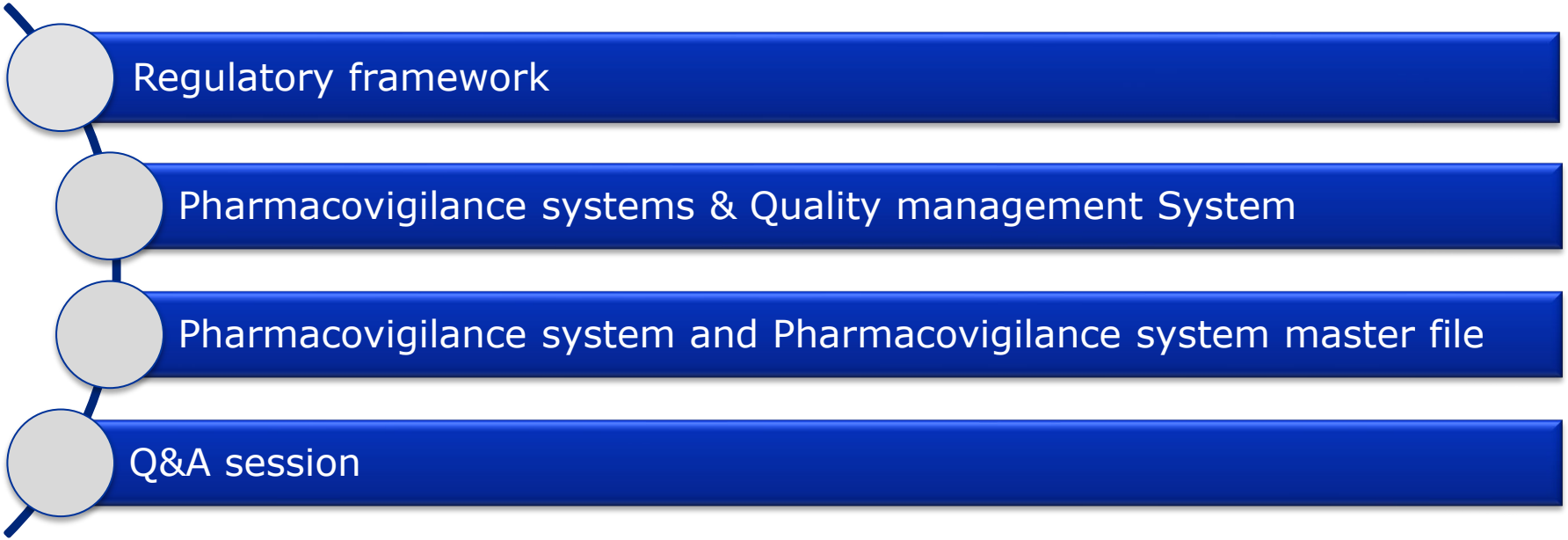
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

VGVP module on Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files

Inspection Office – Quality and Safety of Medicines
On behalf of the Veterinary Medicines Division

Presented by Sophia Mylona on 8 December 2021

Content Summary



Acronyms

- CAPA - corrective and preventive action
- MA - marketing authorisation
- MAA - marketing authorisation application
- MAH - marketing authorisation holder
- MS – Member States
- QMS - quality management systems
- PSMF - pharmacovigilance system master file
- VMP – veterinary medicinal products

Regulatory Framework

EU Veterinary Medicines Legislation

- Regulation (EU) 2019/06
- Commission Implementing Regulation (EU) 2021/1281

Regulation(EU) 2019/6

Legislation	Article	Requirement
Regulation (EU) 2019/6	4	**Definitions: (30) pharmacovigilance, (31) PSMF,** (32) controls
	8	**Summary of PSMF MA dossier requirement**
Section 5	77	Pharmacovigilance responsibilities of the marketing authorisation holder
	78	**Qualified person responsible for pharmacovigilance**
	79	Pharmacovigilance responsibilities of the competent authorities and the Agency
	80	Delegation of tasks by competent authority
	123 and 126	Controls & Specific rules on pharmacovigilance inspections

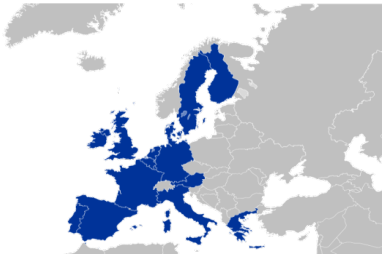
Commission Implementing Regulation (EU) 2021/1281

Legislation	Article	Requirement
Commission Implementing Regulation (EU) 2021/1281 Chapter 1	1	Definitions: quality management system, performance indicator
	2	Pharmacovigilance system
	3	Qualified person responsible for pharmacovigilance
Chapter 2	4	Quality management system for pharmacovigilance
	5-6	Document management system - training
	7-8-9	Performance indicators – Audit – CAPA and change management
Chapter 4	21-25	Pharmacovigilance system master file (PSMF)
Chapter 5	26-27	Controls and inspections by competent authorities

From Directive 2001/82/EC to Regulation (EU) 2019/6

Directive 2001/82/EC

Before 28 January 2022



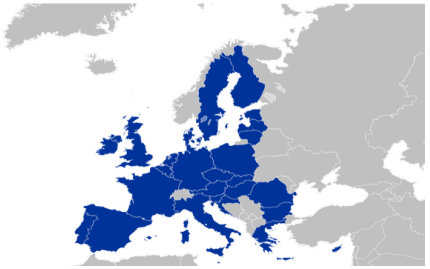
Directive requirements transposed to national legislation

Different requirements for marketing authorisation applications in each MS

Goals: **Simplification, harmonisation** in Europe, support EU action against **antimicrobial resistance**, foster **innovation** and enhance **availability of veterinary** medicinal **products**

Regulation (EU) No. 2019/6

came into effect on 28 January 2019



Applies in all EU MS on 28 January 2022

Common EU requirements for nationally and centrally authorized products

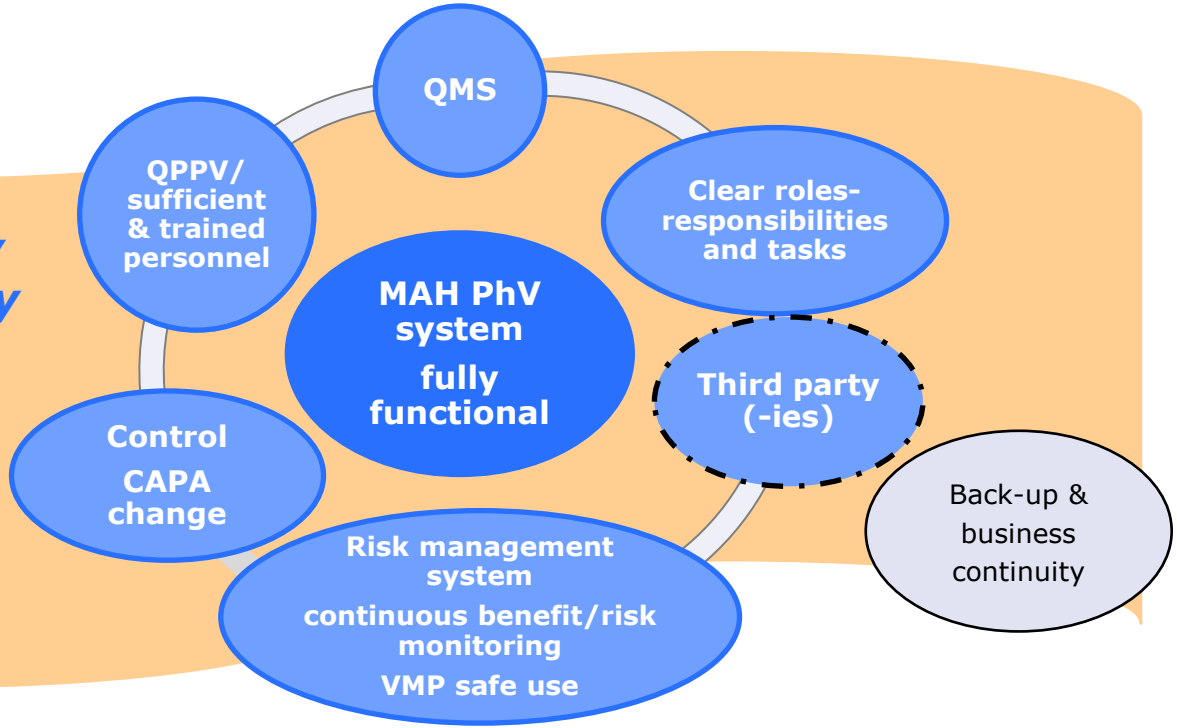
Requirements fit for purpose and not human medicines driven

Repeals Directive 2001/82/EC and amends the provisions of Regulation (EU) 726/2004

Pharmacovigilance system and its Quality Management System (QMS)

Marketing authorisation holders shall establish and maintain a system for collecting, collating and evaluating information on the suspected adverse events concerning their authorized veterinary medicinal products, enabling them to fulfil their pharmacovigilance responsibilities ('pharmacovigilance system').

PhV system clearly and unambiguously documented in the PSMF



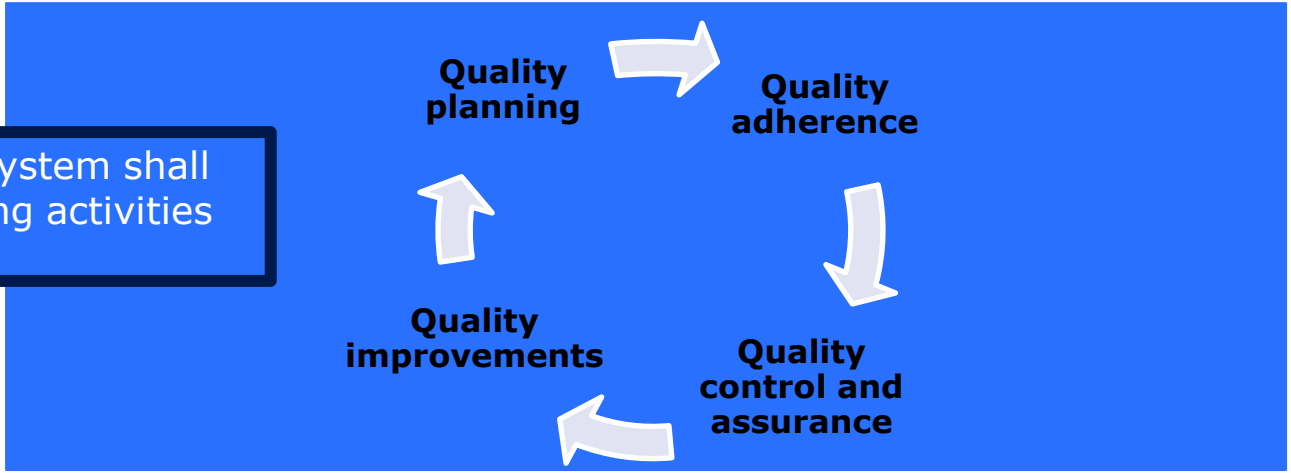
Qualified person for pharmacovigilance (QPPV)

- In case the QPPV has not completed **veterinary surgeon training**, MAH shall make arrangements to **ensure** that **the QPPV is assisted by a veterinary surgeon** on a continuous basis [Commission Implementing Regulation (EU) 2021/1281, Article 3(2)];
- In addition to the QPPV, the marketing authorisation holder shall designate 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 [Regulation (EU) 2019/6, Article 77(3)]. The local or regional representative should report to the QPPV in relation to the pharmacovigilance tasks and responsibilities. The **QPPV may also act as the local representative;**
- The marketing authorisation holders shall ensure that there is an appropriate **procedure in place to identify and deal with any conflicts of interest** of the QPPV [Commission Implementing Regulation (EU) 2021/1281, Article 2(3)].

Quality Management System

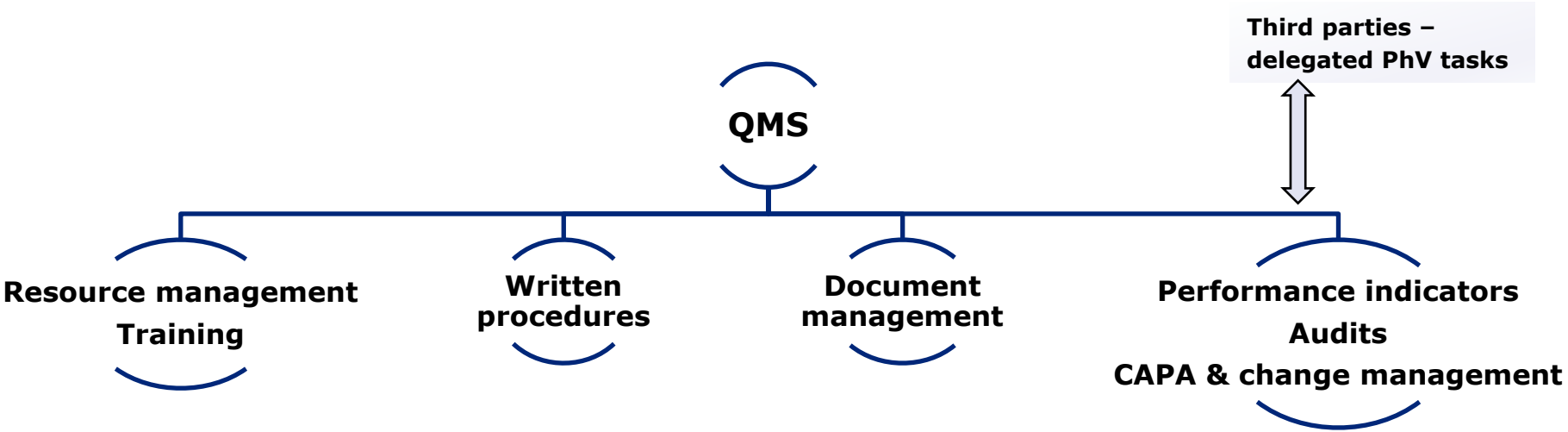
- MAH shall establish and implement an adequate and effective **quality management system for the performance of their pharmacovigilance activities.**
- The quality management system shall be described in the pharmacovigilance system master file.

The quality management system shall be based on all the following activities [IR (EU) 2021/1281, Art. 4(6)]



Quality management System

*'Q**uality management system**' means a formalised system that provides for comprehensive processes, procedures, and responsibilities for achieving quality policies and objectives to coordinate and direct an organisation's activities and improve its effectiveness and efficiency in this regard on a continuous basis.*



Resource management and training

- All personnel involved in the performance of pharmacovigilance activities shall receive **initial and continuous training for their role and responsibilities** in relation to the activities mentioned in Article 4, paragraphs 3 to 6, also including activities related to clinical trials, technical product complaints, standards, sales and marketing;
- MAH shall have a **training management system** in place for **maintaining and developing the competences** of their personnel;
- **Information on training plans and records** for pharmacovigilance activities and a reference to their location shall be kept in **Annex IV**, point (iv) to the **pharmacovigilance system master file.**

MAH shall have a **sufficient number of competent and appropriately qualified and trained personnel** working for them in the performance of pharmacovigilance activities.

Written procedures *to cover at least the following activities*

1. **Initial recording of suspected adverse event**.
2. **Collection of additional data**.
3. **Collation of reports of suspected adverse events and additional data**.
4. **Data handling other than mentioned in points (1) to (3) of this list**.
5. **Evaluation of data**.
6. **Monitoring the quality, integrity and completeness of all information pharmacovigilance database and management of duplicates.**
7. **Recording of adverse event in the Union pharmacovigilance database.**
8. **Archiving of all relevant documents**.
9. **Risk management system including processes for:**
   - 9.1. **signal management**
   - 9.2 **continuous monitoring of the benefit-risk balance of veterinary medicinal products**
   - 9.3. **overarching communication plan**
10. **Document management system**
11. **Training**
12. **Audit**

Document management system

- MAH shall set up and maintain a document management system to keep all documents related to pharmacovigilance activities. Those documents shall be **archived** and indexed to enable **accurate and easy accessibility** throughout the period of record-keeping;
- Documents shall be subject to **version control**, as appropriate;
- Documents and pharmacovigilance data relating to individual authorised **veterinary medicinal products** shall be retained as long as the product is authorised and **for 5 years after the marketing authorisation ceases to be valid.**

Performance indicators

'**Performance indicator**' means an item of information collected at regular intervals to monitor the performance of a system:

- use of relevant performance indicators to continuously monitor the performance of pharmacovigilance activities in relation to the quality requirements in accordance with legislation and guidance;
- the items of information that can be collected at regular intervals to track the performance of the system should be realistic and measurable, such as submission timeliness or quality of reports / reports free of errors;
- a list of these performance indicators including the reason why they have been chosen, if applicable, and a description on how to use them should be included in Section E.3 of the PSMF.

Performance indicators examples

- timelines for reporting adverse events, follow up, quality of reports;
- conduct of signal detection (e.g., conduct of activities on time, writing of reports, signal assessment activities);
- timelines for submission of pharmacovigilance or other safety variation applications;
- an overview of adherence to commitments or obligations relevant to pharmacovigilance.

Audits

- **risk-based audit planning** (risk-based intervals) and rationale documented;
- audits to cover all pharmacovigilance activities to verify compliance with legal requirements and determine pharmacovigilance system effectiveness;
- audits to be conducted **by individuals** who have **no direct involvement in or responsibility for the matters or processes audited;**
- **any third party contracted** to carry out pharmacovigilance activities in whole or in part, on behalf of or in conjunction with MAH, shall accept to be audited by or on behalf of MAHs;
- A **report** shall be drawn up on the results for each audit (and any follow-up audits after the initial one);
- Reports shall be sent to the QPPV and management responsible for the matters audited, as applicable, to ensure that **management cooperates with QPPV to address the findings**.

Corrective and preventive action (CAPA) and change management

- MAHs shall have a process in place for managing CAPA to mitigate:
  - any deviations detected in daily operational work;
  - any deviations detected in audits;
  - inspections' findings.
- CAPA shall include root cause analysis, timelines for action and communication to relevant stakeholders;
- MAHs shall monitor and assess the effectiveness of CAPA;
- CAPA shall be documented for the last 5 years;
- Change management, when and as required.

Pharmacovigilance systems & PSMF

The marketing authorisation holder's pharmacovigilance system

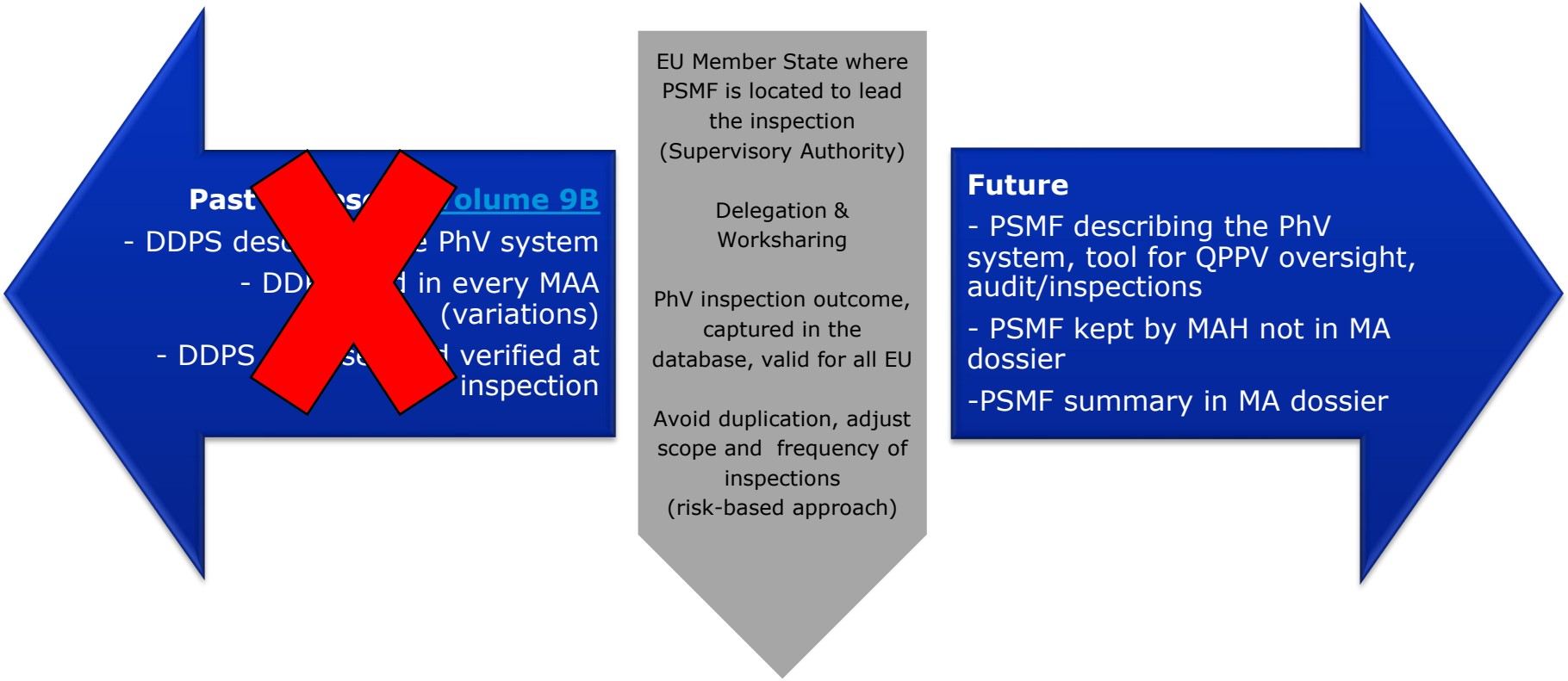
Changes introduced with the new veterinary regulation focus on the following areas:

- Continuous signal management throughout a medicine's lifecycle, based on adverse event reports in the 'Union Pharmacovigilance Database' *(no PSUR submissions)*
- **Maintenance of a pharmacovigilance master file by the MAH describing their safety and efficacy monitoring system**

The marketing authorisation holder shall have in place one or more pharmacovigilance system master files describing in detail the pharmacovigilance system with respect to its authorised veterinary medicinal products. For each veterinary medicinal product, the marketing authorisation holder shall not have more than one pharmacovigilance system master file.

- Pharmacovigilance inspections by regulators (PSMF location)

Main changes and simplifications – ~~DDPS~~ vs PSMF



PSMF summary vs. Pharmacovigilance System master File (PSMF)

Document type	Benefit description of content and submission requirements	MAA dossier	MAH site
PSMF summary	• Content defined in accordance with REG, Art. 8(c) & IR (Art. 23) • Submitted as part of the marketing authorisation dossier • Variation application required if changes (REG. Art 61 – not requiring assessment)	✓	✓
PSMF	• Content defined in accordance with REG, Art. 77(2) & IR (Art. 21-25) • It is kept by the MAH, not part of MA dossier, available upon request (within 7 days) • No variation required for changes (unless summary of PSMF is affected by the change)	X	✓

Change from DDPS to PSMF for products with existing MA:
- No need to update MA dossier with summary of the PSMF
- PSMF in place from 28 January 2022

MA dossier requirements [REG, Art. 8(c) & IR (art. 23)]

Summary of the pharmacovigilance system master file (PSMF)

The summary of the PSMF shall contain the following information:

a) PSMF reference number (i.e., PSMFxxxxxx) ;

b) PSMF location;

c) name, contact details and place of operation of the qualified person responsible for pharmacovigilance;

d) signed statement referred to in Article 22(2)(b), point (i);

"Signed statement from the marketing authorisation holder and the qualified person confirming that the qualified person concerned has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6."

e) type of record management system used for adverse events reports including the name of the database, if applicable.

Pharmacovigilance system master file reference number **Regulation (EU) 2019/6 Article 77(8)**

The qualified person responsible for pharmacovigilance shall ensure that the following tasks are carried out:

a) elaborating and maintaining the PSMF;

b) allocating reference numbers to the **PSMF** and communicating that **reference number** to the pharmacovigilance database for each product;

i. any reference can be selected following the format: **PSMFXXXXXXX (free text field)**

ii. PSMF reference number should be unique for the MAH & for the group of products it relates to

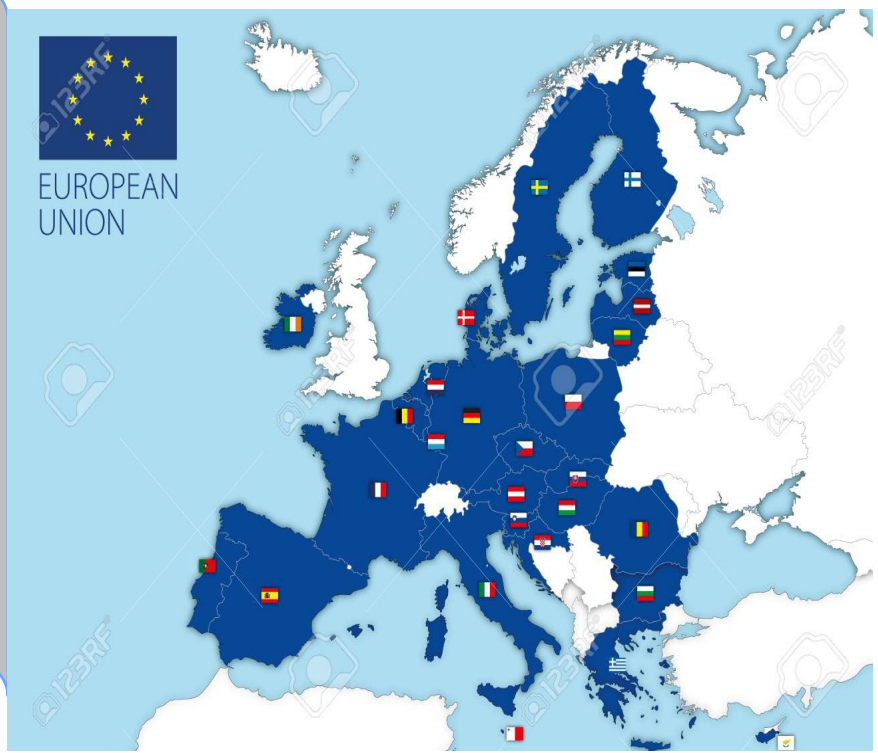
iii. expectation that combination of ***PSMF reference – PSMF location – MAH organization*** will be **unique at EU level**

c) notifying the competent authorities and the Agency, as applicable, of the place of operation.

PSMF location

The PSMF shall be located in the Union

- **at the site where the main pharmacovigilance activities of the marketing authorisation holder are performed, *or***
- **at the site where the qualified person responsible for pharmacovigilance operates.**



PSMF content: main part and annexes

Section A	Information on the PSMF (PSMF reference number, PSMF location)	Annex 1 - logbook
Section B	QPPV, Assisting veterinary surgeon, and back up procedures	Annex 2 - QPPV additional info., e.g. CV, proof of registration with pharmacovigilance database
Section C	Marketing Authorisation holder information	Annex 3 - e.g., list of products, list of regional representatives, list of PhV sites, etc.
Section D	Document management system (including record management system for adverse event recording)	
Section E	Quality management system for pharmacovigilance activities	Annex 4 - list of procedures, list of scheduled and completed audits, etc.
Section F	Contractual arrangements between MAH and third parties concerning pharmacovigilance activities	Annex 5 - lists of tasks delegated (MAH/QPPV), list of contracts/agreements

Pharmacovigilance System Master File (PSMF)

Key messages and availability

- The PSMF is not just a requirement laid down in the legislation, should be **a useful tool for the MAH and QPPV to facilitate oversight** and contribute to the management of and improvement(s) to the pharmacovigilance system;

- The PSMF will be kept by the MAH/QPPV (not part of the MA dossier);

- PSMF may be stored or made available in electronic form;

- PSMF does not need to be printed as hard copy in the physical location, but a copy should be available to competent authorities upon request (printable and searchable);

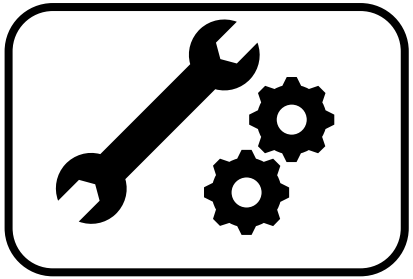
- the media used for storage or making available shall be searchable and shall remain readable over time.

PSMF Maintenance

Keep PSMF **up to date** and **revise it, where necessary**, to take account of experience gained, and of technical and scientific progress

MAH may **update the PSMF on a periodic basis**, to reduce burden, provided that significant **changes, important for PV oversight are tracked on an *ad hoc* basis**

Content of the PSMF **annexes** (PSMF): possible to use of other systems, where the required information is kept, as an alternative for annex /list generation, as long as these alternative systems fulfil the same objectives.

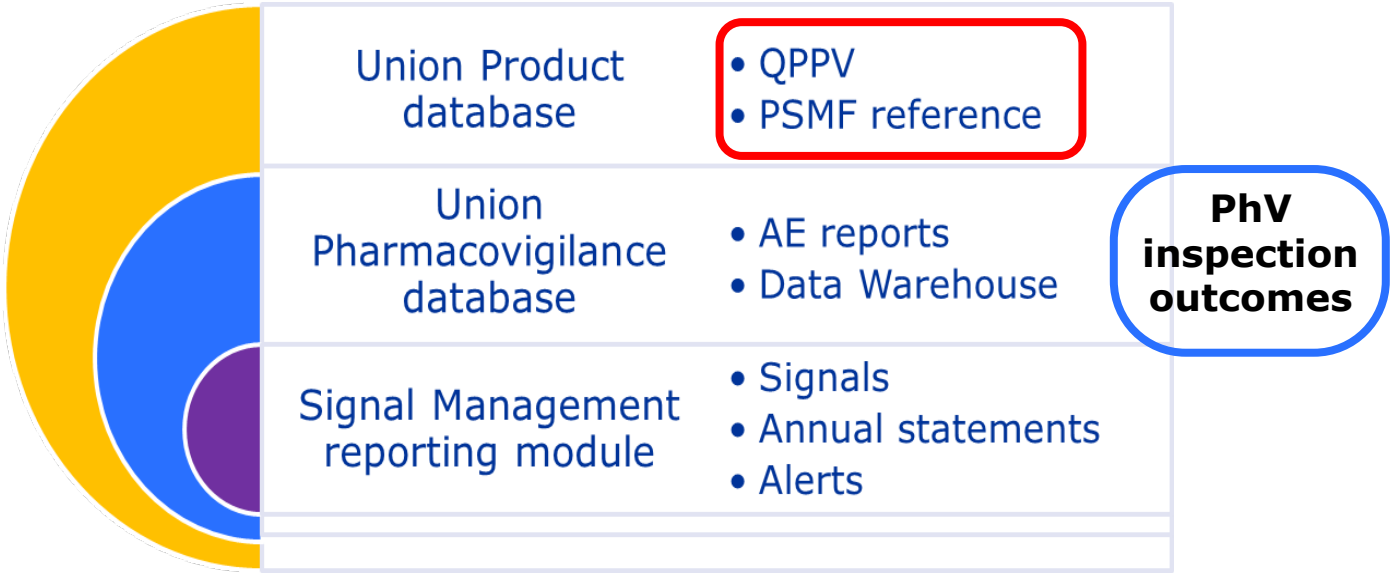


Pharmacovigilance and non-EU information

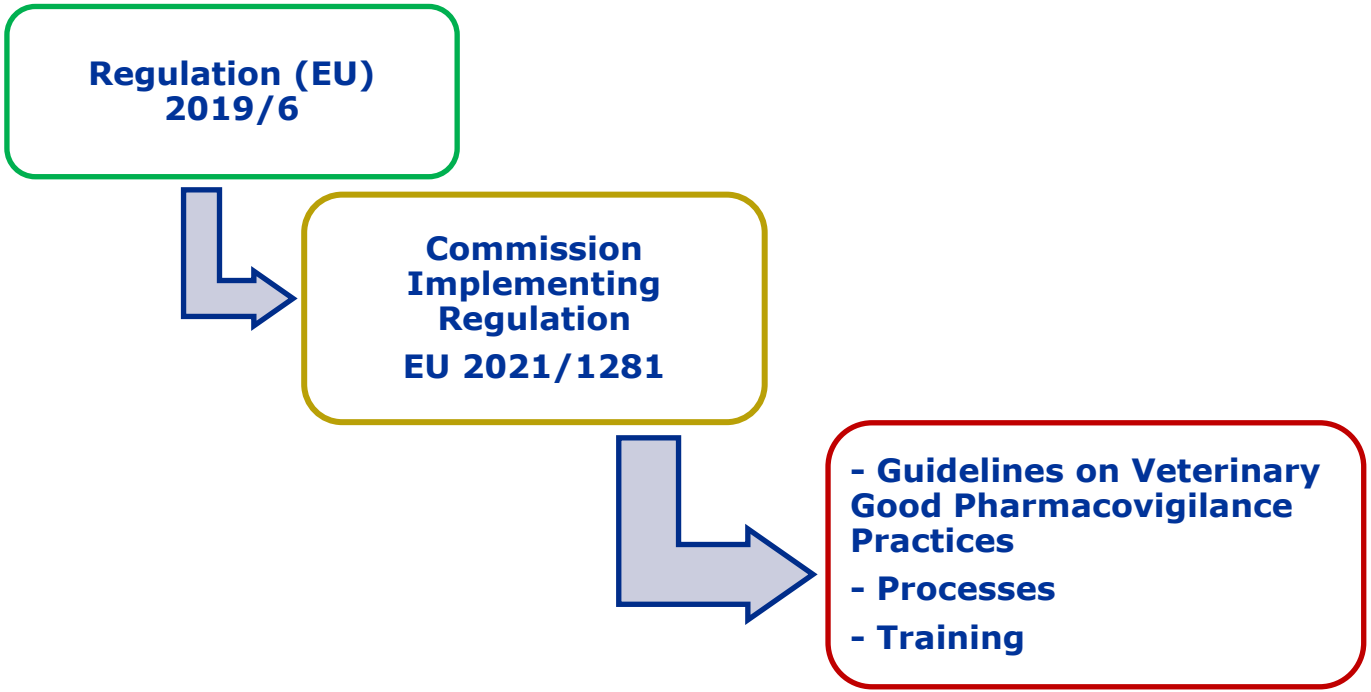
- Persons and functions required under the Regulation 2019/06 have to reside/be located in the EEA (e.g., local or regional representatives, the QPPV etc., information limited to EEA);
- Pharmacovigilance does not stop at EU borders; non-EU information may be required in some cases:
  - Global companies with main pharmacovigilance site(s) outside the Union
  - Adverse events (third country cases) / sources of safety information outside the Union (contracts and agreements)

Pharmacovigilance system master file (PSMF)

Essential DATA systems



Guidance applicable from 28 January 2022



Any questions?

Further information

PhVIns@ema.europa.eu
vetchange.programme@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

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