



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

VGVP module on Controls and Pharmacovigilance Inspections: Introduction and Principles

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

Presented by Calogero Cannavo on 8 December 2021



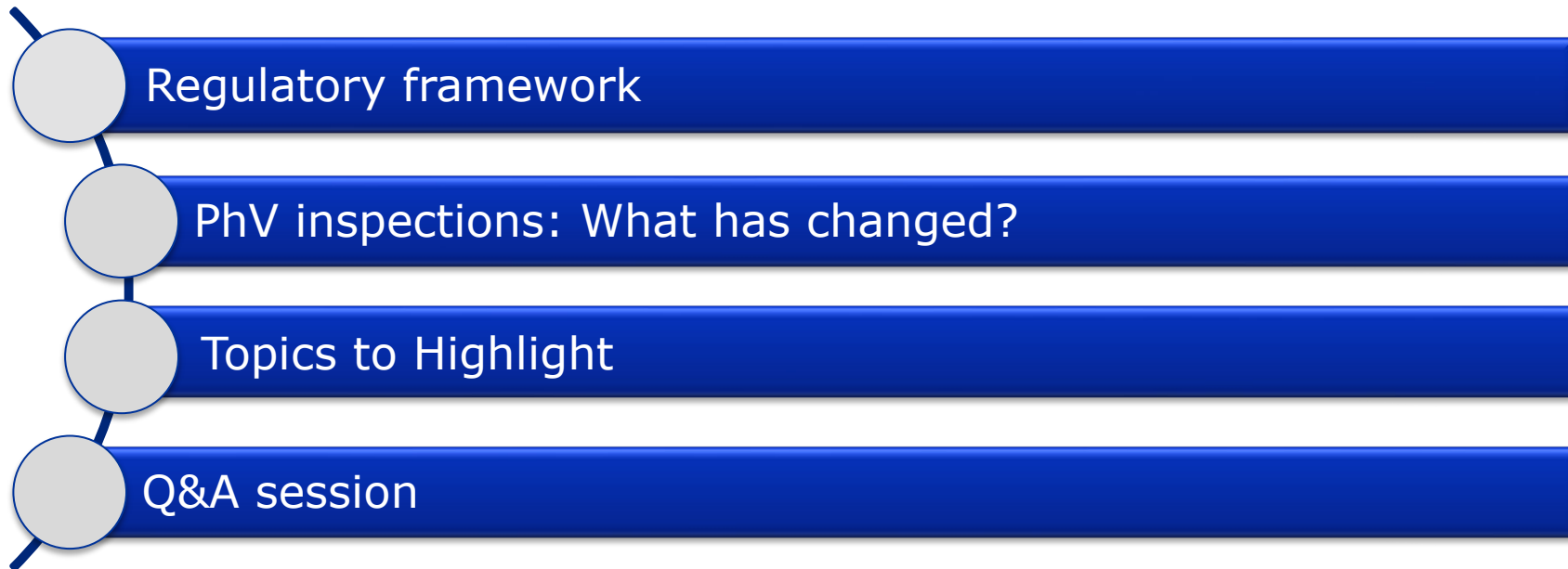


Acronyms

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



Content Summary





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 (32)	Controls means any task performed by a competent authority for the verification of compliance with this Regulation;
	123 (6)	Inspections may be carried out as part of the controls ...
	126	Specific rules on pharmacovigilance inspections



Regulation (EU) 2019/6

Article 126 Specific rules on pharmacovigilance inspections

1. The competent authorities and the Agency shall ensure that all pharmacovigilance system master files in the Union are regularly checked and that the pharmacovigilance systems are being correctly applied.
2. The Agency shall coordinate and the competent authorities shall carry out inspections on the pharmacovigilance systems of veterinary medicinal products authorised in accordance with Article 44.
3. The competent authorities shall carry out inspections on the pharmacovigilance systems of veterinary medicinal products authorised in accordance with Articles 47, 49, 52 and 53.
4. The competent authorities of the Member States in which the pharmacovigilance system master files are located shall carry out inspections of the pharmacovigilance systems master files.
(...)



Commission Implementing Regulation (EU) 2021/1281

Legislation	Article	Requirement
Commission Implementing Regulation (EU) 2021/1281		In order to facilitate the enforcement of pharmacovigilance obligations, the marketing authorisation holder should retain full responsibility for all pharmacovigilance obligations subcontracted to third parties
		Marketing authorisation holders should ensure that they and any third party carrying out pharmacovigilance activities in relation to their veterinary medicinal products make the necessary preparations in order to facilitate controls or inspections by the national competent authorities or the European Medicines Agency
	26	Marketing authorisation holders shall be ready for controls...
	27	Marketing authorisation holders shall be prepared for inspections of their pharmacovigilance system and the corresponding pharmacovigilance system master file...



Commission Implementing Regulation (EU) 2021/1281

Article 26 - Controls

1. Marketing authorisation holders shall be ready for controls in accordance with Article 123 of Regulation (EU) 2019/6 and shall also ensure the following are ready for those controls:
 - a) their qualified person responsible for pharmacovigilance in accordance with Article 77(8) of Regulation (EU) 2019/6; and
 - b) their representatives responsible for the reporting of adverse events in accordance with Article 14(1)(a) and (l) and Article 77(3) of Regulation (EU) 2019/6;
 - c) any other natural or legal person carrying out pharmacovigilance activities in whole or in part, on behalf of or in conjunction with marketing authorisation holders.



Commission Implementing Regulation (EU) 2021/1281

Article 27 - Pharmacovigilance Inspections (1)

1. Marketing authorisation holders **shall be prepared for inspections** of their pharmacovigilance system and the corresponding pharmacovigilance system master file in accordance with Article 123(6) and Article 126 of Regulation (EU) 2019/6 and shall ensure the same for any person mentioned in Article 26(1).
2. Marketing authorisation holders may be inspected on the site where the pharmacovigilance system master file is located or at any other site of those persons inspected in accordance with paragraph 1. With regard to a third party carrying out pharmacovigilance activities, the site to be inspected may be located within or outside the Union.



Commission Implementing Regulation (EU) 2021/1281

Article 27 - Pharmacovigilance Inspections (2)

4. Pharmacovigilance inspections may be either routine inspections or targeted inspections; they may be product-specific or inspections of the general pharmacovigilance system. In the occasion of an inspection, marketing authorisation holders shall:

- a) present proof that they have personnel, systems and facilities in place to meet their pharmacovigilance obligations and that they are ready for inspection at any time;
- b) present proof in regard to their contractual arrangements, including a clear description of the roles and responsibilities of third parties to whom pharmacovigilance activities are subcontracted and provisions for their inspection and audit;
- c) demonstrate that the pharmacovigilance system is in compliance with legislation or relevant pharmacovigilance guideline;



PhV inspections: What has changed?



Regulation (EU) 2019/6 vs Volume 9B of The Rules Governing Medicinal Products in the European Union

What has changed?

- *Regulation (EU) 2019/6 Article 126, 4.* The competent authorities of the Member States in which the **pharmacovigilance system master files are located** shall carry out inspections of the pharmacovigilance systems master files



- *Volume 9B:* The NCA, for inspection of the MAH's pharmacovigilance system, will be the NCA of the MS in whose territory the **MAH's QPPV is located**. Where an additional facility in another MS requires inspection (e.g., a database) the inspection will be carried out by the NCA of the MS in whose territory the facility is located.



Main changes and simplifications: What's new?

Past - present

- DDPS describing the PhV system
- DDPS filed in every MAA (variations)
- DDPS assessed and verified at inspection

**EU Member State
where PSMF is
located to lead the
inspection
(Supervisory
Authority)**

**Delegation and
Worksharing**

**PhV inspection
outcome, captured
in the database,
valid for all EU**

Avoid duplication,
adjust scope and
frequency of
inspections
(risk-based approach)

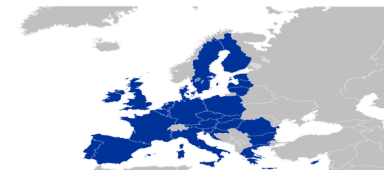
Future

- PSMF describing the PhV system, tool for QPPV oversight, audit/inspections
- PSMF kept by MAH not in MA dossier
- PSMF summary in MA dossier



Supervisory authority Vs National PhV Inspections

- **Supervisory authority (SA) PhV inspections:** SA is responsible for verifying on behalf of the Union that the MAH for the medicinal product and/or any third party carrying out pharmacovigilance activities on their behalf, satisfies the pharmacovigilance requirements laid down in Articles 126(1), (2), and (3) of Regulation (EU) 2019/6 and Commission Implementing Regulation (EU)2021/1281, Article 27. SA inspections are usually system inspections and may cover national specific aspects, if requested by other MS.
- **National non-SA PhV inspections** may still be required to:
 - verify compliance and/or product specific issue with national and EU requirements;
 - follow up at inspection findings upon request from the supervisory authority or another MS.





Delegation of tasks and worksharing

- Regulation (EU) 2019/6, Article 80 includes provisions for a competent authority to **delegate any of the tasks** entrusted to it as referred to in Article 79 to a competent authority in another MS subject to the written agreement of the latter;
- The delegating competent authority shall inform the Commission, the Agency and other competent authorities of the delegation and make that information public;
- MS may enter into **worksharing** initiatives and delegation of responsibilities with other competent authorities to avoid the duplication of efforts;
- This applies also for the SA responsibility to carry out pharmacovigilance inspections (**Delegation of the SA responsibilities**).





Sharing of information

- **Sharing of information is key for cooperation and coordination of inspections at Union level:**

- Planned and conducted inspections;
- Inspection scope and inspection outcomes;



- The Agency and MS shall cooperate to increase the exchange of information on inspections to facilitate risk-based inspection programme and avoid duplication of efforts/inspections.



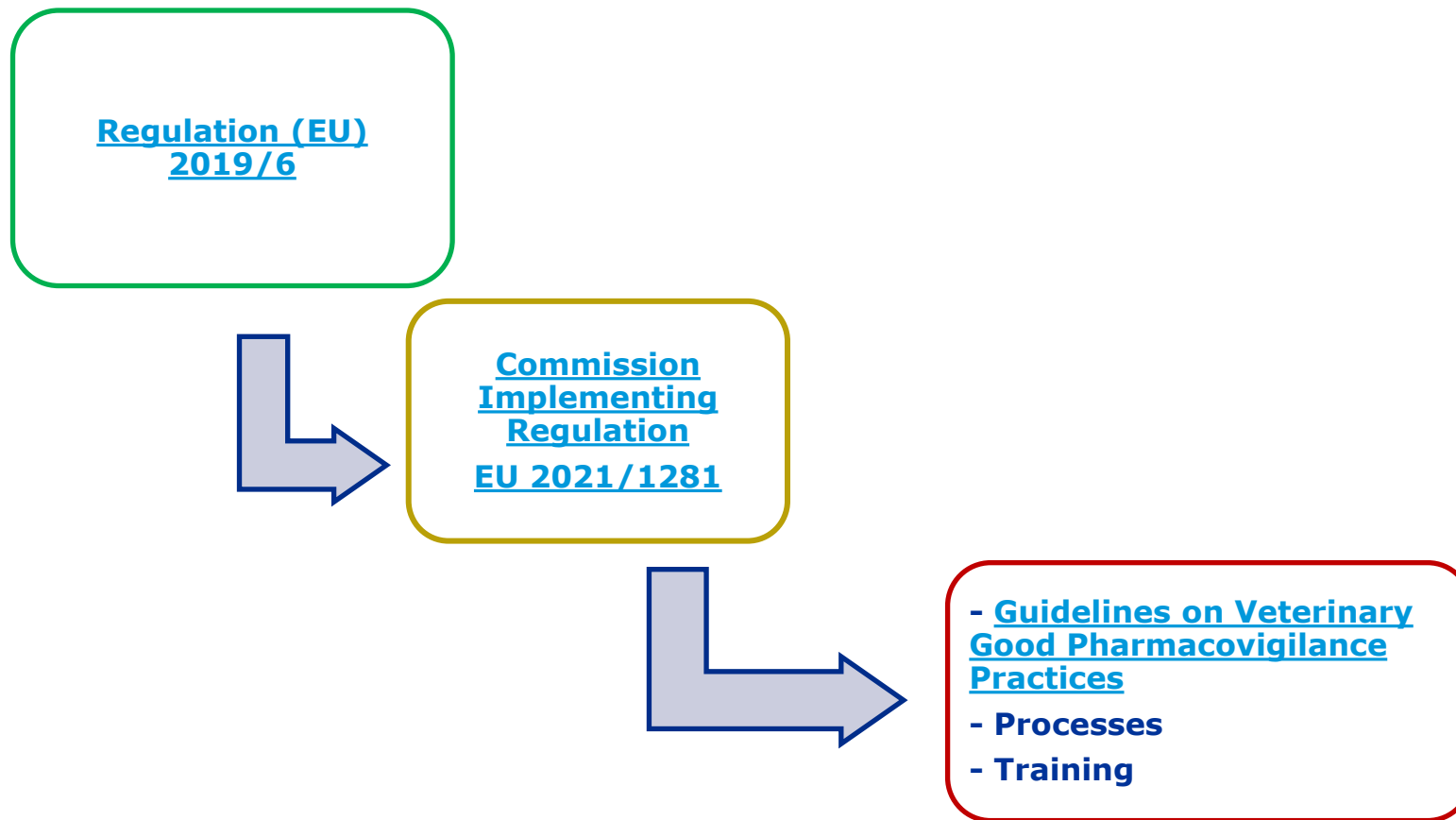
PhV inspection outcomes



Union Pharmacovigilance Database

- The results of the pharmacovigilance inspections shall be recorded in the pharmacovigilance database as referred to in Article 74 of Regulation (EU) 2019/6, accessible to NCAs only.
- MAHs will receive the full IR directly from NCAs.







Topics to highlight



Central Authorised Products (CAPs) inspection programme

- A risk-based programme for routine inspections of MAHs with CAPs is determined by EMA, together with:
 - Supervisory authorities of the Member States
 - PV Inspectors Working Group
 - Committee for Veterinary Medicinal Products (CVMP) and its Pharmacovigilance Working Party
- Inspections of MAHs with CAPs might be specifically requested by CVMP.

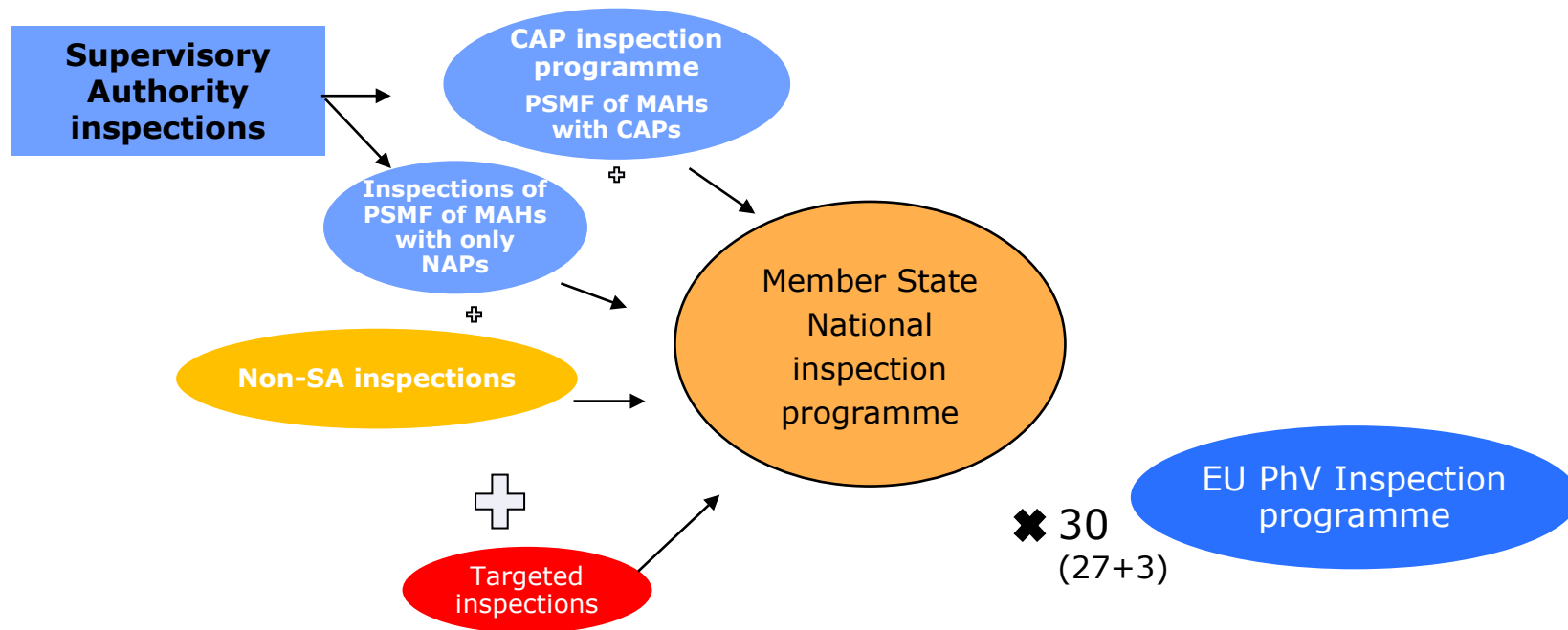


National Inspection Programme

- For PSMF of MAH of non-centrally authorised products (i.e., nationally authorised products), it is the responsibility of the competent authority of the Member State where the PSMF is located, to ensure by means of inspection that the legal requirements governing medicinal products are complied with (SA inspections);
- CAP inspection programme should be also implemented through national inspection programmes;
- Non-SA national inspections may also be needed;
- MS are therefore responsible for the planning and coordination of inspections within their own territory in order to ensure compliance with the legislation and to verify the effectiveness of the MAH's pharmacovigilance system at national and EU level.

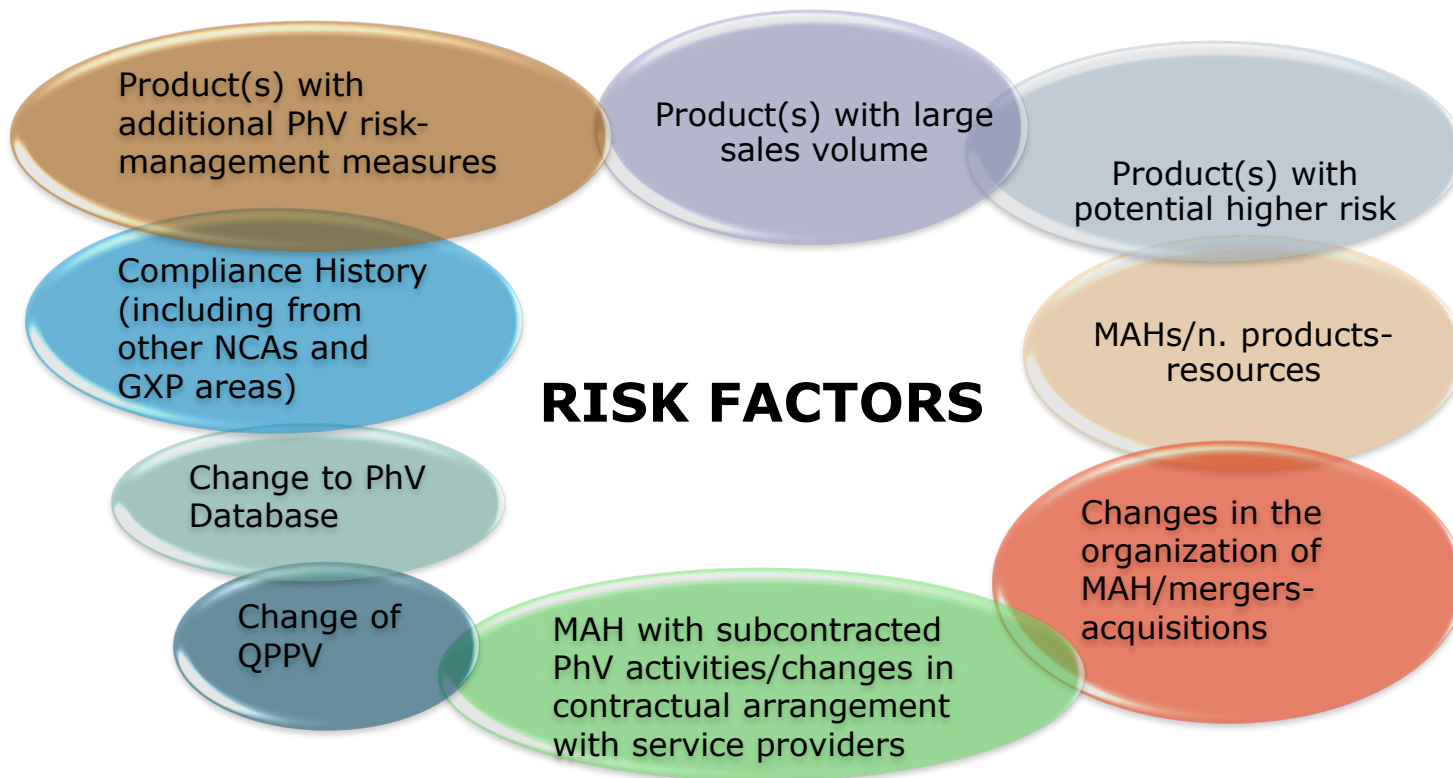


PhV Inspection programmes





Risk Based PhV Inspections Planning



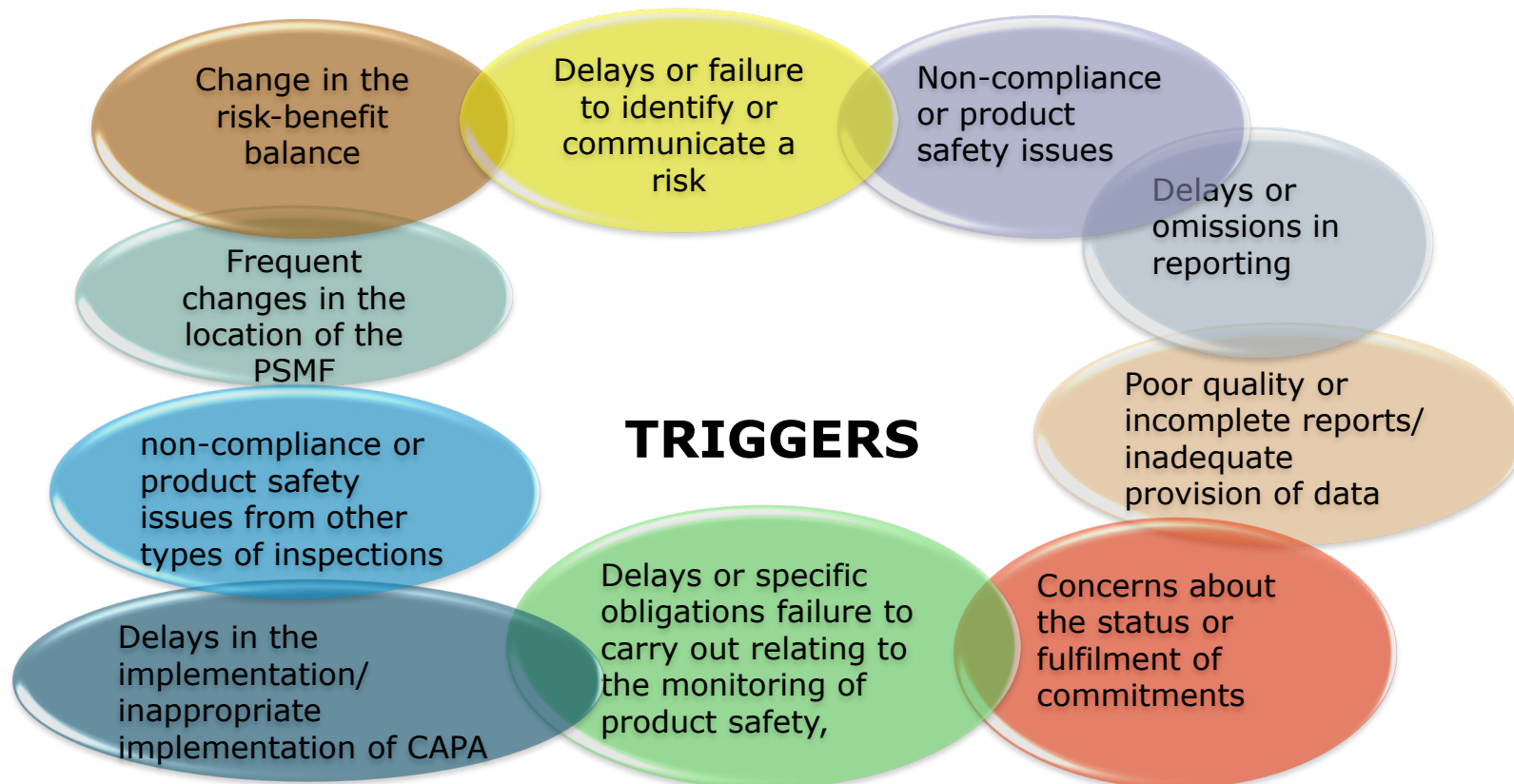


Routine pharmacovigilance inspections - Scope

- **Collection, reporting and recording of suspected adverse events for VMP** (Collecting, receiving and exchanging suspected adverse event reports from all types of sources, sites and departments within the pharmacovigilance system; Data transfer, data management, data coding, suspected adverse event report validation/evaluation, etc.)
- **Continuous benefit-risk balance monitoring** (use of all relevant sources of information for signal detection; Risk management system, including a process for monitoring the benefit-risk balance of products and performing signal management, etc.)
- **Pharmacovigilance system** (roles and responsibilities of MAH/QPPV; QMS; computerised systems; Contracts and agreements, etc.)



Targeted pharmacovigilance inspections





PhV System Vs Product Specific Inspections

PhV system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.

Product-related PhV inspections are focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. The general pharmacovigilance system may still be examined as part of a product-related inspection (e.g., the system used for that product).



Inspection Follow-up

Review of the CAPA

Review of the periodic progress reports

Re-inspection

Submission of previously un-submitted data/variations/impact analyses

Request for issuing safety communications

Communication of the inspection findings to other regulatory authorities in EU and outside EU

Product-related actions



Potential Regulatory Actions and Sanctions

Education and facilitation

Provision of information to other competent authorities/Agency/3rd Country regulator

Inspection and Re-inspection

Warning Letter, non compliance statement or infringement notice

Action against MAH/MA

Financial Penalties



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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