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The VGVP draft modules are released for consultation and may change further, pending the finalisation and publication of the Commission Implementing Regulation laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products.

Guideline on Veterinary Good Pharmacovigilance Practices (VGVP)

Module: Controls and pharmacovigilance Inspections

Draft

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1. Introduction

The verification of compliance of marketing authorisation holders with the legal requirements through risk-based controls in accordance with Article 123 of the Regulation (EU) 2019/6 and Articles 26, 27 of the Commission Implementing Regulation, is of fundamental importance to ensure that the objectives of the Regulation are effectively achieved across the Union. The definition of controls is provided in the Regulation (EU) 2019/6, Article 4(32). As part of controls the competent authorities of the Member States have the power to perform pharmacovigilance inspections of:

- holders of a marketing authorisation for a veterinary medicinal product;
- its qualified person responsible for pharmacovigilance in accordance with Article 77(8) of Regulation (EU) 2019/6;
- the representative(s) responsible for the reporting of suspected adverse events according to Article 14(1)(a) and (l) and Article 77(3) of Regulation (EU) 2019/6;
- any third party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorisation holder

to verify compliance with pharmacovigilance obligations [Commission Implementing Regulation (IR) 2021/XXX Article 27].

The competent authorities and the Agency shall ensure that all pharmacovigilance system master files in the Union are regularly checked and that the respective pharmacovigilance systems are correctly applied [Regulation (EU) 2019/6, Article 126(1)]. Regular checks of pharmacovigilance system master file requirements, as part of controls, may be used to support the risk-based approach to define the frequency of pharmacovigilance inspections.

According to 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. Member States may enter into work-sharing initiatives and delegation of responsibilities with other competent authorities to avoid the duplication of inspections of pharmacovigilance systems [Regulation (EU) 2019/6, Article 126(5)].

The result of inspection shall be communicated to the marketing authorisation holder, the qualified person for pharmacovigilance and, if applicable, a third party to whom pharmacovigilance tasks have been contracted out to. The marketing authorisation holder will be given the opportunity to provide a response to the findings identified [Regulation (EU) 2019/6, Article 123(7)]. This response should include a root cause analysis, further assessment and corrective and preventative action for each finding. The results of pharmacovigilance inspections shall be recorded by the competent authority performing the inspection in the Union pharmacovigilance database [Regulation (EU) 2019/6, Articles 74(1) and 126(6)].

The frequency of inspections should be determined by the competent authorities taking into account the intrinsic risks and information indicating non-compliance in accordance with Article 123(3) of Regulation (EU) 2019/6 and section 2.2 of this Module. This approach allows competent authorities to set up inspection programmes and allocate resources to areas where the risk is the highest. Pharmacovigilance inspections will be planned and coordinated with the aim to promote work-sharing and delegation of responsibilities to avoid duplication of inspections of same pharmacovigilance systems [Regulation (EU) 2019/6, Article 126(5)].

According to Article 126(2) and (3) of Regulation (EU) 2019/6 inspections of the pharmacovigilance systems covering centrally authorised veterinary medicinal products shall be coordinated by the

Agency and carried out by the competent authorities (risk-based programme for routine supervisory authority inspections of MAHs with CAPs, see section 2.4 of this Module), whereas inspections of pharmacovigilance systems covering only nationally authorised products shall be coordinated and carried out by the respective competent authorities (national inspection programmes, see section 2.4 of this Module) .

The scope of this Module is to provide general guidance on the planning, conduct, reporting, follow-up and operation of pharmacovigilance inspections in the EU for monitoring of Marketing Authorisation Holder compliance with pharmacovigilance obligations.

This guidance is applicable to any veterinary medicinal product in the EU, authorised via any marketing authorisation procedure and therefore the requirements proposed for marketing authorisation holders apply also to registration holders for registered homeopathic veterinary medicinal products (Regulation (EU) 2019/6, Article 87(5)).

This module must be read in conjunction with Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (the Regulation) and Commission Implementing Regulation (EU) …/... of XXX laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products <complete reference to the Commission Implementing Regulation when available>.

This Module should also be read in conjunction with the other guidelines on veterinary good pharmacovigilance practices (VGVP), pharmacovigilance inspection procedures and National legislations, as applicable.

2. Structures and Processes of inspections

2.1. Sites to be inspected

The site where the pharmacovigilance system master file (PSMF) is located will be the primary site selected for inspection. Inspection of other sites may also be requested if necessary, to verify the conduct of specific pharmacovigilance activities that cannot be inspected at the pharmacovigilance system master file location or in the case of local national inspection.

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorisation holder may be inspected, in order to confirm their capability to support the marketing authorisation holder’s compliance with pharmacovigilance obligations [IR 2021/XXX, Article 26(1)].

The sites to be inspected may be located in the EU (e.g. pharmacovigilance system master file site/EU QPPV site/location where significant pharmacovigilance activities are conducted) or outside the EU. Inspections of sites outside the EU might be appropriate where the main pharmacovigilance centre, databases and/or activities are located outside the EU and it would be otherwise inefficient or impossible to confirm compliance from a site within the EU. Member States and the Agency shall cooperate in the coordination of inspections in third countries to avoid duplication of activities and ensure the best use of resources.

The type and number of sites to be inspected should be selected to ensure that the key objectives within the scope of the inspection are met.

Third parties that form part of a pharmacovigilance system should be inspection-ready and should accept to be audited and inspected, as necessary, and this should be reflected in the relevant agreements [IR 2021/XXX, Article 26(1)].

2.2. Inspection Planning

Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of protection of public and animal health and of the environment. A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

The frequency and extent of all inspection types shall be appropriate to the potential risks associated with the respective veterinary medicinal products and the inspected party.

As a general approach, a marketing authorisation holder should be inspected regularly, and the inspection frequency will be adjusted on the basis of risk-based considerations in accordance with the factors listed in this section.

In order to ensure that inspection resources are used in an efficient way, the scheduling and conduct of inspections will be driven by the preparation of inspection programmes. Sharing of information and communication between inspectors and assessors within one Member State as well as between inspectors and assessors of different authorities in different Member States is important to ensure successful prioritisation and targeting of these inspections.

According to Article 123(3) of Regulation (EU) 2019/6 risk-based controls and inspections shall be carried out by the competent authorities taking account of, as a minimum, the intrinsic risks associated with the activities carried out by the inspected entity and the location of their activities, the past record of compliance based on the results of previous controls, where applicable, any information that might indicate non-compliance and the potential impact of non-compliance on public health, animal health, animal welfare and the environment.

Factors which may be taken into consideration, as appropriate, by the competent authorities when establishing risk-based pharmacovigilance inspection programmes include, but are not limited to:

- inspection related factors:
  - Compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP).
  - Re-inspection date recommended by the inspectors or assessors as a result of a previous inspection.
- product related factors:
  - Product(s) with potential higher risk to human or animal health or the environment.
  - Product(s) with additional pharmacovigilance risk-management measures [Regulation (EU) 2019/6, Article 79(5)].
  - Product(s) with large sales volume, i.e. products associated with large animal exposure in in the EU.
  - Product(s) with limited alternative on the market in the EU.
- marketing authorisation holder related factors:
  - Marketing authorisation holder that has never been subject to a pharmacovigilance inspection.

- Marketing authorisation holder with many products on the market in the EU.
- Resources available to the marketing authorisation holder for the pharmacovigilance activities they undertake.
- Marketing authorisation holder with no previous marketing authorisations in the EU.
- Negative information and/or safety concerns raised by competent authorities, other bodies outside the EU or other areas (i.e. GCP, GMP, GLP and GDP).
- Changes in the marketing authorisation holder organisation, such as mergers and acquisitions.

- pharmacovigilance system related factors:
  - Marketing authorisation holder with sub-contracted pharmacovigilance activities (function of the qualified person responsible for pharmacovigilance in the EU (QPPV), reporting of safety data, sub-contract of pharmacovigilance system master file management, etc.).
  - Multiple firms employed to perform pharmacovigilance activities.
  - Change of QPPV since the last inspection.
  - Changes to the pharmacovigilance safety database(s), which may include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data.
  - Changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted or in pharmacovigilance system master file management.
  - Other information available (e.g. assessment from other regulatory authorities).

National competent authorities and the Agency may solicit information from marketing authorisation holders that is not readily available in the Union Product database or the Union pharmacovigilance database, but which is an essential factor to consider for inspection programme preparation and maintenance. Major changes in the pharmacovigilance system that are not part of the pharmacovigilance system master file summary (e.g. subcontracting or change in subcontracting pharmacovigilance activities) may be collected by Member States until further improvements of the functionalities of the Union pharmacovigilance database are implemented or other means of collection of the required information is agreed by the Member States inspectorates to facilitate the communication of major changes in the pharmacovigilance system essential for risk-based inspection planning.

2.3. Supervisory Authority and national competent authority inspections

According to Regulation (EU) 2019/6, Article 126(4) the competent authority of the Member State in which the pharmacovigilance system master file is located shall carry out the inspections of the pharmacovigilance system master file. This Member State is designated as the supervisory authority for the corresponding pharmacovigilance system and this role is applicable for veterinary medicinal products authorised via any marketing authorisation procedure. The supervisory authority for pharmacovigilance inspections is responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product and/or any third party carrying out pharmacovigilance activities on their behalf, satisfies the pharmacovigilance requirements laid down in Article 126(1), (2), and (3) of Regulation (EU) 2019/6 and Commission Implementing Regulation (EU) Xxx, Article 27. Aspects of the pharmacovigilance system at global level may be checked, if necessary.

Where relevant or on request, and in particular where the main pharmacovigilance tasks are conducted at a site in a Member State different from the pharmacovigilance system master file location Member State or for product-specific issues, the Supervisory Authority inspectorate may request assistance by another Member State´s inspectorate where the site of main pharmacovigilance activities is located or the concerned product is marketed, as appropriate. The Supervisory Authority role may also be delegated to another Member State and in this case the delegation of activities should be recorded and communicated to the Agency and the Member States, as described in section 2.5 of this Module.

In addition to the Supervisory Authority inspections conducted on behalf of the Union, national competent authorities, that do not have the supervisory authority role, shall have the right to inspect any site, including third parties, as necessary, in order 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 Member State.

2.4. Inspection programmes

The establishment of inspection programmes will ensure that Marketing authorisation holders' pharmacovigilance system master files and the respective pharmacovigilance systems are inspected regularly, and that the inspection frequency is adjusted following risk-based approach in accordance with the factors in section 2.2 of this Module.

In the context of centrally authorised products (CAPs), a risk-based programme for routine supervisory authority inspections of MAHs with CAPs will be determined by the Agency in conjunction with the concerned Member States, the Pharmacovigilance Inspectors Working Group (PhV IWG), the Committee for Medicinal Products for Veterinary Use (CVMP) and its Pharmacovigilance Working Party. These inspections should be prioritised based on the potential risk to animal, public health and the environment, considering the factors listed in section 2.2. This routine inspection programme will be separate from any targeted inspections, but if a targeted inspection takes place it may replace the need for one under this programme, dependent on its scope.

In the context of nationally authorised products (NAPs), if the same pharmacovigilance system is used for products with a variety of authorisation types (including mutual recognition, decentralised and national), then the supervisory authority inspection in the CAP programme should be applicable for all products covered by that system. In case the pharmacovigilance system covers only NAPs then the supervisory authority inspection should be part of the concerned Member State´s national inspection programme.

Each national competent authority should prepare a yearly inspection programme that will be adjusted to include:

- the routine supervisory authority inspections of the programme related to CAPs;
- the supervisory authority inspections related to pharmacovigilance system master files) only covering NAPs, if applicable;
- any non-supervisory authority pharmacovigilance inspections of sites in or outside the Member State territory, as necessary. Each competent authority should prioritise the inspections in its national programme based on the inspection result in the Union pharmacovigilance database and other information available on the pharmacovigilance system and potential non-compliance. The information available should be used to determine the inspection timing and scope for the

Supervisory Authority inspections and the need and scope of non-supervisory authority inspections, where applicable.

Member States should also consider possibilities for work-sharing and delegation of inspection activities for part or the full scope of the planned inspections as discussed in section 2.5 and adjust their programmes accordingly, to avoid duplication of effort and increase inspection efficiency.

Committee for Veterinary Medicinal Products (CVMP) requested inspections for CAPs

Pharmacovigilance inspections related to marketing authorisation holders of CAPs might be specifically requested by the CVMP, in particular in the following situations:

- When additional sites within EU are identified for inspection and require joint inspections involving the Member State concerned by that site and the supervisory authority (work-sharing, e.g. joint inspection with inspectors from different Member State authorities and/or inspections at two or more sites in different Member States belonging to one marketing authorisation holder or being contracted third parties under one pharmacovigilance system master file).
- Based on PhV WP-V recommendation (e.g. re-inspection as consequence of a previous negative inspection leading to a more targeted inspection; for complex pharmacovigilance systems and/or covering products authorised via different marketing authorisation procedures).
- When a Member State supervisory authority prefers to follow this route.
- In the case of a targeted inspection (triggers for this type of inspection can be found in section 2.7.2.).
- When pharmacovigilance sites in third countries are identified for inclusion in the inspection.

2.5. Delegation of tasks and work-sharing

In line with Article 126(5) and pursuant to Article 80 of Regulation (EU) 2019/6 work-sharing and delegation for pharmacovigilance inspections is possible. The use of Supervisory Authority is introduced for authorities inspecting on behalf of the whole Union, as a way of work-sharing, on the basis of the national competent authority of the Member State where pharmacovigilance system master file is located regardless of type of marketing authorisation procedure [Regulation (EU) 2019/6, Article 126(2) and (3)]. Such delegation of tasks and work-sharing is described below.

According to Article 80 (1) of the Regulation, a competent authority may delegate any of the tasks entrusted to it, including controls and inspections to a competent authority in another Member State provided that the delegation request is accepted by the Member State proposed and the agreement is captured in writing. The delegating competent authority shall inform the Commission, the Agency and other competent authorities of the delegation of the task and make that information public [Regulation (EU) 2019/6, Articles 79 and 80].

The delegation of the Supervisory Authority role for pharmacovigilance controls and inspections should be officially recorded and made available to all Member States in a Union delegation reference list and it should be valid until a new Member state accepts the role in writing or the Member state where the pharmacovigilance system master file is located resumes its role. At the initial period of delegation close communication and potentially joint inspection(s) may be required between the previous and the new Supervisory authority.

In addition to the Supervisory Authority role, Member States may establish other work-sharing arrangements in relation to controls and inspections, if necessary.

2.6. Sharing of information

The Agency and the Member States shall cooperate to facilitate the exchange of information on inspections, and in particular:

- information on inspections planned and conducted in order to avoid unnecessary repetition and duplication of activities in the EU and optimise the inspection resources;
- the result of pharmacovigilance inspections, captured in the Union pharmacovigilance database, in accordance with Article 74(1) of Regulation (EU) 2019/6 by the inspecting authority including:
  - the competent authority of the Member State conducting the inspection (identified via the user making the entry);
  - PSMF reference number(s) (defining the Supervisory Authority);
  - information on whether the competent authority of the Member State conducting the inspection is the Supervisory authority for this pharmacovigilance system master file (i.e. Supervisory Authority inspection);
  - name and address of the site inspected (i.e. pharmacovigilance system master file location site or other);
  - date(s) of inspection;
  - high level outcome and follow up (CAPA) information.
- the inspection report (IR) or the summary outcome in English if the IR is not in English including:
  - information on major and critical findings and corrective and preventive action plan agreed (progress status/timelines) to focus on in future inspections;
  - information on marketing authorisation holder delegation of tasks and contracts with third parties/partners for pharmacovigilance key tasks in case of complex company structures.

2.7. Inspection types and inspection scope

There are two main types of pharmacovigilance inspections, routine and targeted inspections, as described in sections 2.7.1 and 2.7.2 of this module. In addition, irrespective of whether an inspection is routine or targeted it can also fall in multiple categories as described in sections 2.7.3, 2.7.4 and 2.7.5 below.

The inspection scope will depend on the type of inspection (e.g. routine or targeted, system or product specific, re-inspection, remote inspection), on the objectives of the inspection as well as the coverage of any previous inspections by competent authorities of Member States.

Pharmacovigilance 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 pharmacovigilance inspections are primarily 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).

The following elements should be considered when preparing the scope of the inspection, as applicable:

- Information supplied in the pharmacovigilance system master file;
- Information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the Agency such as EudraVigilance reporting;
- Specific triggers (see section 2.7.2 below for examples of triggers).

It may be appropriate for additional data to be requested in advance of an inspection in order to select appropriate sites or clarify aspects of the pharmacovigilance system.

2.7.1. Routine pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections. One or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance.

Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

Routine pharmacovigilance inspections conducted on behalf of the EU should examine compliance with EU legislation and guidance, and the scope of such inspections should include the following elements, as appropriate:

- Collection, reporting and recording of suspected adverse events for veterinary medicinal products:
  - Collecting, receiving and exchanging suspected adverse event reports from all types of sources, sites and departments within the pharmacovigilance system, including from those firms subcontracted by the marketing authorisation holder to fulfil marketing authorisation holder's pharmacovigilance obligations and departments other than their safety department.
  - Data transfer, data management, data coding, including the appropriate use of terminology (e.g. the use of medically important terms), suspected adverse event report validation and suspected adverse event report evaluation. In addition to examples of suspected adverse events from within the EU, examples of suspected adverse events reported from outside the EU should be examined as part of this review (if applicable).
  - Follow-up of suspected adverse event reports.
  - Recording of adverse events in the Union pharmacovigilance database according to the requirements and timeliness of such recording.
  - Record keeping and archiving of all relevant documents.
- Continuous safety monitoring:
  - Use of all relevant sources of information for signal detection (see Module XX – Signal Management, section 2.2).
  - Risk management system, including a process for monitoring the benefit-risk balance of products and performing signal management, processes to take appropriate action to minimize identified risks and communication plan [IR 2021/XXX, Article 16].

- The inclusion of post-marketing surveillance study data in continuous safety monitoring.

- Pharmacovigilance system:
  - QPPV roles and responsibilities, e.g. access to the quality management system, the pharmacovigilance system master file, performance indicators, audit and inspection reports, and their ability to take action to improve compliance.
  - The roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system.
  - Accuracy, completeness and maintenance of the pharmacovigilance system master file.
  - Quality and adequacy of training, qualifications and experience of staff.
  - Coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes.
  - Fitness for purpose of computerised systems or other appropriate recording system for the management of adverse event data and pharmacovigilance related data [IR 2021/XXX, Article 10(2e)].
  - Contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and whether they are adhered to.
  - Document management system [IR 2021/XXX Article 5], including archiving arrangements that ensure the safety and the timely availability of pharmacovigilance data and other relevant data for the pharmacovigilance system.
  - Communication in accordance with good veterinary pharmacovigilance practices.
  - The inspection may include the system for the fulfilment of conditions of a marketing authorisation and marketing authorisation holder commitments, as they relate to any of the above safety topics.

2.7.2. Targeted pharmacovigilance inspections

Targeted pharmacovigilance inspections are undertaken when a trigger is recognised, and an inspection is considered an appropriate way to examine the issues. Targeted inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. Targeted inspections may arise when, for example, one or more of the below listed triggers are identified:

- Risk-benefit balance of the product:
  - Change in the risk-benefit balance where further examination through an inspection is considered appropriate.
  - Delays or failure to identify or communicate a risk or a change in the risk-benefit balance.
  - Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the national competent authorities or Agency, as applicable.
  - Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the national competent authorities and/or the Agency.

- Suspension with no advance notice to the competent authorities.

- Reporting obligations:
  - Delays or omissions in reporting in the Union pharmacovigilance database.
  - Poor quality or incomplete reports.
  - Inconsistencies between reports and other information sources.
- Requests from competent authorities:
  - Failure to provide the requested information or data within the deadline specified by the competent authorities.
  - Poor quality or inadequate provision of data to fulfil requests for information from the competent authorities.
- Fulfilment of commitments:
  - Concerns about the status or fulfilment of commitments.
  - Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorisation.
  - Poor quality of reports requested as specific obligations.
- Inspections:
  - Delays in the implementation or inappropriate implementation of corrective and preventive actions.
  - Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP).
  - Inspection information received from other authorities (EU or non-EU), which may highlight issues of non-compliance.
- Others:
  - Concerns following review of the pharmacovigilance system master file.
  - Non-inspection related information received from other authorities, which may highlight issues of non-compliance.
  - Other sources of information or complaints.
  - Frequent changes in the location of the pharmacovigilance system master file and shared pharmacovigilance system master file may also be taken into account.

The scope of targeted inspections should depend on the specific trigger(s) described above and may also include the QPPV involvement and awareness of product-specific issues and in-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

2.7.3. Announced and unannounced inspections

It is anticipated that the majority of inspections will be announced i.e. notified in advance to the inspected party, to ensure the availability of relevant individuals for the inspection and allow preparation for a smooth conduct of the inspection. However, on occasion, it may be appropriate to

conduct unannounced inspections or to announce an inspection at short notice (e.g. when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

2.7.4. Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors should be assessed in order to prioritise re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriately corrective and preventive actions in response to an earlier inspection.

2.7.5. Remote inspections

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorisation holder or firms employed by the marketing authorisation holder. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside the EU or a third party service provider is not available at the actual inspection site, but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and pharmacovigilance system master file, via remote access. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions), in accordance with the guidance on Remote pharmacovigilance inspections of MAHs during a crisis situation - Points to consider. Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the inspection. The logistical aspects of the remote inspection should be considered following liaison with the marketing authorisation holder. Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection has revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

2.8. Inspection follow-up

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up should be required until a corrective and preventive action plan is completed. The below listed follow-up actions should be considered to be performed by the Competent Authority, as appropriate:

- Review of the marketing authorisation holder's corrective and preventive action plan.
- Review of the periodic progress reports, when deemed necessary.
- Re-inspection to assess appropriate implementation of the corrective and preventive action plan.
- Requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities.
- Requests for issuing safety communications, including amendments of marketing and/or advertising information.
- Requests for a meeting with the marketing authorisation holder to discuss the deficiencies, the impact of the deficiencies and action plans.

- Communication of the inspection findings to other regulatory authorities (see section 2.6 above).
- Other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions relating to the marketing authorisations).

2.9. Regulatory actions and sanctions

Under EU legislation, in order to protect public health, animal health and the environment, competent authorities are obliged to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance obligations is detected, the necessary action should be judged on a case-by-case basis. What action is taken should depend on the potential negative public health impact of the non-compliance(s). Any instance of non-compliance may be considered for enforcement action. Action may be taken by the Agency, the Commission or the competent authorities of the Member States as appropriate. The Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties [Regulation (EU) 2019/6, Article 135]. In the event of non-compliance, possible regulatory options include, as applicable:

- education and facilitation: national competent authorities may communicate with marketing authorisation holder representatives (e.g. in a meeting) to summarise the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the marketing authorisation holder's proposals for corrective and preventive actions;
- provision of information to other competent authorities, the Agency or third country regulators under the framework of confidentiality arrangements;
- inspection: non-compliant marketing authorisation holders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- warning letter, non-compliance statement or infringement notice: these are non-statutory or statutory instruments in accordance with national legislation which competent authorities may issue stating the legislation and guideline that has been breached, reminding marketing authorisation holders of their pharmacovigilance obligations or specifying the steps that the marketing authorisation holder should take and in what timeframe in order to rectify the noncompliance and in order to prevent a further case of non-compliance;
- competent authorities may consider making public a list of marketing authorisation holders found to be seriously or persistently non-compliant;
- actions against a marketing authorisation(s) or authorisation application(s) e.g.:
  - Urgent Safety Restriction.
  - Variation of the marketing authorisation.
  - Suspension or revocation of the marketing authorisation.
  - Delays in approvals of new marketing authorisation applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorisations.
  - Product recalls e.g. where important safety warnings have been omitted from product information.
  - Action relating to marketing or advertising information.
  - Amendments or suspension of studies due to product-specific safety issues.

519 – Administrative penalties, usually fixed fines or based on company profits or levied on a daily
520 basis.

521 – Referral for criminal prosecution (in accordance with national legislation).

522 *2.10. Qualification and training of inspectors*

523 Inspectors who are involved in the conduct of pharmacovigilance inspections requested by their
524 Member States or by the CVMP should be officials of, or appointed by, the Member State in accordance
525 with national regulation and follow the provisions of the national competent authority. It is
526 recommended that inspectors are appointed based on their experience and requirements defined by
527 the national competent authority. The inspectors should undergo training to the extent necessary to
528 ensure their competence required for preparing, conducting and reporting inspections. If not acquired
529 by their experience, they should be trained in pharmacovigilance processes and requirements in such
530 way that they comprehend the different aspects of a pharmacovigilance system. Documented
531 processes should be in place in order to ensure that inspection competencies are maintained. In
532 particular, inspectors should be kept updated with the current status of pharmacovigilance legislation
533 and guidance. Training and experience should be documented individually and evaluated according to
534 the requirements of the applicable quality system of the concerned competent authority.

535 The competent authorities shall have procedures or arrangements in place to ensure that staff
536 performing controls and inspections are free from any conflict of interest [Regulation (EU) 2019/6,
537 Article 123(8)].

538 *2.11. Inspection procedures*

539 Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up
540 and documented in accordance with the legislative requirements, good pharmacovigilance practices
541 and the union procedures for pharmacovigilance inspections related to veterinary medicinal products.
542 that should cover at least, the following processes:

543 • Sharing of information.

544 • Coordination of pharmacovigilance inspections in the EU.

545 • Coordination of third country inspections (including inspections of contractors in third countries);

546 • Preparation of pharmacovigilance inspections.

547 • Conduct of pharmacovigilance inspections.

548 • Reporting of pharmacovigilance inspections and inspection follow-up.

549 • Sanctions and enforcement in case of serious non-compliance.

550 • Recommendations on the training and experience of inspectors performing pharmacovigilance
551 inspections.

552 In addition, guidance on marketing authorisation holder preparedness for facilitation of
553 pharmacovigilance inspections and controls should be made available.

554 These procedures and guidance will be revised and updated as deemed necessary. New procedures
555 may also be developed when the need is identified in relation to the inspection process.

Definitions

Please refer to the VGVP Glossary (EMA/118227/2021) for relevant definitions.