

4 September 2026  
EMA/119871/2012 Rev 2\*

## Guideline on good pharmacovigilance practices (GVP)

### Module III – Pharmacovigilance inspections (Rev 2)

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|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Date for coming into effect of first version                                                                                                               | 13 December 2012  |
| Date for coming into effect of Revision 1                                                                                                                  | 16 September 2014 |
| Draft Revision 2 reviewed by the Agency's Pharmacovigilance Inspectors' Working Group (PhVIWG)                                                             | 2 June 2026       |
| Draft Revision 2 agreed by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) and finalised by the Agency in collaboration with Member States | 6 July 2026       |
| Draft Revision 2 agreed by the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh)                                      | 16 July 2026      |
| Draft Revision 2 agreed by the Head of Human Medicines Division as final under delegated authority by the Executive Director                               | 4 September 2026  |
| Date for coming into effect of Revision 2*                                                                                                                 | 10 September 2026 |

\* Revision 2 includes the following:

- Incorporating the new legal provisions as per Articles 6(3) and (4) and Article 13(1a) of Implementing Regulation (EU) No 520/2012 as amended by Commission Implementing Regulation (EU) 2025/1466 of 22 July 2025 in relation to subcontracting in III.A. and III.B.3.;
- Deleting the mention of clinical trials, now under governed by Regulation (EU) No 536/2014, in III.B.1.4.;
- Updating legal references to Regulation (EU) 2024/568 in relation to fees in III.C.6.;
- Updating references and information on web access to referenced documents in III.B.5. and throughout the Module;
- Alignments with the referenced Union procedures throughout the Module;
- Clarifications in the light of experience with remote inspections in III.B.1.7.;
- Strengthening of a risk-based inspection cycle in III.C.4.3.;
- Providing a clarification regarding timing of document provision in III.C.5.;
- Overall editorial improvements, specifying legal references for clarity, and alignments with revisions of this and other GVP Modules.

**Note:** As the Implementing Regulation (EU) 2025/1466 was subject to public consultation in the EU, Revision 2 of GVP Module III was not subject to public consultation.

See websites for contact details

European Medicines Agency [www.ema.europa.eu](http://www.ema.europa.eu)  
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## III.A. Introduction

This Module contains guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in the EU and outlines the role of the different parties involved. General guidance is provided under [III.B.](#), while [III.C.](#) covers the overall operation of pharmacovigilance inspections in the EU.

In this GVP Module, all applicable legal requirements are referenced as explained in the [GVP Introductory Cover Note](#) and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”. Directive 2001/83/EC as amended is referenced as ‘DIR’, Regulation (EC) No 726/2004 as amended as ‘REG’ and the Commission Implementing Regulation (EU) No 520/2012 as amended as “IR”.

In order to determine that marketing authorisation holders comply with pharmacovigilance obligations established within the EU, and to facilitate compliance, competent authorities of the Member States concerned shall conduct, in cooperation with the Agency, pharmacovigilance inspections of marketing authorisation holders or third parties subcontracted for pharmacovigilance tasks (which includes third parties subcontracted directly by the marketing authorisation holder and third parties further subcontracted by such subcontracted third parties [IR Art 6(3)]) [IR Art 13(1a)]. Such inspections shall be carried out by inspectors appointed by the national competent authorities and empowered to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorisation holder or any third parties subcontracted by the marketing authorisation holder or by a subcontracted third party to perform the activities described in Title IX of Directive 2001/83/EC in accordance with Articles 111(1), 111(1d) and 111(1g). In particular, marketing authorisation holders are required to provide, on request, the PSMF, which will be used to for planning and conducting inspections [DIR Art 23(4), REG Article 16(3a)] (see [GVP Module II](#)). Furthermore, any third party subcontracted to conduct pharmacovigilance tasks in whole or in part on behalf of or in conjunction with marketing authorisation holders may be inspected by the competent authorities, even if the obligation of the third parties to agree to be inspected by competent authorities has not yet been included in the subcontract [IR Art 13(1a)]. The third party has the obligation to agree to be inspected by competent authorities in the subcontract [IR Art 6(3)]. This applied mutatis mutandis to the third parties that subcontract the tasks subcontracted to them by the marketing authorisation holder [IR Art 6(3)]. Also, where a subcontracted third party subcontracts (a) task(s) to another third party, inspections arrangements should be clearly documented [IR Art 6(3)]. The objectives of pharmacovigilance inspections are to:

- Determine that the marketing authorisation holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;
- Identify, record and address non-compliance;
- Use the inspection results as a basis for enforcement action, where considered necessary.

For marketing authorisation holders of centrally authorised products, it is the responsibility of the supervisory authority for pharmacovigilance to verify, on behalf of the EU, that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Directive 2001/83/EC [REG Art 19]. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the PSMF is located [REG Art 18(3)]. The PSMF shall be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the EU where the qualified person responsible for

pharmacovigilance in the EU (QPPV) operates [IR Art 7(1)]. The supervisory authority may conduct pre-authorisation inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system [REG Art 19(1)].

For marketing authorisation holders of non-centrally authorised products (i.e. nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure), it is the responsibility of the competent authority of the Member State concerned, in cooperation with the Agency, to ensure by means of inspection that the legal requirements governing medicinal products are complied with. This cooperation shall consist of the sharing of information between national competent authorities and the Agency concerning inspections that are planned and those that have been conducted [DIR Art 111(1)]. There should be cooperation between national competent authorities and the Agency to minimise duplication and maximise the use of available resources. National competent authorities and the Agency will make use of the shared information on planned and conducted inspections to facilitate this and to adapt the scope and/or timing of their inspections.

Pharmacovigilance inspection programmes will be implemented, which will include routine inspections scheduled according to a risk-based approach and will also incorporate for-cause inspections, which have been triggered to examine suspected non-compliance or potential risks, usually with impact on a specific medicinal product(s).

The results of an inspection shall be provided to the inspected entity, who shall be given the opportunity to comment [DIR Art 111(3) and (8)]. Any non-compliance should also be rectified by the marketing authorisation holder in a timely manner through the implementation of a corrective and preventive action plan.

If the outcome of the inspection is that the marketing authorisation holder does not comply with the pharmacovigilance obligations, the Member State concerned shall inform the other Member States, the Agency and the European Commission in accordance with **III.C.1.** [DIR Art 111(8)].

Sharing of information and communication between inspectors and assessors from the Pharmacovigilance Risk Assessment Committee (PRAC) and from the Committee for Medicinal Products for Human Use (CHMP), is very important in relation to issues of EU interest and, where considered appropriate, for the proper follow-up of inspections and the provision of recommendations on actions to be taken.

Where 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 [DIR Art 111(8)]. Regulation (EC) No 658/2007 also empowers the European Commission to impose financial penalties on marketing authorisations holders to ensure the enforcement of certain obligations connected with marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004.

## **III.B. Structures and processes**

### ***III.B.1. Inspection types***

#### **III.B.1.1. Pharmacovigilance system and medicinal product-related inspections**

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, medicinal product-specific examples may be used to demonstrate the operation of the system.

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

### **III.B.1.2. Routine and for-cause 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 optimise supervisory activities should be implemented. These inspections are usually pharmacovigilance system inspections, and one or more specific medicinal 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.

For-cause pharmacovigilance inspections are undertaken when a trigger is recognised, and an inspection is considered an appropriate way to examine the issues. For-cause 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 medicinal product. However, full pharmacovigilance system inspections may also be performed resulting from a trigger. For-cause inspections may arise when, for example, one or more of the triggers listed below are identified:

- Risk-benefit balance of the medicinal 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 safety issues for a medicinal product identified during the monitoring of pharmacovigilance activities by the national competent authorities and/or the Agency;
  - Suspension or withdrawal of the medicinal product with no advance notice to the competent authorities;
- Reporting obligations (expedited and periodic):
  - Delays or omissions in reporting;
  - 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 risk management plan (RMP) commitments;
  - Delays or failure to carry out specific pharmacovigilance obligations, 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 within or outside the EU, which may highlight issues of non-compliance;
- Others:
  - Concerns following review of the PSMF;
  - Non-inspection related information received from other authorities, which may highlight issues of non-compliance;
  - Other sources of information or complaints.

### **III.B.1.3. Pre-authorisation inspections**

If considered necessary, the supervisory authorities for pharmacovigilance may conduct pre-authorisation inspections to verify the accuracy and successful implementation of the pharmacovigilance system as it has been described by the applicant for a marketing authorisation through the centralised procedure in support of the marketing authorisation application [REG Art 19]. Pre-authorisation pharmacovigilance inspections are inspections performed before a marketing authorisation is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as described by the applicant. Pre-authorisation inspections are not mandatory but may be requested in specific circumstances in accordance with the **Union Procedures for Pharmacovigilance Inspections**<sup>1</sup>. To avoid performing unnecessary inspections which may delay the granting of a marketing authorisation, the following aspects may be considered:

- The applicant has not previously operated a pharmacovigilance system within the EU or is in the process of establishing a new system;
- Previous information (e.g. inspection history and non-compliance notifications or information from other authorities) indicates that the applicant has a poor history or culture of compliance. If the marketing authorisation holder has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorisation pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the pharmacovigilance system before a new authorisation is granted;
- Due to medicinal product-specific safety concerns, it may be considered appropriate to examine the applicant's ability to:

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<sup>1</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

- Implement product-specific risk minimisation measures (RMM) and related activities; or
- Meet specific safety conditions which may be imposed; or
- Manage routine pharmacovigilance for the product of concern (e.g. anticipated significant increase in adverse reaction reports when compared to previous products).

In most cases, a risk assessment based on a combination of product-specific and pharmacovigilance system-related issues should be performed before a pre-authorisation pharmacovigilance inspection is requested.

If the outcome of the pre-authorisation inspection raises concerns about the applicant's ability to comply with the requirements laid down in the Regulation and the Directive, the following recommendations may be considered:

- Not granting the marketing authorisation;
- Re-inspection prior to marketing authorisation to confirm that critical findings and recommendations have been addressed;
- Granting the marketing authorisation with the recommendation to perform an early post-authorisation pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the EU routine programme of pharmacovigilance inspections (see [III.B.2.](#));
- Imposition of safety conditions to the marketing authorisation [based on DIR Art 21a and REG Art 9(4)].

### **III.B.1.4. Post-authorisation inspections**

Post-authorisation pharmacovigilance inspections are inspections performed after a marketing authorisation has been granted and are intended to examine whether the marketing authorisation holder complies with its pharmacovigilance obligations. They can be any of the types mentioned under [III.B.1.1.](#) and [III.B.1.2.](#).

### **III.B.1.5. 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. 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).

### **III.B.1.6. Re-inspections**

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will 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.

### **III.B.1.7. Remote inspections**

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorisation holder or third parties subcontracted by the marketing authorisation holder or any further subcontracted third party.

The inspectorate may decide on a case-by-case basis whether a remote inspection will be sufficient to gain an adequate overview of the functioning of the marketing authorisation holder's pharmacovigilance system. This decision should take into consideration whether it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and PSMF, via remote access. Different information technology (IT) solutions may be used to provide access to electronic systems and maintain communication with and support to inspectors.

Specific examples of cases for remote inspections are where key sites for pharmacovigilance activities are located outside the EU or a third party is not available at the actual inspection site, or when there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic or travel restrictions).

Remote inspections should follow the [Union Procedure on the Coordination of EU Pharmacovigilance Inspections](#) and the [Union Procedure on the Preparation, Conduct and Reporting of EU Pharmacovigilance Inspections](#)<sup>2</sup>. Further details are deliberated in the [Remote Pharmacovigilance Inspections of MAHs During a Crisis Situation – Points-to-Consider](#)<sup>3</sup>.

### **III.B.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 public health protection. A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

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 is important to ensure successful prioritisation and targeting of these inspections.

Factors which may be taken into consideration, as appropriate, by the competent authorities when establishing 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;
- **Medicinal product related factors:**
  - Additional pharmacovigilance activities or risk-minimisation activities;

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<sup>2</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

<sup>3</sup> See <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspectors-working-group>



- Marketing authorisation with conditions associated with safety, e.g. requirement for post-authorisation safety studies (PASS) or designation for additional monitoring;
- Large sales volume, i.e. products associated with large patient exposure in the EU;
- Limited availability of alternative treatment;
- Marketing authorisation holder-related:
  - Marketing authorisation holder that has never been subject to a pharmacovigilance inspection;
  - Marketing authorisation holder markets many medicinal products in the EU;
  - Resources available to the marketing authorisation holder for their pharmacovigilance obligations;
  - Marketing authorisation holder with no previous marketing authorisation in the EU;
  - Negative information and/or safety concerns raised by an authority or a body outside the EU or arising from other areas (i.e. GCP, GMP, GLP and GDP);
  - Changes in the marketing authorisation holder organisation, such as mergers and acquisitions;
- Marketing authorisation holder's Pharmacovigilance system-related:
  - Extent and number of third parties involved in sub-contracted pharmacovigilance activities (e.g. function of the QPPV, reporting of safety data);
  - Change of QPPV since the last inspection;
  - Changes to the pharmacovigilance safety database(s), which could 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 third parties or the sites at which pharmacovigilance is conducted;
  - Delegation or transfer of PSMF management.

National competent authorities and the Agency may solicit information from marketing authorisation holders for risk-based inspection planning purposes if it is not readily available elsewhere.

### ***III.B.3. Sites to be inspected***

The sites to be inspected may be located in the EU (e.g. PSMF location or EU QPPV site) 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 [DIR Art 111(1)].

Any third party subcontracted to conduct pharmacovigilance tasks 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, even if the obligation of the third parties to agree to be inspected by competent authorities has not yet been included in the subcontract [IR Art 13(1a)].

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

### **III.B.4. Inspection scope**

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by competent authorities of Member States and whether it is a pharmacovigilance system or medicinal product-related inspection (see III.B.1. for types of inspection, inspection triggers and points to consider for the different types of inspection).

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

- Information supplied in the PSMF;
- Information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the Agency such as EudraVigilance reporting and data quality audits;
- Specific triggers (see III.B.1.2. for examples);

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.

#### **III.B.4.1. Routine pharmacovigilance inspections**

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:

- Individual case safety reports (ICSRs):
  - Collecting, receiving and exchanging ICSRs from all types of sources, sites and departments within the pharmacovigilance system, including from those third parties subcontracted by the marketing authorisation holder or any further subcontracted third party to conduct pharmacovigilance activities, and from departments other than pharmacovigilance;
  - Assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality. In addition to examples of ICSRs from within the EU, examples of ICSRs reported from outside the EU should be examined as part of this review (if applicable);
  - Follow-up and outcome recording, e.g. final outcome of cases of exposure in pregnancy and medical confirmation of consumer-reported events as appropriate;
  - Reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
  - Record keeping and archiving for ICSRs;
- Periodic safety update reports (PSURs), as applicable:
  - Completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
  - Addressing safety topics, providing relevant analyses and actions;
  - Formatting according to requirements;
  - Timeliness of submissions;
- Ongoing safety evaluation:

- Use of all relevant sources of information for signal detection;
- Appropriately applied methods for analysis;
- Appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
- Implementation of the RMP, or other commitments, e.g. conditions of the marketing authorisation;
- Timely identification and provision of complete and accurate data to the competent authority(ies), in particular in response to specific requests for data;
- Implementation of approved changes to safety communications and product information, including internal distribution and external publication;
- Non-interventional studies:
  - Reporting of ICSRs from non-interventional studies according to Directive 2001/83/EC, and the receiving, recording and assessing of these reports;
  - Submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PSURs), where applicable, PASS or post-authorisation efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
  - Appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
  - Inclusion of study data in ongoing safety evaluation;
- Pharmacovigilance system:
  - QPPV roles and responsibilities, e.g. access to the quality system, the PSMF, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
  - Roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system;
  - Accuracy, completeness and maintenance of the PSMF;
  - Quality and adequacy of training, qualifications and experience of staff members;
  - Coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
  - Fitness for purpose of computerised systems;
  - Contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance and are adhered to.

The inspection may include the system for the fulfilment of conditions of a marketing authorisation and the implementation of RMM and conduct of related activities, as they relate to any of the above safety topics.

### **III.B.4.2. For-cause inspections**

The scope of the inspection will depend on the specific trigger(s). Some, but not all of the elements listed in **III.B.4.1.** and below may be relevant:

- QPPV involvement and awareness of medicinal product-specific issues;
- In-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

### **III.B.4.3. Re-inspections**

For the scope of a re-inspection, the following aspects should be considered:

- Review of the status of the pharmacovigilance system and/or corrective and preventive action plan(s) resulting from previous pharmacovigilance inspection(s);
- Review of significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection (e.g. change in the pharmacovigilance database, company mergers or acquisitions, significant changes in subcontracted activities, change in QPPV);
- Review of process and/or product-specific issues identified from the assessment of information provided by the marketing authorisation holder, or not covered in a prior inspection.

The scope of re-inspection will depend on inspection history. It may be appropriate to conduct a complete system review, for example if a long time has elapsed since the previous inspection, in which case the elements listed in **III.B.4.1.** may be considered for the inspection scope, as appropriate.

### **III.B.5. Inspection process**

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up, shared and documented in accordance with the agreed **Union Procedures for Pharmacovigilance Inspections**<sup>4</sup>, supporting harmonisation for the mutual recognition of pharmacovigilance inspections within the EU. Improvement and harmonisation of inspection conduct is promoted by agreed processes and procedures, joint inspection(s) and sharing of experience and training by national competent authority inspectorates.

### **III.B.6. Inspection follow-up**

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. The following follow-up actions should be considered, 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;

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<sup>4</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

- Communication of the inspection findings to other authorities (including those outside the EU);
- 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 or clinical trial authorisations).

Sharing information and communication between inspectors and assessors is important for the proper follow-up of inspections. Details of the processes relating to interaction between inspectors and assessors and inspection follow-up are elaborated further in the [Union Procedures for Pharmacovigilance Inspections](#)<sup>5</sup>.

### **III.B.7. Regulatory actions and sanctions**

Under EU legislation, in order to protect public health, competent authorities are obliged to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action. Action may be taken by the Agency, the European Commission or the competent authorities of the Member States as appropriate. Where 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 [DIR Art 111(8)]. Moreover, the European Commission is empowered to impose financial penalties on the holders of marketing authorisations to ensure the enforcement of certain obligations connected with marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004 [REG Art 84a].

In the event of non-compliance, possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

- 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 authorities 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 must take and in what timeframe in order to rectify the non-compliance 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.:

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<sup>5</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

- Urgent safety restriction;
- Variation of the marketing authorisation;
- Suspension or revocation of the marketing authorisation;
- Delays in granting of new marketing authorisation applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorisations;
- Requests for pre-authorisation inspections;
- 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 clinical trials due to medicinal product-specific safety issues;
- Administrative penalties, usually fixed fines or based on company profits or levied on a daily basis;
- Referral for criminal prosecution with the possibility of imprisonment in accordance with national legislation.

### ***III.B.8. Record management and archiving***

The principles and requirements to be followed are elaborated further in the [Union Procedures for pharmacovigilance inspections](#)<sup>6</sup>.

### ***III.B.9. Qualification and training of inspectors***

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by their Member States or by the CHMP should be officials of, or appointed by, the Member State in accordance with national regulation and follow the provisions of the national competent authority. A sufficient number of competent and appropriately qualified and trained pharmacovigilance inspectors should be available.

It is recommended that inspectors are appointed based upon their experience and the minimum requirements defined by the national competent authority. In addition, consideration should be given to the recommendations for training and experience described in the [Union Procedures for Pharmacovigilance Inspections](#)<sup>7</sup>.

The inspectors should undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting and reporting inspections. They should also be trained in pharmacovigilance processes and requirements in such way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

Documented processes should be in place to ensure that inspection competencies are maintained. In particular, inspectors should be kept updated with the current status of pharmacovigilance legislation and guidance.

Training and experience should be documented individually and evaluated according to the requirements of the applicable quality system of the concerned competent authority.

<sup>6</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

<sup>7</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

### **III.B.10. Quality management of pharmacovigilance inspection process**

Quality of the pharmacovigilance inspection process is managed by the national competent authorities and covered by their pharmacovigilance systems and associated quality systems, meaning that the process is also subject to audit. Guidance on establishment and maintenance of a quality assured pharmacovigilance system is provided in [GVP Module I](#).

Quality and consistency of the inspections is facilitated by the [Union Procedures for Pharmacovigilance Inspections](#)<sup>8</sup>.

## **III.C. Operation of the EU network**

### **III.C.1. Sharing of information**

The Agency and the Member States shall cooperate [DIR Art 111(1)] 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;
- Information on the scope of the inspection in order to focus future inspections;
- Information on the outcome of the inspection, in particular when the outcome is that the marketing authorisation holder does not comply with the requirements laid down in legislation and relevant guidance. A summary of the critical and/or major findings and a summary of the corresponding corrective and preventive actions with their follow-up(s)

should be exchanged.

The exchange and sharing of information and the communication across the EU are elaborated further in the [Union Procedures on Pharmacovigilance Inspections](#)<sup>9</sup>.

### **III.C.2. Role of the European Medicines Agency**

#### **III.C.2.1. General role of the Agency**

Regarding the monitoring of compliance with regulatory pharmacovigilance obligations and pharmacovigilance inspections, the roles of the Agency are set out in Article 57(1)(c) and Article 57(1)(i) of Regulation (EC) No 726/2004 and can be summarised as follows:

- Coordination of the monitoring of medicinal products for human use which have been authorised within the EU, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;
- Coordination of the verification of compliance with pharmacovigilance obligations.

Pharmacovigilance inspections coordinated by the Agency are performed by the supervisory authority concerned as outlined in [III.C.4.2](#). The supervisory authority may be assisted by other national competent authorities, when required.

As part of this coordination role the Agency is responsible for:

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<sup>8</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

<sup>9</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

- Establishing and maintaining processes through the Pharmacovigilance Inspectors' Working Group (PhVIWG) to support the consistency and quality of pharmacovigilance inspections of marketing authorisation holders with centrally authorised products conducted by inspectorates of the national competent authorities;
- Coordinating and ensuring the implementation of a risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products (see [III.B.2.](#)) enabling the timely sharing of information on planned and conducted pharmacovigilance inspections between Member States, with the aim of reducing duplication of inspection activity and facilitating mutual recognition of inspection findings;
- Coordinating for-cause inspections, as requested by the CHMP. If a for-cause inspection has been or will be conducted in a similar timeframe as a routine one, it may replace the need for the planned routine inspection and the programme shall be revised to reflect this;
- Coordinating third country inspections: The Agency shall cooperate in the coordination of inspections in third countries [DIR Art 111(1)]. Member States should liaise with the Agency when the need for an inspection of a third country site is identified in order to ensure productive use of pharmacovigilance inspection resource in the interests of the EU;
- Communication and follow-up of inspections of EU interest across the Agency, the PRAC, the CHMP, the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMD(h)), the EU regulatory network and with third country authorities, whenever confidentiality arrangements are in place to facilitate this.

### **III.C.2.2. Role of the Pharmacovigilance Risk Assessment Committee (PRAC)**

The PRAC may make recommendations on the need and scope of for cause pharmacovigilance inspections related to medicinal products of EU interest.

The PRAC may, in relation to issues of EU interest and where considered appropriate, review the outcome of pharmacovigilance inspections and assess marketing authorisation holder-related corrective and preventive action plan submission(s) in order to make or endorse further recommendations on actions to be taken and their follow-up.

The PRAC is also responsible for providing input in the preparation of and agreeing on the risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products outlined in [III.B.2](#) and [III.C.4.3.](#).

### **III.C.2.3. Role of the Committee for Medicinal Products for Human Use (CHMP)**

The CHMP is responsible for the request of pharmacovigilance inspections in the context of the centralised authorisation procedure and for the endorsement of the recommendations made by the PRAC in relation to the outcome of these inspections and their follow-up. The CHMP is also responsible for the adoption of the risk-based programme for routine pharmacovigilance inspections outlined in [III.B.2.](#) and [III.C.4.3.](#).



### **III.C.3. Role of the European Commission**

For medicinal products authorised under Regulation (EC) No 726/2004, the European Commission may request at any point in time the Agency to coordinate the conduct of a pharmacovigilance inspection if public health information in the possession of the European Commission so mandates.

### **III.C.4. Role of the Member States**

#### **III.C.4.1. General considerations**

Member States should establish the legal and administrative framework within which pharmacovigilance inspections operate, including the definition of the rights of inspectors for inspecting pharmacovigilance sites and access to pharmacovigilance data.

Member States should provide sufficient resources and appoint adequately qualified inspectors to ensure effective determination of compliance. The inspector(s) appointed may be accompanied, when needed, by expert(s) on relevant areas. A Member State may also request assistance from another Member State, in which case, access to the inspection sites and data by the Member State providing assistance is desirable.

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up, shared and documented in accordance with the agreed **Union Procedures for Pharmacovigilance Inspections**<sup>10</sup>.

The scheduling and conduct of these inspections should be determined by the preparation of inspection programmes based on a systematic and risk-based approach as outlined in **III.B.2.** and **III.C.4.3.**

The national competent authorities, when preparing inspection programmes, should verify the inspection status of the marketing authorisation holders they plan to inspect by considering the information shared on planned or conducted inspections under the programmes in other Member States in order to assure coordination of inspection activities, prevent unnecessary duplication and to make the most efficient use of inspection resources.

When the pharmacovigilance system which a national competent authority plans to inspect is the same as that already inspected by another national competent authority, sharing of information on the scope and outcomes of previous inspections and consideration of the national supervisory requirements, can help to define the objective, scope and timing of that national inspection.

A common repository, accessible to all Member States, the Agency and the European Commission, facilitates this information sharing on pharmacovigilance inspections.

#### **III.C.4.2. Role of the supervisory authority**

The concept of the supervisory authority applies only in relation to centrally authorised products. The supervisory authority for the conduct of pharmacovigilance inspections shall be the competent authority of the Member State in which the PSMF file is located [REG Art 18(3)].

The supervisory authorities for pharmacovigilance are responsible for verifying on behalf of the EU that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Directive 2001/83/EC and Regulation 726/2004/EC. They may, if this is

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<sup>10</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/compliance-marketing-authorisation/pharmacovigilance-inspections-veterinary-medicines/pharmacovigilance-inspection-procedures-human>

considered necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system [REG Art 19(1)].

Where the sites selected to be inspected are located outside the EU, the same supervisory authority as above will be responsible for the inspection on behalf of the EU. Where relevant or on request, and in particular for medicinal product-specific issues, the inspection may be conducted or assisted by inspector(s) from the Rapporteur or Co-Rapporteur Member State and/or expert(s) from the Rapporteur or Co-Rapporteur Member State or from other Member States as appropriate.

### **III.C.4.3. Inspection programmes**

A programme for routine inspections for centrally authorised products is determined by the Agency in conjunction with the supervisory authorities of the Member States, the PhVIWG, the PRAC and the CHMP. These inspections are prioritised based on the potential risk to public health, considering the factors listed in III.B.5.. As a general approach, a marketing authorisation holder should be inspected on the basis of risk-based considerations: In principle an inspection should be conducted within 4 years after the date of marketing authorisation of its first medicinal product, and thereafter a 4-years inspection cycle should be used, but this may be shortened or lengthened based on an on-going risk assessment.

If the same pharmacovigilance system is used for a variety of authorisation types (centralised and national, mutual recognition and decentralised authorisation procedures), then the results of a supervisory authority inspection may be applicable for all products covered by that system.

This routine inspection programme is separate from any for-cause inspection, but if a for-cause inspection takes place it may replace the need for one under this programme, dependent on its scope.

Member States are also responsible for the planning and coordination of pharmacovigilance inspections within their territory in relation to products authorised nationally or via the mutual recognition or decentralised procedures in order to ensure compliance with the legislation within their own Member States and to verify the effectiveness of the marketing authorisation holder's pharmacovigilance system at national level.

As indicated in III.C.4.1., based on the information from other inspections, the national competent authority should prioritise the inspections in its national programme and use the information for the preparation of an appropriate scope for the national inspection. For example, national competent authorities may seek to verify the fulfilment of requirements concerning the national implementation of specific RMM, national communications concerning safety, locally conducted safety studies, or issues linked to national healthcare systems. A broader examination of pharmacovigilance applied to particular medicinal products of national interest may also be appropriate if this was not covered within the scope of a supervisory authority inspection.

### **III.C.5. Role of marketing authorisation holders and applicants**

Marketing authorisation holders with authorised products and applicants who have submitted new applications under the centralised procedure are subject to pharmacovigilance inspections (see III.B.1.). Therefore, both have responsibilities in relation to inspections, including but not limited to the following:

- Always to be "inspection-ready" as inspections may be unannounced;
- Maintain and make the PSMF permanently and immediately available to the inspectors at the site where it is kept as required by Article 7(3) of Commission Implementing Regulation (EU) No

520/2012; where the PSMF is kept in electronic form, it is sufficient that the data stored in electronic form is directly available at the site where the PSMF is kept;

- Ensure that the sites selected for inspection, which may include those of third parties subcontracted by the marketing authorisation holder or a further subcontracted third party for pharmacovigilance tasks, agree to be inspected before the inspection is performed;
- Make available to the inspectors any information and/or documentation required for the preparation or during the conduct of the inspection within the given deadline;
- Ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;
- Ensure that relevant pharmacovigilance data is accessible at a single point within the EU [DIR Art 107(1)];
- Ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings.

### ***III.C.6. Inspection fees***

For inspections requested by the CHMP, an inspection fee(s) and inspectors' expenses are charged in accordance with the Regulation (EU) 2024/568. For pharmacovigilance inspections performed in the context of national, mutual recognition and decentralised procedures similar fees may or may not apply depending on the legal requirements of the Member State carrying out the inspection.

### ***III.C.7. Transparency***

Information on the conduct and outcome of pharmacovigilance inspections and their follow-up may be made publicly available.