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Inspections

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PROCEDURE FOR COORDINATING PHARMACOVIGILANCE INSPECTIONS REQUESTED BY THE CVMP

Ad Hoc PhV Inspectors Working Group

Applies to: EMEA, EU/EEA Inspectorates	
Summary of scope: This SOP describes the different steps of the PhV inspection process and particularly the interfaces between Member States inspection services and the EMEA.	
Keywords: PhV Inspection, Coordination, CVMP	**Public**
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1 INTRODUCTION

Only Pharmacovigilance (PhV) inspections requested by the CVMP are detailed in this procedure. The legal basis for PhV inspections of Centrally Approved Products for veterinary use is to be found in Regulation (EC) No. 726/2004:

- Article 57 (1) (i), which provides that the Agency shall, within its Committees, undertake the following tasks: " coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations".

Guidance regarding PhV inspections can be found in section 5 of the guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products published as a standalone guideline under Volume 9B of The Rules Governing Medicinal Products in the European Union.

The pharmacovigilance regulatory obligations placed on Marketing Authorisation Holders (MAHs) are laid down in Regulation (EC) No. 726/2004, and Directive 2001/82/EC as amended. Guidelines on the interpretation of legislative pharmacovigilance requirements are published in Volume 9B of The Rules Governing Medicinal Products in the European Union.

Any MAH of a Centrally Authorised Product (CAP) can be subject to inspection. To obtain assurance that MAHs are complying with pharmacovigilance regulatory obligations, the CVMP may request a PhV inspection. There should be collaboration with Competent Authorities to minimise duplication and maximise coverage. The scheduling and conduct of these inspections will be driven by risk analysis criteria.

The objectives of a PhV inspection requested by the CVMP are:

- To verify that the MAH has personnel, systems and facilities in place to meet their regulatory obligations for CAPs,
- To check whether the safety information included in a CAP dossier and related product information (Summary of Product Characteristics etc.) appears credible and accurate, especially applicable to targeted inspections,
- To help the MAH improve compliance,
- To use the inspection results as a basis for enforcement action.

Inspections will be routine as well as targeted to MAHs suspected of being non-compliant. During the conduct of the inspection or preparation of the reports the inspectors may decide to inform EMEA on particular urgent significant findings in advance of the circulation of the inspection reports. The results of an inspection will be routinely provided to the inspected MAH who will be given the opportunity to comment on the findings.

2 APPLICABILITY OF THIS PROCEDURE AND DEFINITION OF TERMS

2.1 Inspectorates and Inspectors to whom this procedure applies

For the purpose of this procedure the following inspectorates may be involved:

- From all EU/EEA countries where sites are to be inspected,
- From the same country as the CVMP Rapporteur/Co-Rapporteur,
- From other EU/EEA countries if needed.

The inspectorates involved appoint the Inspectors performing the tasks and duties described in this procedure. The process of designating the inspectorates involved is described in sections 3.1.3 and 3.1.4.

2.2 Definition of terms

2.2.1 Reporting Inspectorate

The Inspectorate from an EU/EEA State requested and accepting to designate the Reporting Inspector.

2.2.2 Reporting Inspector

The Inspector designated by the Reporting Inspectorate to co-ordinate the preparation of the inspection, the conduct of the inspection and the activities of the inspectors.

The Reporting inspector has the following general duties:

- co-ordinating the
  - preparation of the inspection
  - practicalities of the inspection (with the inspectors and the MAH)
  - conduct of the inspection
  - preparation of the reports by the inspectors involved,
- checking that the timelines for the inspection are kept,
- writing and co-signing the Inspection Overview when applicable i.e. for multi-site inspections with one inspection report per site inspected,
- acting as the main communication point between the inspection team and the EMEA Inspection Sector. The Reporting Inspector and the EMEA Inspection Sector are responsible for the communication between the inspectorates and inspectors involved, the Rapporteur/Co-Rapporteur and the CVMP. The system of communication should, however, be flexible and there can be direct communication between the involved parties, including the assessors, where this is more practical,
- management of the live central archive related to the PhV inspection,
- the Reporting Inspector may also be the Lead Inspector (see below) for one or more sites.

2.2.3 Lead Inspector

The Inspector who has the following duties for the PhV inspection of at least one inspection site:

- evaluation of the feasibility of the inspection as requested and discussion with the Reporting Inspector,
- organisation of the practicalities of the inspection with the inspectee,
- leading the conduct of the inspection on site,
- communication between the inspectee and the Reporting Inspector/EMEA Inspection Sector. The system of communication should however be flexible and there can be direct communication between the involved parties where this is more practical. In any case, the Reporting Inspector shall be kept informed about this communication outcome,
- writing and signing the Inspection Report,
- reviewing and co-signing the Inspection Overview when applicable.

The Reporting Inspector and Lead Inspector will be the same person when only one site is concerned by the inspection.

2.2.4 Inspection Report (IR)

Details about the definition, availability, signatures, language and content of the IR can be found in a separate procedure Ref. EMEA/INS/PhV-V/3.

2.2.5 Inspection Overview (IO)

Details about the definition, availability, signatures, language and content of the IO can be found in a separate procedure Ref. EMEA/INS/PhV-V/3.

3 STEPS OF THE PROCEDURE

The CVMP in conjunction with the competent authority of the Member State in whose territory the MAH's qualified person responsible for pharmacovigilance is located and the applicable pharmacovigilance and inspectors' working parties, will determine a programme for inspection in relation to CAPs. These inspections will be prioritised based on the potential risk to public or animal health or the environment, the nature of the products, extent of use, number of products that the MAH has on the EEA market, etc., and other risk factors. This programme will be separate from any targeted inspection, but if a targeted inspection takes place it may replace the need for one under this programme depending on its scope.

In cases where a competent authority has carried out, or intends, within the required timeframe, to carry out, an inspection covering the scope of a CVMP request, this inspection will suffice and its results will be made available to the CVMP.

The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet their regulatory obligations for CAPs. These inspections may be requested with one or more specific products selected as examples for which specific information can be traced and verified through the various processes, in order to provide practical evidence of the functioning of the pharmacovigilance system of the MAH and the compliance with their regulatory obligations.

Times allowed for conduct of each step of the initiation, conduct and completion of the inspection are provided in appendix 2. These times, shown in square brackets, should be considered as indications and can be modified if necessary. The inspection process will be integrated into the assessment process, when applicable (e.g. an inspection may be related to, or arise from, the assessment of a PSUR). Appendix 1 contains process maps illustrating the designation of the Reporting and Lead Inspectorates/Inspectors. Appendix 2 contains a tabular presentation of the time intervals for different steps of the inspection process. The timelines for practicalities e.g. discussion of findings and conclusions (including the possibility of a teleconference between the inspection team members), and signature of reports, should be established by the inspection team prior to the inspection for each IR.

3.1 Early activities of EMEA and CVMP representatives in developing a request

EMEA and CVMP should determine the time allowed for this step.

3.1.1 Preparation and adoption of the inspection request

At any time after the Marketing Authorisation has been granted the Rapporteur and Co-Rapporteur or other CVMP delegation may signal that in their opinion a PhV inspection is necessary. The selection of sites to be inspected and the determination of the scope of the inspection are made by communication between the Rapporteur/Co-Rapporteur (and their assessors), the EMEA Inspection Sector and the competent authority of the Member State in whose territory the MAH's qualified person responsible for pharmacovigilance is located. The selection of sites and scope of the inspection may be further refined by discussion with the potential inspectorates/inspectors. Therefore, a draft inspection request will become final once all relevant parties, including the inspectorate of the Member State in whose territory the MAH's qualified person responsible for pharmacovigilance is located and the potential inspectorates/inspectors agree on the inspection scope and the sites to be inspected.

This request will set out a time-frame for the conduct of the inspection. This time-frame will be agreed with the CVMP and inspectorate(s) involved, taking into account the reasons for the request and any link between the request and a particular procedure that may be ongoing or anticipated (e.g. PSUR review, renewal of the Marketing Authorisation, etc).

The request should be made to the CVMP using the applicable PhV inspection request form. The EMEA Head of Inspection Sector signs the request. This request should clearly state the site(s) to be inspected, the grounds and scope of the inspection and, if applicable, a list of specific questions to be addressed during the inspection (system and /or product related) in line with any concerns from the CVMP, any other issues relevant to the inspection and the target date for the availability of the inspection report(s). The PhV inspection can proceed once the inspection request is adopted by the CVMP.

3.1.2 Communication of the inspection request

After the adoption by the CVMP, the request is forwarded to the EMEA Inspection Sector for co-ordination.

3.1.3 Designation of the Reporting Inspectorate

A contact point for the purpose of deciding on the availability of the inspectorate to perform an inspection is appointed by each Member State Inspectorate(s) and notified to the EMEA.

One EU/EEA Inspectorate is designated as the "Reporting Inspectorate". In principle, the Reporting Inspectorate should be from the competent authority of the Member State in whose territory the MAH's qualified person responsible for pharmacovigilance is located. However, if for any reason, this competent authority cannot fulfil this task or it is more appropriate for another Member State to take this responsibility, the EMEA Inspection Sector should determine the availability of other Inspectorates and designate another Reporting Inspectorate. The EMEA designates the Reporting Inspectorate according to the following sequence, subject to the availability of inspector(s):

- Competent authority of the Member State in whose territory the MAH's qualified person responsible for pharmacovigilance is located;
- Or where applicable the Member State where the site to be inspected is located when this site is not located in the Member State of the MAH's qualified person responsible for pharmacovigilance nor in a third country;
- Rapporteur Member State;
- Co-Rapporteur Member State;
- Other Member States;

Where relevant or on request, and in particular for product specific issues, the competent authority of the Member State in whose territory the MAH's qualified person responsible for pharmacovigilance is located may be assisted, or the inspection (in a third country) may be conducted, by an inspector and/or expert from the Rapporteur/Co-Rapporteur National Competent Authority.

If an inspectorate wishes to request the assistance of another inspectorate they indicate this to the EMEA within 5 working days.

The CVMP adopted inspection request is sent simultaneously to the contact person in the Member State concerned for information and indication of potential availability to participate in the inspection team. Member States may send trainees, subject to considerations of the size of the inspection team. Such trainee participation will not give rise to a share of the inspection fee, or claim of expenses from the applicant.

The Member State inspectorate undertaking the Reporting Inspectorate role ensures effective communication with the Rapporteur, Co-Rapporteur and the relevant assessors.

3.1.4 Designation of the inspection team

EMEA Inspection Sector checks the availability of the Inspectorate(s) in EU/EEA, which is(are) invited to conduct the requested inspection. When it is not feasible for the selected Inspectorate to carry out the requested parts of the inspection, the competent authority of that country may ask, in co-ordination with the EMEA, another Inspectorate to conduct the inspection.

Each Inspectorate concerned by the inspection is in charge of the designation of at least one appropriately qualified inspector, appointed by the National Competent Authority, to be part of the inspection team.

For each selected site, one Lead Inspector should be designated (this may be the same or different people for the different sites selected).

3.1.4.a) PhV inspections in EU/EEA countries

Where the inspection site is located in the EU/EEA the Lead Inspector will be from the Inspectorate in the country where the site(s) to be inspected is located. This does not prevent a Lead Inspector of one site to be involved, as an inspection team member, in the inspection of another related site located in a different EU/EEA country.

When it is not feasible for the Inspectorate of the country where the inspection site is located to carry out the requested parts of the inspection, the competent authority of that country may ask, in co-ordination with the EMEA, another Inspectorate to lead the inspection.

3.1.4.b) PhV inspections in third countries

For inspection in third countries the Reporting Inspector, and/or (Co)-Rapporteur State/other inspectors from EU/EEA States may act as Lead Inspector.

EMEA will contact local authorities in third countries as appropriate. Inspectors are responsible for all visas and permission and appointments.

The CVMP will be informed in case there are no inspection resources available.

3.1.5 Communication of the Inspection Request to the Reporting and Lead Inspectorates and contract for the inspection

The inspection request is communicated to the Reporting Inspectorate and Lead Inspectorates by the EMEA.

The EMEA prepares the contract for the inspection in accordance with the Article 62(3) of Regulation (EC) No. 726/2004, and other relevant procedures.

3.1.6 Announcement of the inspection to the MAH

The EMEA notifies the MAH, in accordance with the EMEA SOPs, that an inspection has been requested, using a standard letter. In the announcement letter the MAH is requested to ensure cooperation of all inspected parties and to confirm in writing that the sites accept to be inspected and that they will make all required documents available, for direct access by the inspectors. The MAH is also requested in this letter to prepare copies of an initial set of documents for provision to the inspectors in line with section 5 of the guideline on monitoring of compliance with PhV regulatory obligations and PhV inspections for CAPs. The inspectors can then supplement this list with additional requests to the MAH. The EMEA is responsible for arranging further communication, between inspectorates and the MAH.

3.2 Inspection preparation: [20]* days

Each Inspectorate concerned is in charge of the designation of at least one appropriately qualified inspector to be part of the inspection team, who can act as Lead Inspector.

3.2.1 Technical preparation

Concerned Inspectorates should participate in the discussion about the feasibility of the inspection as requested and the time schedule. Any change in the sites selected for inspection should be adopted by the CVMP.

The preparation of the inspection should take [20]* days after the delivery of the documents requested from the MAH to the inspectorates.

3.2.2 Co-ordination of travel and accommodation arrangements.

The inspection team makes contact directly with the MAH, who is requested to make the appropriate arrangements on behalf of the inspection team.

3.3 Site inspection: [30]* days

During this period inspections are conducted at different sites and these occur in parallel or sequentially, especially when inspection issues identified in one site need to be followed in another site to be inspected. The conduct of the inspection is described in a separate document (EMEA/INS/PhV-V/2)

3.4 Writing and circulation of inspection reports: [80]* days

The preparation of inspection reports is detailed in a separate procedure Ref. EMEA/INS/PhV-V/3.

During the conduct of the inspection or preparation of the reports, the inspectors may decide to provide particular urgent significant findings, in advance of the circulation of the inspection reports. This is to provide advance warning of particular problem issues that may require urgent attention. These particularly significant findings warranting urgent attention should be reported as early as possible during the preparation of the different reports by the Lead Inspector to the Reporting Inspector and by the Reporting Inspector to the EMEA Inspection Sector. The EMEA Inspection sector will inform the Rapporteur/Co-Rapporteur and the CVMP as appropriate.

For each site inspected, the Lead Inspector prepares an IR and forwards it to the Reporting Inspector within [70]* days after the completion of the inspection.

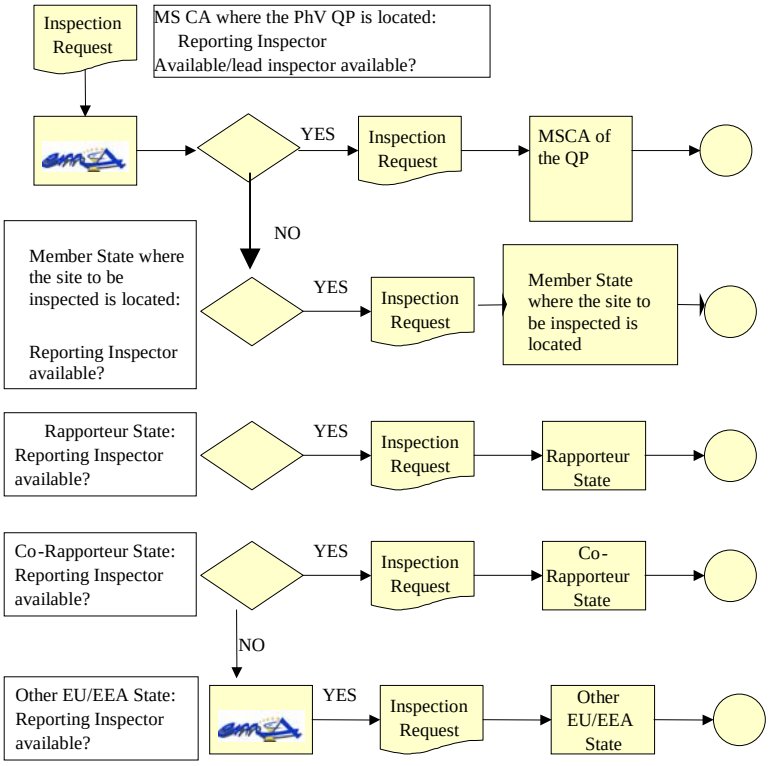
When more than one site is inspected and therefore more than one inspection report is available, the Reporting Inspector will also be responsible for the preparation of the IO. The IO, which will include the individual reports as attachments, should be forwarded to EMEA within [80]* days after the completion of the inspection.

In cases where an EU/EEA competent authority has carried out, or intends, within the required timeframe, to carry out, an inspection covering the scope of a CVMP request, the inspection report will be made available to the Reporting Inspector for the preparation of the IO.

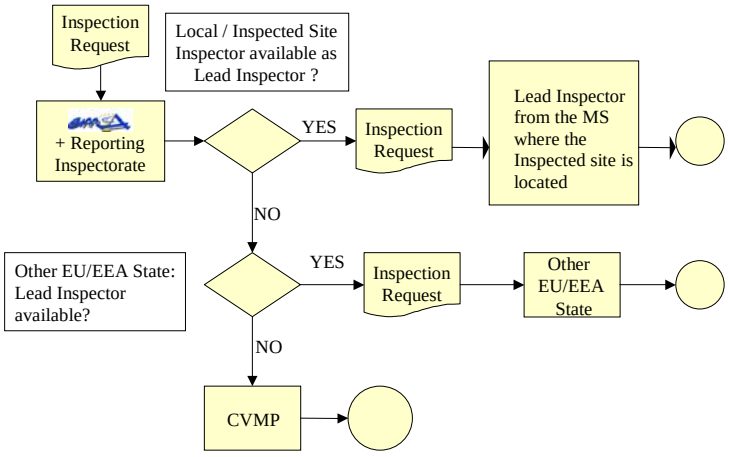
Appendix 1: Process Maps for the Designation of Inspectorates and Inspectors involved

- **Reporting Inspectorate**
- **Lead Inspectorates (sites in EU/EEA Countries)**
- **Lead Inspectorates (sites in Third Countries)**

Process Map:
Decision Tree PhV Reporting Inspector Selection

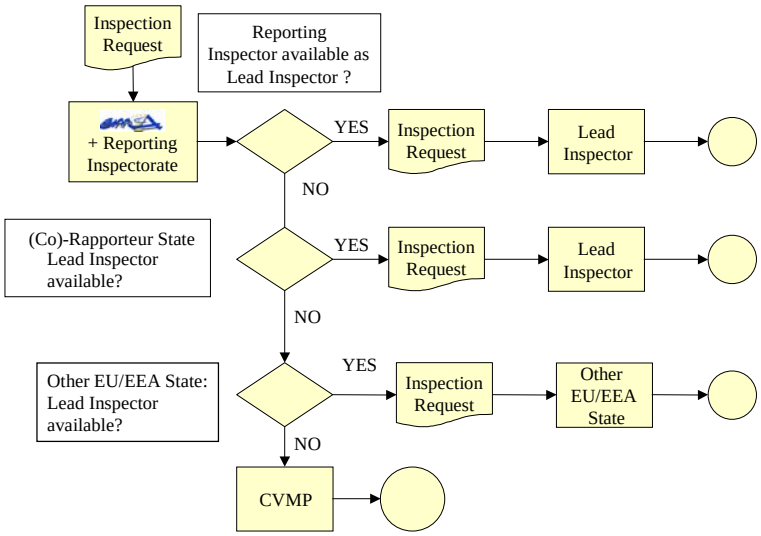


Process Map:
Decision Tree PhV Lead Inspector Selection for Inspection in EU/EEACountry



Process Map:

Decision Tree PhV Lead Inspector Selection for Inspection in Third Country



Appendix 2:

Table of process steps and projected time intervals for these

ACTIVITIES RELATED TO PhV INSPECTIONS REQUESTED BY CVMP: INDICATIVE TIME SCHEDULE ✸

STEPS OF THE PROCEDURE	TIME ALLOWED	
1. Early activities of EMEA / CVMP Request for a PhV inspection Initial selection of sites Set up of overall time schedule Designation of the Reporting Inspectorates First contacts EMEA / Inspectorates concerned Notification of the inspection to MAH	To be determined by EMEA/CVMP Notify MAH within [10] days of CVMP meeting Notify Reporting inspectorate and other inspectorate(s) within [10] days of CVMP meeting Forwarding of required documents, (within [10] days of CVMP meeting	
2. Inspection preparation Notification / announcement of site inspections Preparation of the inspection plan Obtaining and reviewing required documents Finalisation of travel arrangements with the MAH	[20] days ✸ after the delivery of the documents requested from the MAH to the inspectorates	
3. Site inspection	[30] days ✸	
4. Writing and circulation of the reports Writing of the Inspection Report Reply from the inspectee /party(ies) responsible (include this as an attachment to the IR) Comments from the inspectors to the Inspectee's response (include this as an attachment to the IR) and submission of the IR to the Reporting Inspectorate. Where applicable, writing the Inspection Overview	 [30] days ✸ [30] days ✸ [10] days ✸ [10] days ✸	 Total: [80] days* ✸
5. Review of the reports by EMEA for adherence to applicable reference texts and EMEA guidelines.	[5] days ✸	

** The EMEA should be notified as soon as possible by the Reporting Inspector of any urgent significant finding relating to the functioning of the MAH pharmacovigilance system and in particular the risk/benefit of the product(s) concerned by this inspection.*

✸Times allowed to complete each step of the initiation, conduct and termination of the inspection are provided in this table. These times, shown in square brackets, should be considered as indications and can be modified if necessary e.g. the times for the preparation of the inspection report can be extended when the inspectors request information from the inspectee, which is necessary for the completion of the report.

Appendix 3: References and list of documents used in the preparation of this procedure

REFERENCES FOR THE PREPARATION OF THIS DOCUMENT

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Official Journal L 136, 30/4/2004 p. 1 - 33).

- Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Official Journal L 311, 28/11/2001 p. 1- 66). As amended.

- Volume 9B- Guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products, March 2007.

- Council Regulation (EC) No 297/95, of 10 February 1995, on fees payable to the European Agency for the Evaluation of Medicinal Products (Official Journal L 35, 15/2/1995 p. 1 - 5 CONSLEG - 95R0297 - 19/12/1998 - 15 p.). As Amended.

- Procedure for conducting Pharmacovigilance inspections requested by the EMEA (EMEA SOP INS/PhV-V/2).

- Procedure for reporting of Pharmacovigilance inspections requested by the EMEA (EMEA SOP INS/PhV-V/3).

- Rules for the implementation of Council Regulation (EC) 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products.