19 November 2014
EMA/INS/PhV/226163/2014
Procedure no: INS/PhV-V/3 Rev1

Procedure for reporting of pharmacovigilance inspections requested by the CVMP

Agreed by Pharmacovigilance Inspectors Working Group	25 September 2014
Date for coming into effect	30 September 2014

Keywords	***Pharmacovigilance inspection, reporting, IR, CVMP***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Procedure for reporting of pharmacovigilance inspections requested by the CVMP

Table of contents

1. Introduction

Only pharmacovigilance (PhV) inspection reports related to inspections requested by the Committee for Medicinal Products for Veterinary Use (CVMP) are detailed in this procedure.

The definitions, selection and duties of the involved parties (reporting inspector, lead inspector, etc.) are provided in the "Procedure for co-ordinating pharmacovigilance inspections requested by the CVMP" Ref. EMEA/INS/PhV-V/1 and the legal basis of such inspections is to be found in Article 57(1)(i) of Regulation (EC) No. 726/2004.

When a PhV inspection has been performed, the PhV inspection report is used to inform CVMP on the status of compliance by the marketing-authorisation holder (MAH) and assist in determining further steps, if needed, to improve compliance and may be also used as a basis for enforcement action.

Inspections are co-ordinated by the Agency Compliance and Inspections Department and conducted by the EU/EEA national inspectors.

The request for an inspection is made by CVMP in a document stating the grounds for the inspection, its scope and identifying sites to be inspected as well as any other information relevant to the inspectors.

2. Definition of terms

See definitions of reporting inspectorate, reporting inspector, lead inspector in the "Procedure for co-ordinating pharmacovigilance inspections requested by the CVMP" Ref. INS/PhV-V/1.

See definitions of inspection report and inspection overview under section 3.1.1 and 3.2.1 of this procedure, respectively.

3. Preparing inspection reports

For each site inspected an inspection report (IR) is prepared addressing the minor, major and critical findings reported for each site. For multiple site inspections, an inspection overview (IO) will also be prepared, addressing the major and critical findings recorded for all sites, providing an evaluation of the impact of the findings, and a recommendation on the actions to be taken. During the conduct of the inspection or preparation of the reports the inspectors may decide to inform the Agency on particularly urgent major or critical findings in advance of the circulation of the inspection report(s).

Exceptionally, in some circumstances it may be appropriate to generate only one report for two or more sites, even though these represent separate inspections (e.g. where a particular process at a MAH is inspected at two or more sites globally, but it is useful to combine the findings as they address elements of the same process). These remain separate site inspections nonetheless. If this is to apply it will be indicated in the CVMP adopted inspection request, that a single report is requested combining the results for a group of specified sites. In this circumstance, the reporting inspector will indicate this to the Agency during the preparation of the draft inspection request. There could be circumstances where the decision to generate only one report for two or more sites may occur after the inspection request has been made and in this case the reporting inspector will communicate this to the Agency as soon as this decision is taken.

3.1. Responsibilities of the lead inspector

3.1.1. The inspection report (IR)

The lead inspector(s) appointed by the inspectorate(s) concerned prepare(s) an inspection report (IR) for each site inspected. Appendix 1 gives an example of a format for an IR of a PhV site.

The IR is prepared according to a common standard and will be ready within [30]* days after the completion of the inspection. Where multiple sites are inspected in sequence the IR may be prepared [30]* days from the last day of inspection, at the last site inspected. During this timeframe the inspectors involved and also the reporting inspector should have reviewed, commented and agreed to the content of the report.

* The times shown in square brackets in appendix 2 of procedure EMEA/INS/PhV-V/1 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 inspected entity, which is necessary for the completion of the report. In this case, “the end of the inspection” will be the date that this information is supplied by the MAH.

The IR should be sent to the MAH with a request for comments on major factual errors, points of disagreement and/or remedial actions to be provided, to the lead inspector, within [30]* days of receipt of the report. Section D.2 of appendix 1 provides guidance for responding to inspection findings and lead inspectors may either communicate this guidance as part of the IR (as it appears in the template) or as part of the cover letter/separate communication to the MAH. The lead inspector copies the IR and cover letter to the inspection team members.

If a response is not received within the stipulated time frame, the absence of a reply should be recorded in the IR. Upon receipt of comments, these should be assessed by the inspectors, considering whether they have an impact, if any, on the initial inspection report and whether or not the proposed corrective and preventive actions (CAPA) are acceptable. This assessment should be included in the final version of the IR and issued within [10]*working days of receipt of the MAH response.. The IR will be signed by the lead inspector and other inspectors as required by local legal requirements and SOPs. Each inspector should nominate a proxy who may sign on their behalf or agree with the reporting inspector that the latter may sign on their behalf, if they are not available when the report needs to be signed. Signatures may be scanned and sent to the reporting inspector, if appropriate.

The target dates for the availability of the inspection reports are agreed and stated in the inspection request adopted by CVMP.

3.1.2. Language of inspection report (IR)

The IR is written in English, unless required by local regulations to be in local language. In the latter case the inspection report will be translated /modified into English under the responsibility of the lead inspector.

3.1.3. Content of inspection report (IR)

The IR should reflect the inspection procedure as described in “Procedure for conducting pharmacovigilance inspections requested by the CVMP (INS/PhV-V/2)”. There should be an evaluation of the compliance with EU and local regulations and EU guidelines. The validity and reliability of the data submitted should be evaluated in accordance with the scope of the inspection and issues identified in the request for the inspection. The compliance of the pharmacovigilance system with the

EU requirements and the company's adherence to the described system should be evaluated. The IR, should include, at least the basic items indicated in the IR template in appendix 1.

Each finding should be classified as minor, major or critical (see appendix 4 for definitions). Each finding should refer to the regulatory requirement to which it relates.

The IR will contain an evaluation of the significance of any non-compliance and provide a summary of the minor, major and critical findings. It will also contain an overall conclusion on whether the PhV system complies with EU/local regulations and the potential subsequent risk for the public/animal health and/or the environment and where several sites are inspected, this should be included in the IO. In case of deficiencies, a recommendation should be given on the need for the MAH to implement corrective and preventative action plan taking into account the nature of the deviations and the need for a re-inspection to evaluate the implementation of such plan. The IR should include an indication of any opportunity given to the MAH to comment; if and when comments were received, and whether these were accepted or not. The MAH responses and the inspectors' evaluation of the MAH responses will be included in the final IR according to the template in appendix 1. If applicable, additional documents and information may be added to the IR as appendices.

Section 3.4 of Procedure Ref. EMEA/INS/PhV-V/1 describes the provision of relevant inspection findings in advance of the circulation of the inspection report(s).

3.1.4. Preparing and forwarding the IR

The final version of the IR should be prepared by the lead inspector within [70]* days after the completion of the inspection and should be signed by the lead inspector and other inspectors as required.

3.2. Responsibilities of the reporting inspector

The reporting inspectorate nominates the reporting inspector. It is the duty of the reporting inspector to monitor the timely production of the IR(s). The reporting inspector and lead inspector will be the same person when only one site is concerned by the inspection. The reporting inspector may also be the lead inspector for one or more sites.

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 inspection overview, following the guidance and proposed format in appendix 2.

In the case 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, this inspection will suffice and the inspection report will be made available to the Agency. In case the inspection report is not written in English a translation of this inspection report or the completed template included in appendix 3 should be made available. When a summary translation is provided, the topics related to the scope of the CVMP request should be specifically addressed. In case the inspection is part of a multi-site inspection requested by the CVMP, the Agency will forward this inspection report to the reporting inspector for the preparation of the IO, whenever this national inspection covers the scope of the CVMP request.

Any questions related to the reports are handled by the reporting inspector, who is responsible for the necessary communication with the lead inspectors, the Agency's Compliance and Inspections Department, CVMP, PhV WP, (co)-rapporteur and the assessors.

3.2.1. The inspection overview (IO)

The reporting inspector will prepare an inspection overview combining the results of the multi-site inspection addressing major and critical findings and including a statement on the potential impact of all the deficiencies found and a recommendation on the actions to be taken (e.g. corrective and preventative plan (CAPA), re-inspection, monitoring of compliance–quality and/or timeliness etc). The IO will be written in English and will be approved and signed by the lead inspectors who have contributed to the inspection. Each individual inspection report will be attached to this IO as an appendix. Appendix 2 gives an example of a format for the IO.

The IO should be forwarded to EMEA within [80]* days after the completion of the inspection.

4. Submission and acceptance of the inspection reports

4.1. Review of the format of the IR

A review of the reports is conducted on behalf of the CVMP by the Agency Compliance and Inspections Department. The Agency will check the format of the IR for adherence to:

- the procedures established by the PhV Inspectors Working Group (PhV IWG);
- the inspection request adopted by the CVMP;
- and citation of applicable regulations and guidelines.

Any difficulties encountered by this review will be notified to the reporting inspectorate in writing, with a deadline for revision or other remedial action.

If the reporting inspectorate does agree with the Agency, they will provide a revised version or other remedial action within the timeframe agreed. If the reporting inspectorate does not agree with the Agency the reasons should be explained. If the Agency still considers that there is a problem with the report, the rapporteur/co-rapporteur and CVMP will be sent the report and a document describing the point(s) of disagreement.

In the event of outstanding disagreement, the report and problems identified are circulated to the PhV Inspectors Working Group, for peer review, by written procedure. Seven calendar days will be allowed for response, after which the responses will be collated and appended to a final recommendation made by the Agency's Compliance and Inspections Department, which will be communicated to the rapporteur/co-rapporteur, CVMP and the reporting inspectorate.

The IR will be managed in accordance with the "Statements of principles governing the partnership between the national competent authorities and the European Medicines Agency".

4.2. Communication between inspectors, (co)-rapporteur and assessors

Direct communication is encouraged between the reporting inspector, the lead inspectors, (co)-rapporteur and assessors and the Agency's Compliance and Inspections Department as early as possible in the process of preparing reports. After the reports are finalised and signed the discussion on matters such as evaluation and interpretation of findings described in the report may continue.

4.3. Forwarding the IR to CVMP

The Agency's Compliance and Inspections Department forwards the IR or the IO (for multi-site inspections) to the rapporteur/co-rapporteur and CVMP according to the Agency's internal procedures.

The rapporteur/co-rapporteur and CVMP considers the content and findings of the report and may ask for clarification or additional information from the inspection team. The Agency Compliance and Inspections Department will promptly inform the reporting inspector of the need for these clarifications/additional information or any recommendation/conclusion decided at the CVMP.

The Agency Compliance and Inspections Department will forward the final IR or the IO to the MAH after informing the CVMP, whenever it has not been previously forwarded to the MAH directly by the reporting inspector according to national procedures, in which case the reporting inspectorate should copy EMA to keep it informed and in order to avoid duplication of information.

4.4. Follow-up of the inspection report

Some inspection reports will require follow-up due to the major and/or critical findings. The IR conclusions should recommend any follow-up to be requested of the MAH. The conclusion should recommend further inspection if considered necessary.

Where there are follow-up documents to be reviewed this review should be led the reporting inspector in conjunction with the rapporteur/co-rapporteur, the Agency's PhV inspection coordinator and the Agency's project manager.

Where an evaluation, by the reporting inspector, of the responses is required, this should be done in conjunction with the relevant lead inspectors and a short written evaluation provided simultaneously to the rapporteur/co-rapporteur and the Agency (inspection coordinator and veterinary medicines department, as applicable).

The timelines for such review will need to be agreed on a case-by-case basis with the rapporteur/co-rapporteur and the Agency (inspection coordinator and veterinary medicines department). In case the documentation to be reviewed is product specific the rapporteur/co-rapporteur may take the lead, if necessary.

The reporting inspector and lead inspectors should ensure, to the extent possible, that deputies are nominated to provide input where they are not available themselves. In some cases the reporting inspector may need to provide the evaluation alone if the lead inspector(s) is not available in the timeframe required.

Appendix 1 - Inspection report (IR) format

Click here for the template.

Note: If a response is not received by the inspected entity within the stipulated time frame, the absence of a reply should be recorded in the IR.

Appendix 2 - Inspection overview (IO) format

Click here for the template.

Note: If a response is not received by the inspected entity within the stipulated time frame, the absence of a reply should be recorded in the IO.

Appendix 3 - Template for collecting information on pharmacovigilance issues for the attention of the inspectors / assessors

Click here for the template.

Appendix 4 - Classification of inspection findings

1. Critical: A deficiency in one or more pharmacovigilance processes or practices that represents a serious violation of applicable legislative requirements and/or guidance and/or leads to a seriously deficient pharmacovigilance system with a high level of risk to animal or public health. Critical findings require immediate action.

Remark: deficiencies classified as critical may include a pattern of deviations classified as major.

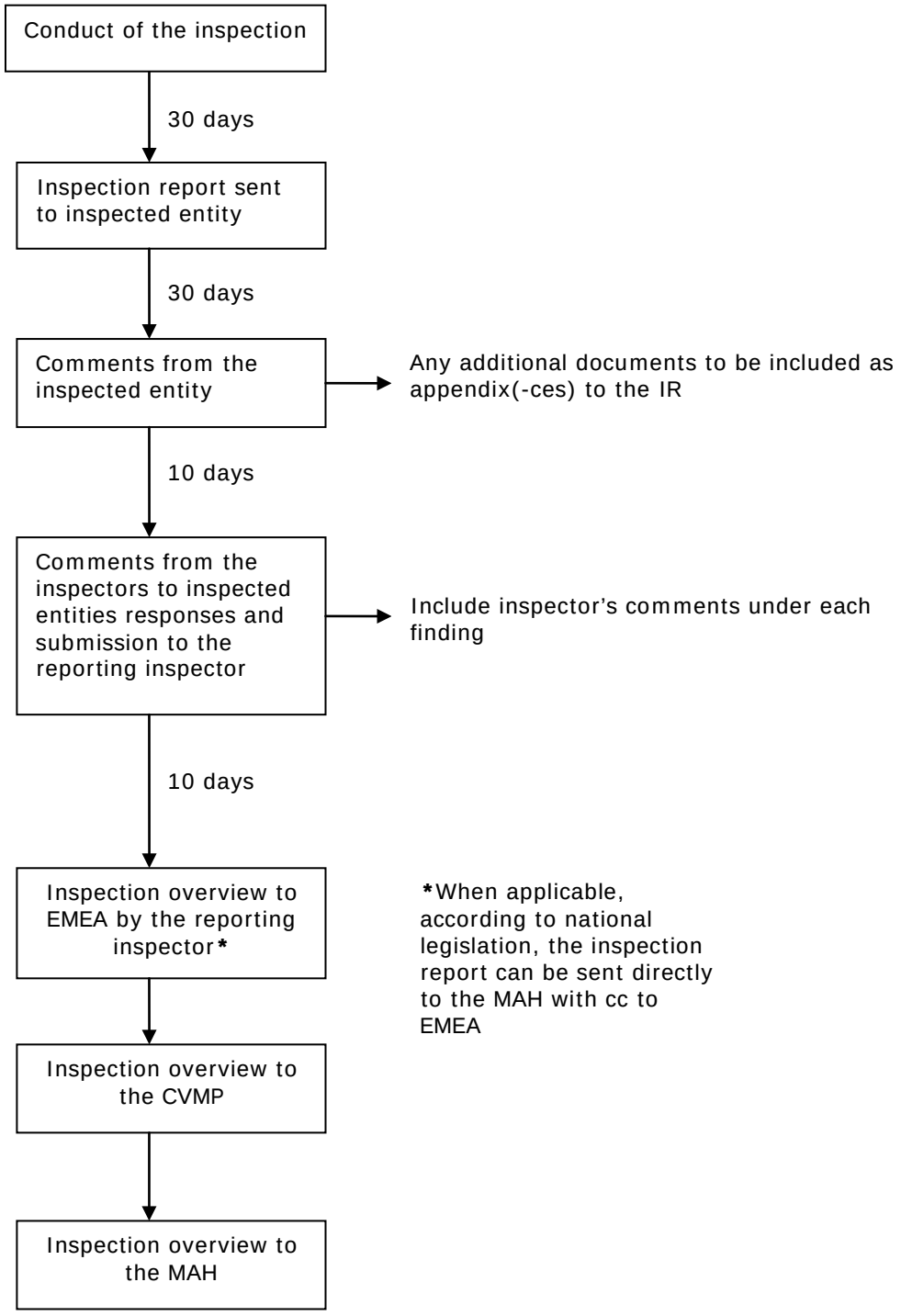
2. Major: A non-critical deficiency in the pharmacovigilance system, practices or processes that represents a violation of applicable legislative requirements and/or guidance and could potentially adversely influence or pose a risk to animal or public health.

Remark: deficiencies classified as major may include a pattern of deviations classified as minor.

3. Minor: A deficiency in the pharmacovigilance system, practices or processes that represents a deviation from applicable legislative requirements and/or guidance and would not be expected to adversely affect or pose a risk to animal or public health.

Comments and/or recommendations: Observations that might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future. This is not a deviation.

Appendix 5 - Flow-chart for the reporting process



Appendix 6 - References for the preparation of this document

Council Regulation (EC) No. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended.

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, as amended.

Volume 9 of the rules governing medicinal products in the European Union – Volume 9B - Pharmacovigilance for Medicinal Products for Veterinary Use - Guidelines on Pharmacovigilance for Medicinal Products for Veterinary (version October 2011).

VICH Topic GL 24 on Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs).

Procedure for coordinating pharmacovigilance inspections requested by the CVMP (INS/PhV-V/1).

Procedure for conducting pharmacovigilance inspections requested by the CVMP (INS/PhV-V/2).