The European Medicines Agency
Inspections

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Superseded by Union Procedures

PROCEDURE FOR REPORTING OF PHARMACOVIGILANCE INSPECTIONS REQUESTED BY THE CHMP

GCP Inspectors Working Group

Applies to: EMEA, EU/EEA Inspectorates	
Summary of scope: This SOP describes the content of PhV inspection reports and the process of their approval and the distribution to the EMEA.	
Keywords: PhV Inspection, Reporting, IR, CHMP	**Restricted**
Supersedes: N/A	

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1 INTRODUCTION

Only PhV Inspection Reports related to inspections requested by the CHMP 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 PhV Inspections requested by the EMEA" Ref. EMEA/INS/PhV/1 and the legal basis of such inspections is to be found in articles 19(1) 44(1) and 57(1)(i) of Regulation (EC) No. 726/2004.

When a PhV inspection has been performed, the PhV Inspection Report is used to inform CHMP on the status of compliance by the 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 EMEA Inspection Sector and conducted by the EU/EEA national inspectors.

The request for an inspection is made by CHMP 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 PhV Inspections requested by the EMEA" Ref. INS/PhV/1.

See definitions of Inspection Report and Inspection overview under section 3.1.1 and 3.2.1, respectively.

3 PREPARING INSPECTION REPORTS

For each site inspected an Inspection Report (IR) is prepared. 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 EMEA on particularly urgent critical findings in advance of the circulation of the inspection reports.

Exceptionally, in some circumstances it may be appropriate to generate only 1 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 CHMP 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 EMEA during the preparation of the draft inspection request. There could be circumstances where the decision to generate only 1 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 EMEA 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 prepares an Inspection Report 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 of the end 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/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 inspectee, 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 or remedial actions to be provided, to the Lead Inspector, within [30]* days of receipt of the report. 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 as an appendix. Upon receipt of comments, these should be included in the final version of the IR as an appendix. The inspectors will consider the responses of the MAH and will indicate, in form of an appendix as well, whether or not these are acceptable and what impact, if any, they have on the original inspection findings within [10]* days of receipt of the comments from the MAH.

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. Signature may be obtained by fax, and the originals mailed to the Reporting Inspector.

The target dates for the availability of the inspection reports are agreed and stated in the Inspection Request adopted by CHMP.

3.1.2 Language of IR

This Inspection Report (IR) is prepared according to a common standard 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 IR

The IR should reflect the inspection procedure as described in "Procedure for conducting PhV inspections requested by the EMEA (INS/PhV/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 companies adherence to the describe system should be evaluated. The IR should be printed on the paper with the Lead Inspectorate/Reporting Inspectorate (as applicable) national authority heading or on plain A4 paper.

At least the following basic items should be recorded:

1. Administrative information on what was inspected, where, when and who was present.
2. Scope and reasons for the inspection.
3. Reference texts and documents for the inspection.
4. Summary of the of the organisation of the MAH PhV system, including an overview of the system, the QP function, the handling and reporting of AE data, trend analyses/signal generation, the databases used, the organisation of quality assurance and quality control and the archiving (alternatively cross-reference should be made to a specified version of the Detailed Description of the Pharmacovigilance System provided by the applicant as part of the MAA- additional site specific detail relevant to the inspection could be added in the IR if needed to assist understanding of the scope of the inspection as conducted and the inspection findings).
5. Documents reviewed prior and during the inspection.
6. Status of compliance with EU and local regulations and CHMP and ICH guidelines.
7. An indication of any opportunity given to the MAH to comment; if and when comments were received, and whether these were accepted or not.

These items should be described in the IR and the findings classified as minor, major and critical deviations (see appendix 3 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-compliances and provide a summary of the 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 public health and where several sites are inspected, this may 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 an inspection to evaluate the implementation of such plan.

Section 3.4 of Procedure Ref. EMEA/INS/PhV/1 describes the provision of relevant inspection findings in advance of the circulation of the inspection reports.

3.1.4 Preparing and forwarding the IR

The final version of the IR should be prepared, signed and sent by the Lead Inspector to the Reporting Inspectorate within [70]* days after the completion of the inspection.

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 IRs. 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.

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 CHMP request, this inspection will suffice and the inspection report will be made available to EMEA. A translation of this inspection report or a summary inspection report, in accordance with the format included in appendix 3, should be made available in English when the inspection report is not in English. When a translation is provided, the topics identified in appendix 3 should be addressed. In case the inspection is part of a multi-site inspection requested by the CHMP, EMEA will forward this Inspection Report to the Reporting Inspector for the preparation of the IO, whenever this national inspection covers the scope of the CHMP request.

Any questions related to the reports are handled by the Reporting Inspector, who is responsible for the necessary communication with the Lead Inspectors, EMEA Inspection Sector, CHMP, 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 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 with 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 forward 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 CHMP by the EMEA Inspection Sector. The EMEA will check the format of the IR for adherence to:

- the procedures established by the Ad Hoc Meeting of GCP Inspection Services,
- the Inspection request adopted by the CHMP,
- 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 EMEA, they will provide a revised version or other remedial action within the timeframe agreed. If the Reporting Inspectorate does not agree with the EMEA the reasons should be explained. If the EMEA still considers there is a problem with the report, the Rapporteur/Co-Rapporteur and CHMP 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 GCP Inspectors Working Group Meeting (Pharmacovigilance stream), 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 EMEA Inspection sector, which will be communicated to the Rapporteur/Co-Rapporteur, CHMP 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 EMEA Inspection Sector 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 CHMP

The EMEA Inspection Sector forwards the IR or the IO (for multi-site inspections) to the Rapporteur/Co-Rapporteur and CHMP according to the EMEA internal procedures.

The Rapporteur/Co-Rapporteur and CHMP considers the content and findings of the report and may ask for clarification or additional information from the inspection team. The EMEA Inspection Sector will promptly inform the Reporting Inspector of the need for these clarifications/additional information or any recommendation/conclusion decided at the CHMP.

The EMEA Inspection Sector will forward the final IR or the IO to the MAH after informing the CHMP, 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 EMEA 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 critical or major findings. Where there are follow-up documents to be reviewed this review should be led by the Rapporteur/Co-Rapporteur in conjunction with the Reporting inspector, EMEA PhV inspection coordinator and EMEA product team leader.

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 EMEA (inspections coordinator and Product Team Leader).

The timelines for such review will need to be agreed on a case-by-case basis with the Rapporteur/Co-Rapporteur and the EMEA (inspections coordinator and Product team leader).

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.

The IR conclusions should recommend any follow-up to be requested of the MAH. The conclusion should recommend further inspection if considered necessary.

APPENDIX 1- INSPECTION REPORT FORMAT

A. ADMINISTRATIVE INFORMATION
A.1. PRODUCTS
A.2. MARKETING AUTHORISATION HOLDER
A.3. INSPECTION

B. BACKGROUND AND GENERAL INFORMATION
B.1. REASON FOR THE INSPECTION
B.2. SCOPE OF THE INSPECTION REQUEST (insert CHMP scope document and comment on amendments to the scope)

C. DESCRIPTION OF INSPECTION AND FINDINGS
C.1. CONDUCT OF THE INSPECTION
C.2. PERSONS MET DURING INSPECTION (Details can be included in an appendix)
C.3. FINDINGS RELATED TO THE PHARMACOVIGILANCE SYSTEM AND PRODUCT SPECIFIC ISSUES
C.3.1. QP function
C.3.1.1 Job description
C.3.1.2 Qualifications
C.3.1.3 Training
C.3.1.4. Deputising
C.3.2. Organisational structure
C.3.2.1 PhV system
C.3.2.2 Interfaces with partners and sub-contractors
C.3.2.3 Interfaces with other departments of the company (CT, medical information, quality complaints, legal etc.)
C.3.3. SOPs
C.3.4. Personnel
C.3.4.1 Job description
C.3.4.2 Qualifications
C.3.4.3 Training
C.3.5. Databases
C.3.6. AE reporting
C.3.6.1. General Overview of ADR reporting to EU Competent Authorities and EMEA
C.3.6.2. Periodic Safety Update Reports
C.3.6.3. Clinical trial and consumer-care programme safety reporting/post-authorisation safety surveillance study reporting overview
C.3.6.4. Procedures for trend analysis/signal generation
C.3.7. Quality Control and Quality Assurance
C.3.6.1. Quality Control
C.3.6.2. Quality Assurance
C.3.8. Archiving

D. SUMMARY AND EVALUATION OF FINDINGS AND CONCLUSIONS
D.1. SUMMARY OF FINDINGS
D.2. CONCLUSIONS
D.3. RECOMMENDATIONS
D.4. CONCLUSIONS REGARDING THE RESPONSES FROM THE INSPECTEE

E. SIGNATURE AND DATE

F. APPENDICES
F.1. Response relating to the MAH/ Comments from the inspectors of the response- if warranted
F.2. Reference Texts
F.3. documents requested prior to, during and after the inspection
F.4. Other appendices as required

APPENDIX 2- INSPECTION OVERVIEW FORMAT

A. ADMINISTRATIVE INFORMATION
A.1. PRODUCTS
A.2. MARKETING AUTHORISATION HOLDER
A.3. INSPECTION

B. BACKGROUND AND GENERAL INFORMATION
B.1. REASON FOR THE INSPECTION
B.2. SCOPE OF THE INSPECTION REQUEST
B.3. REFERENCE TEXTS

C. DESCRIPTION OF INSPECTION AND FINDINGS (Critical and Major findings)
Include these headings as applicable:
C.4.1. QP function
C.4.1.1 Job description
C.4.1.2 Qualifications
C.4.1.3 Training
C.4.1.4. Deputising
C.4.2. Organisational structure
C.4.2.1 PhV system
C.4.2.2 Interfaces with partners and sub-contractors
C.4.2.3 Interfaces with other departments of the company (CT, medical information, quality complaints, legal etc.)
C.4.3. SOPs
C.4.4. Personnel
C.4.4.1 Job description
C.4.4.2 Qualifications
C.4.4.3 Training
C.4.5. Databases
C.4.6. AE reporting
C.4.6.1. ADR reporting to EU Competent Authorities and EMEA
C.4.6.2. Periodic Safety Update Reports
C.4.6.3. Clinical trial and consumer-care programme safety reporting/post-authorisation safety surveillance study reporting overview
C.4.6.4. Procedures for trend analysis/signal generation
C.4.7. Quality Control and Quality Assurance
C.4.7.1. Quality Control
C.4.7.2. Quality Assurance
C.4.8. Archiving

D. SUMMARY AND EVALUATION OF FINDINGS AND CONCLUSIONS
D.1. SUMMARY OF FINDINGS
D.2. CONCLUSIONS
D.3. RECOMMENDATIONS

E. SIGNATURE AND DATE

F. APPENDICES
F.1. IR site 1
F.2. IR site 2
F.3. …….

APPENDIX 3- FORMAT OF THE PhV SUMMARY REPORT

A. ADMINISTRATIVE INFORMATION

A.1. NAME OF THE MARKETING AUTHORISATION HOLDER

A.1. NAME OF THE SITES INSPECTED WITH FULL ADDRESS

Is the site inspected:

- Part of the MAH company ☐
- Sub-contactor/CRO ☐
- Licensing/Co-Marketing Partner ☐
- Other: _____ ☐

A.2. NAME AND ADDRESS OF THE SITE WHERE THE QPPV IS LOCATED

A.3. INSPECTION REFERENCE NUMBER

A.5. NAME(S) OF THE INSPECTOR(S) OR/AND "EXPERTS" PARTICIPATING IN THE INSPECTION.

A.6. DATE(S) OF INSPECTION

B. BACKGROUND AND GENERAL INFORMATION

B.1. SCOPE OF THE INSPECTION REQUEST

D. SUMMARY AND EVALUATION OF FINDINGS AND CONCLUSIONS

D.1. SUMMARY OF FINDINGS RELATED TO THE PHARMACOVIGILANCE SYSTEM AND PRODUCT SPECIFIC ISSUES

D.2. CONCLUSIONS ON THE ACCEPTABILITY OF THE PHV SYSTEM AND THE COMPLIANCE OF THE MAH WITH PHV OBLIGATIONS

D.3. RECOMMENDATIONS FOR FURTHER ACTIONS

E. SIGNATURE AND DATE

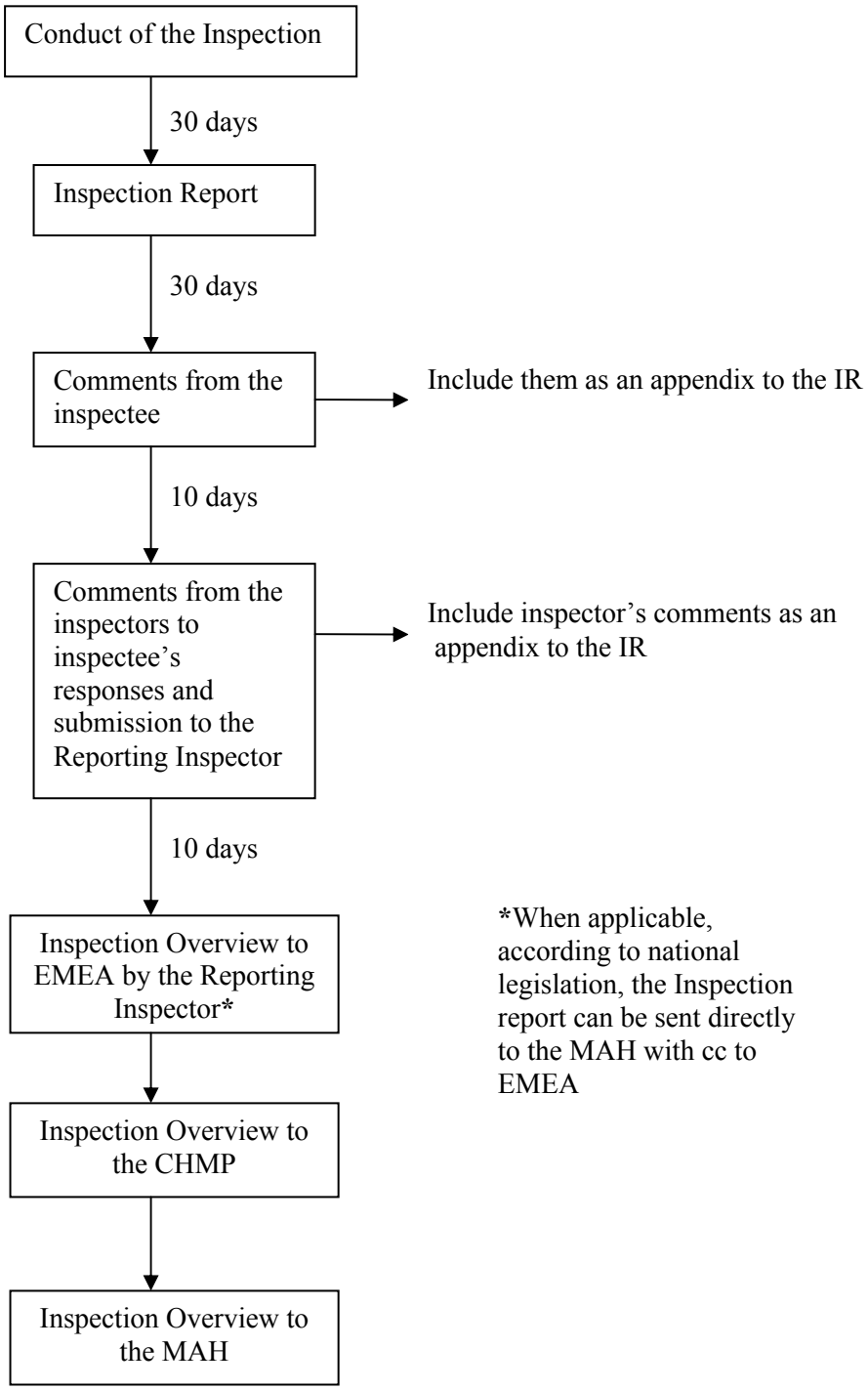
APPENDIX 4- CLASSIFICATION OF INSPECTION FINDINGS

Critical: a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major: a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor: a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

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.

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Official Journal L 311, 28/11/2001 p. 67 - 128). As amended.

- The Rules Governing Medicinal Products in the European Union, EudraLex Volume 9A- EU Pharmacovigilance rules for Medicinal Products for Human and Veterinary Use, Notice to Marketing Authorisation Holders, April 2007.

- Procedure for co-ordinating Pharmacovigilance inspections requested by the EMEA (EMEA SOP INS/PhV/1).

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

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