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Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections

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This guideline replaces EMEA/INS/GCP/218148/2007 "Procedure for conducting pharmacovigilance inspections requested by the Committee for Medicinal Products for Human Use (CHMP)" and EMEA/INS/GCP/391114/2005 "Procedure for reporting of pharmacovigilance inspections requested by the CHMP".



Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections

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1. Introduction

The pharmacovigilance regulatory obligations placed on marketing-authorisation holders (MAH) are laid down in Regulation (EC) No 726/2004, Directive 2001/83/EC and the Commission Implementing Regulation (EU) No 520/2012. Guidelines on the interpretation of legislative pharmacovigilance requirements are published in the adopted good pharmacovigilance practices (GVPs) Module III – pharmacovigilance inspections.

In accordance with Article 111(1) of Directive 2001/83/EC, the competent authorities of the Member States (MSs) shall, in cooperation with the Agency, ensure that the legal requirements governing medicinal products are complied with, by means of inspections. GVP Module III (pharmacovigilance inspections) states that pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures consistent with agreed Union pharmacovigilance inspection procedures developed by the European Union (EU) Pharmacovigilance Inspectors Working Group (PhV IWG) to support harmonisation for the mutual recognition of pharmacovigilance inspections within the EU. Union procedures are published to compliment GVP Module III.

Preparation of a risk-based programme for pharmacovigilance inspections is presented in the Union procedure on the coordination of EU pharmacovigilance inspections. Follow-up issues consequent to inspections – above those of common corrective and preventive actions (CAPA) procedures – are detailed in the Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products.

In Union procedures on pharmacovigilance inspections, any reference to Regulation (EC) No 726/2004 and Directive 2001/83/EC refers to the Regulation and Directive respectively, always including their latest amendments.

2. Scope

This procedure constitutes a guideline in preparing, conducting and reporting national competent authority (NCA) pharmacovigilance inspections and outlines the steps taken of the Committee for Medicinal Products for Human Use (CHMP) requested pharmacovigilance inspections. Addition of particulars or modifications may be applied to meet the objectives of the different types of inspections (see GVP Module III.B.1.). The responsibility for conducting and reporting lies with the inspectorate involved, i.e. the inspector(s) selected with the specified roles. This procedure does not include follow-up issues outside of routine CAPA procedures. Those are covered under the Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products.

3. Procedure

3.1. Preparation

Preparation encompasses those activities undertaken after the selection of an MAH, or third party, for a pharmacovigilance inspection and prior to inspection conduct. It involves prospective planning to ensure inspection objectives are achieved. Activities include but are not limited to:

- allocating resource to conduct the inspection;
- announcing the inspection to the inspected entity;
- making the necessary logistical arrangements;
- defining the inspection scope and agenda (i.e. the inspection plan).

These activities are undertaken by the Member State competent authority(ies) responsible for conducting the inspection, and involve interaction with the inspected entity as needed. Interaction with the body requesting the inspection, if different to the Member State competent authority conducting the inspection (e.g. Pharmacovigilance Risk Assessment Committee (PRAC), CHMP, other Member State competent authority), may also be necessary.

3.2. Resource allocation

- Inspector(s) should be appointed for an inspection, taking into consideration national procedures, as well as the Union procedures entitled “Recommendations on the training and experience of inspectors performing pharmacovigilance inspections”, as appropriate. For the selection of involved parties for CHMP requested inspections, refer to the Union procedure on the coordination of EU pharmacovigilance inspections.
- The definitions, and duties of the involved parties (reporting inspector, lead inspector, etc.) are provided under the “Definitions” section of the Union procedure on the coordination of EU pharmacovigilance inspections.
- The combination of inspectors and inspection days should be sufficient to ensure the inspection objectives are achieved.

3.3. Announcing the inspection

- NCAs have the right to inspect at any time. In exceptional circumstances, an inspection may be performed without prior notice. This could arise, for example, in the conduct of a “for cause” inspection to investigate an immediate public health or compliance concern.
- However, routine practice is for advance notice of the intent to inspect a pharmacovigilance system to be given to a company (MAH and/or third parties). The period of notice served should be sufficient to enable organisation of logistical arrangements and review of relevant data. Unnecessarily long notice periods should be avoided. As guidance, a period of six to eight weeks is considered sufficient for a routine inspection. However, national procedures may apply different time periods, as appropriate.
- The Member State competent authority should prepare the announcement of the inspection following national procedures. Announcement communications could include, for example, the

name of the inspector(s), MAH, the objectives and nature of the inspection (i.e. routine systems, product specific, pre authorisation, for cause inspection) and if known, the proposed address of the inspection site(s). Additional information, including the pharmacovigilance system master file (PSMF) number, any specific product authorisations to be reviewed, the intention to perform the inspection remotely, if applicable, can be added, as appropriate.

- The announcement should be issued to the relevant contact person, requesting confirmation of the inspected entity's availability, and that access to all required documents/databases will be provided. If the relevant contact person is not the EU qualified person for pharmacovigilance (QPPV) that contact person should be requested to inform the EU QPPV.
- A request for the inspected entity to submit information for the purposes of inspection preparation should be made. The inspection type (e.g. systems or product specific) and objectives will determine the pre-inspection documentation required, however, requests will routinely include submission of the pharmacovigilance system master file. Additional supportive data demonstrating how the pharmacovigilance system operates or, describing specific issues of interest may also be requested, as appropriate. The timeline and method of submission of documentation should be clearly defined for the inspected entity.
 - The timeline provided should be adapted by the lead inspector, as needed.

The intent to perform an inspection at a site, located in a third country, or in a Member State different to the competent authority performing the inspection, should be communicated to the local authorities or Member State competent authority, as appropriate. When the site is located in another Member State, the inspectorate of that Member State must be notified of the inspection. In such cases, a joint inspection may be performed or the requesting Member State could ask the competent authority in that Member State to conduct the inspection on their behalf i.e. may submit a triggered inspection request. If a national inspection is to be conducted in a third country, then the Agency should be notified, in accordance with the Union procedure on the coordination of EU pharmacovigilance inspections. For details on the announcement (including timelines) of CHMP requested inspections, refer to the Union procedure on the coordination of EU pharmacovigilance inspections.

3.4. General considerations for preparation

- Inspector(s) should familiarise themselves with the pharmacovigilance system and any relevant product specific issues, prior to the inspection. Information submitted by the inspected entity, as well as data available through the EU regulatory network, may be considered, as follows:
 - Data submitted by the inspected entity as outlined in section 3.3.
 - Prior pharmacovigilance inspection history, e.g. information on pharmacovigilance inspection outcomes communicated by Member State competent authorities and compiled by the Agency.
 - Prior GxP inspection history, where appropriate both originating from the Member State competent authority conducting the inspection and from other sources including other Member State competent authorities and the Agency.
 - Information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the Agency, such as eudravigilance reporting metrics and data quality audits.

- Feedback from other competent authority functions, in particular pharmacovigilance assessors. For supervisory authority inspections, feedback from the PRAC and CHMP rapporteur teams on any issues deemed relevant to the inspection should be sought.
- The scope of the inspection (i.e. aspects of the pharmacovigilance system that will be inspected) should be defined, based on the inspection type, objectives, the information reviewed and GVP guidance. The scope should be documented in accordance with national procedures, and described in the inspection report.
- The scope of supervisory authority inspections should be in line with the requirements outlined in section III.B.4.1 of GVP Module III. All of the areas listed in this section should be covered in the scope of an initial supervisory authority inspection. Additional areas may be examined, as appropriate. The scope of supervisory authority re-inspections may be adjusted, as appropriate, depending on, for example, previous findings, changes to the system/company and any new safety or compliance issues that have been identified. Other routine inspections should also be conducted taking into account the scope defined in section IIIB.4.1 of GVP Module III. Consideration should be given to avoid duplication of inspections conducted by a supervisory authority, or other Member State competent authority, when feasible. In that regard, there may be circumstances when a more limited scope, or more detailed inspection of specific aspects, can be performed. For example, when appropriate, national inspections of a local affiliate office may focus on review of local processes, including but not limited to collection of safety data in that Member State, interface with the QPPV, implementation of risk-minimisation measures and communication with the local Member State competent authority.
- It is recommended that inspectors prepare an inspection plan, which may include:
 - The objectives and scope of the inspection.
 - Identification of the inspection team members and their respective roles, if more than one inspector is going to conduct the inspection.
 - The date and place, where the inspection is to be conducted.
 - Identification of the functional units to be inspected.
 - Identification of documents/electronic tools which will be reviewed, and to which access is required, in so far as is possible.
 - The expected time and duration for each major inspection activity (premises, processes etc.).
 - The schedule for the final meeting.
 - Relevant aspects of the inspection plan, for example the agenda and document access requirements, may be shared with the inspected entity in advance, to ensure the availability of relevant personnel and documentation.
- Other logistical/general considerations are, as follows:
 - It should be verified that the site(s) selected for inspection, and included in the inspection announcement, are appropriate with respect to ensuring the objectives of the inspection can be achieved. Where additional sites or, a change in site is necessary, an amended announcement should be issued, in accordance with Section 3.3.

- If teleconference(s) are planned during the inspection with experts, assessors, MAH personnel located off site etc. This should be identified in advance, in so far as is possible.
- If upon agreement from the body commissioning the inspection, it is decided to conduct a remote inspection, the inspected entity should be contacted to make the necessary arrangements. The inspected entity should be requested to provide a description of the electronic tools available to facilitate inspection conduct. Consideration should be given to any compatibility issues that may arise, and where feasible, testing should be performed in advance. Back up arrangements should also be considered.
- Inspections conducted outside of routine programmes such as those arising from within the Member State competent authority responsible for conducting that inspection should follow national procedures. Any communication between competent authorities and/or the Agency should be documented.

4. Conduct of the inspection

The inspection activities will be carried out according to the details set up in the inspection plan. The inspection plan can be amended during the inspection, for example, to ensure that the inspection's objectives are achieved. Any amendment to the plan should be documented.

Information to fulfil the inspection can be collected by, for example:

- review of relevant documents;
- examination of computer systems;
- conduct of interviews;
- review of internal and external communication e.g. log books, registries, communication with authorities etc.

Any refusal of access to records and retrieval of documentation which the inspector(s) has a legal right to access, should be documented in the inspection report. This should then be communicated with the authority requesting the inspection for further action and decision on consequences.

4.1. Opening meeting

Prior to start of the inspection, an opening meeting must take place between the inspection team and the company being inspected. The chair of the meeting should be the lead inspector.

The purpose of the opening meeting is to:

- introduce the inspection team;
- explain the regulatory framework for the conduct of the inspection;
- provide information about the scope and the objectives of the inspection;
- clarify logistics, timeframes and other references included in the inspection plan;
- introduce the MAH representatives attending the inspection;
- allow the company to present an overview of the pharmacovigilance system;

- clarify with the MAH representatives whether there are any anticipated difficulties foreseen in relation to the conduct of the inspection.

4.2. Review of documentation, processes and systems

The documents and processes to be reviewed during an inspection will depend on the type, scope and focus of the inspection, for example a “for cause” inspection may focus on particular issues of concern, or defined parts of the pharmacovigilance system and inspections at local affiliates may have a different scope to inspection of global pharmacovigilance sites . Appendix 1, section C provides a list of items that could be reviewed during an inspection. However, this list is not exhaustive and should be amended as necessary to ensure the scope of the inspection is met.

4.3. Inspection observations

All inspection observations should be documented. If appropriate, copies should be made of records containing inconsistencies or illustrating non-compliance.

4.4. Closing meeting with the inspected entity

At the end of the inspection, the inspector(s) should conduct a closing meeting with the company being inspected. The QPPV should ensure his/her team attends the meeting. The purpose of the closing meeting is to:

- explain the grading definitions for findings;
- explain the procedures and timelines for distribution of the report, response and any follow-up measures;
- present a summary of the inspection findings to ensure that the results of the inspection are clearly understood;
- provide the inspected party with an opportunity to correct misconceptions and misunderstandings in response to the findings.

An inspection may consist of visits to more than one location. If appropriate, a closing meeting may be held at each location inspected.

Exceptional circumstances may occur which require premature termination of inspection. In such event the deviations from the inspection plan and the reason for early termination should be documented in the inspection report.

5. Reporting of the inspection

5.1. Preparing inspection reports

For each site inspected an inspection report (IR) should be prepared. The inspection reporting process should follow a Member State competent authority procedure. For CHMP requested inspections, the specific additional provisions noted in this procedure should be complied with.

For CHMP requested inspections involving multiple site inspections, an inspection overview (IO) will also be prepared, addressing only 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 critical findings in advance of the circulation of the inspection reports.

There could be circumstances where it may be appropriate to generate only one report for two or more sites, even though these represent separate inspections. Such circumstances can occur, for example if different sites were inspected but it is useful to combine the findings in the report. For CHMP requested inspections the reporting inspector will communicate this to the Agency as soon as this decision is taken so that it is documented and, if possible, it is also indicated in the CHMP adopted inspection request.

5.2. The inspection report (IR)

The inspection report should be prepared by the members of the inspection team and usually coordinated by the lead inspector or, reporting inspector in the case of CHMP requested inspections. Appendix 1 gives an example of the format for an IR of a pharmacovigilance site. This format should be used for CHMP requested inspections. For other inspections, national formats may be used. The content of the IR should be reviewed/agreed by the members of the inspection team. For CHMP requested inspections, the IR will be signed by the lead inspector and other inspectors as required. Signatures may be scanned and sent to the reporting inspector, if appropriate.

The IR should be issued in a timely manner after the end of the inspection. For CHMP requested inspections, the IR should be issued within 30* working days. Where a combined IR is prepared, the time is calculated from the last day of the last inspection (or from when the last post-inspection document has been received). The IR and cover letter/e-mail should be sent to the MAH by the inspectorate/NCA prior to finalisation, with a request for comments, including for example, comments on major factual errors, points of disagreement and corrective and preventive actions (CAPA). For CHMP requested inspections, the CAPA should be provided by the MAH within a defined time period of 30* working days after receiving the report, and in accordance with the dates outlined on the CHMP adopted inspection request. If a response is not received within the stipulated time frame, the absence of a reply should be recorded in the IR.

The MAH response should be assessed by the inspectors, including the impact of comments on the inspection findings, if any, and the adequacy of the proposed CAPA. For CHMP requested inspections, 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 final adopted IR will be signed by the lead inspector and other inspectors as required by national legal requirements and national competent authority standard operating procedures (SOPs). If the proposed CAPA or the timelines of requested actions are not accepted, additional follow up procedures should be defined in writing.

When the CAPA proposed by the MAH is acceptable, the inspection may be closed. For CHMP requested inspections, prior to closure of the inspection the MAH should clarify in writing that all CAPA actions will be completed as scheduled. Thereafter a confirmation on inspection completion will be issued. For those inspections conducted under the national programme, the national inspectorate should provide the Agency with the inspection reports (or a summary of the

* The time shown should be considered as indications and can be modified if necessary

inspection report when the inspection report is not written in English) whenever there are critical findings and/or major findings, and information on how these issues are being addressed (e.g. summary of the CAPA for critical and major findings) should also be provided. Appendix 3 provides a template for pharmacovigilance inspection outcome sharing.

In the case of CHMP requested inspections, the report prepared by the lead inspector will be sent to the reporting inspector and by the reporting inspector to the Agency Compliance and Inspections Department. When applicable, for each site inspected, the lead inspector prepares an IR and forwards it to the reporting inspector within 70* working days after the completion of the inspection.

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

5.3. Content of IR

An IR template of a pharmacovigilance inspection report is provided in appendix 1. This could be used as an example for national inspection reports but should always be used for CHMP requested inspections.

The classification of inspection findings is provided in appendix 4. Each finding should refer to the regulatory requirement to which it relates.

Furthermore, comments from the inspectors may be described as appropriate.

The IR can contain an overall conclusion on whether the pharmacovigilance system complies in general or in relation to the inspected sections, with the relevant regulations within the EU or in accordance with local requirements, as appropriate.

In the case of CHMP requested inspections, the following additional points should be taken into consideration:

1. Language of the IR

This 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 IR will be translated into English under the responsibility of the lead inspector.

2. Content of the IR

The IR will contain an evaluation of the significance of any non-compliance and provide a summary of the major and critical findings. It will also contain an overall conclusion regarding compliance of the pharmacovigilance system with EU/local regulations and the potential subsequent risk for public health and where several sites are inspected. This may be included in the inspection overview described below.

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

3. Review of the format of the IR

A review of the reports is conducted on behalf of the CHMP by the Agency Compliance and Inspections Department, within 5 calendar days from receiving the report. The Agency will check the format of the IR for adherence to:

- the procedures established by the PhV IWG;
- the inspection request adopted by the CHMP;
- citation of applicable regulations and guidelines.

Non adherence(s) encountered by this review will be notified to the reporting inspectorate in writing, with a deadline for revision or other remedial action.

The reporting inspectorate shall provide a revised version or other remedial action within the timeframe agreed, and if not, an explanation for the non-adherence(s) should be provided. If the explanation for non-adherence is not agreed by the Agency, the rapporteur/co- rapporteur and CHMP will be sent the report and a document describing the point(s), as appropriate.

In the event of outstanding issues relating to non-adherence, the report, issues identified and reporting inspector explanation are circulated to the PhV IWG, 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 Compliance and Inspections Department, 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. The inspection overview (IO)

The reporting inspector will prepare an IO, where applicable, 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 preventive 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 forwarded to the Agency within 80* working days after the completion of the inspection.

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

Direct communication is encouraged between the reporting inspector, the lead inspectors, (co)-rapporteur and assessors and Agency 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.

For an overview of the timelines of CHMP requested inspections refer to Annex 2 of the Union procedure on the coordination of EU pharmacovigilance inspections.

6. Forwarding the IR/IO to CHMP/PRAC and inspection follow-up

The Agency Compliance and Inspections Department will circulate the final IR/IO to the CHMP/PRAC. The IR/IO conclusions should recommend any follow-up to be requested by the MAH. The conclusion should recommend further inspection, if considered necessary.

* The time shown should be considered as indications and can be modified if necessary

For pharmacovigilance inspections with findings that may impact the robustness of the benefit-risk profile of concerned medicinal product(s), refer to the Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products.

5.4. Record management and archiving

The principles and requirements to be followed will be described in the Union procedure on record keeping and archiving of documents obtained or resulting from the pharmacovigilance inspections.

References

- 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, as amended.
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Union code relating to medicinal products for human use, as amended.
- Commission Implementing Regulation (EU) No 520/2012, on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.
- Guideline on good pharmacovigilance practices (GVP) - Module I – Pharmacovigilance systems and their quality systems.
- Guideline on good pharmacovigilance practices (GVP) - Module III – Pharmacovigilance inspections.
- Union procedure on the coordination of EU pharmacovigilance inspections.
- Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products.
- Union procedure on sharing of pharmacovigilance inspection information.
- Union recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

Appendix 1 –Pharmacovigilance inspection report

Click [here](#) for the template.

Appendix 2- Inspection overview (IO)

Click [here](#) for the template.

Appendix 3- Pharmacovigilance inspection outcome sharing

Click [here](#) for the template.

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

Comment: the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.