PROEDURE FOR CONDUCTING PHARMACOVIGILANCE INSPECTIONS REQUESTED BY THE CHMP

GCP Inspectors Working Group

Applies to: EMEA, EU/EEA Inspectorates

Summary of scope: This SOP provides unified standards on the conduct of pharmacovigilance inspections that are applicable for any site to be inspected at the request of the CHMP.

Keywords: : Conduct, pharmacovigilance inspection, QPPV Restricted

Supersedes: N/A

Finalisation Date

Adoption GCP Inspectors Working Group 04 September 2007
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1 PURPOSE

In accordance with EU and local member state legislation and guidelines, marketing authorisation holders are required to fulfil certain pharmacovigilance and drug safety obligations. To allow competent authorities to monitor compliance of marketing authorisation holders (MAHs) with their obligations, direct inspections of pharmacovigilance systems by the competent authorities may be conducted.

The legal basis for the conduct of pharmacovigilance inspections is detailed in Article 19(1) of Regulation (EC) No 726/2004 and Article 111(d) of Directive 2001/83/EC. In addition, further details relating to the co-ordination and conduct of EU pharmacovigilance inspections are given in Volume 9A, Part I, section 2 “Requirements for the Detailed Description of Pharmacovigilance Systems, monitoring of Compliance and Pharmacovigilance Inspections”.

The focus of these inspections is on the MAH’s systems for management of pharmacovigilance data as well as on the conduct of the pharmacovigilance for selected centrally authorised products in order to complete the assessment performed by the CHMP of the safety processes in place and safety reporting for centrally authorised products to the EMEA. This includes, but is not limited to, spontaneously reported adverse drug reactions, those adverse events from clinical trials, which are subject to expedited reporting, PSURs, ASRs, RMPs, PIPs and signal detection activities. In addition, the MAH’s ability to identify and report to competent authorities, all important safety information from clinical trials on medicinal products with a marketing authorisation, may be subject to inspection.

These inspections may be conducted at a single site or at several sites. The inspection sites may be in an EU member state and/or a non-EU territory. The inspections may be routine or triggered by specific concerns.

During routine inspections the inspection should confirm that any Detailed Descriptions of Pharmacovigilance that have been submitted to competent authorities by the Marketing Authorisation Holder accurately reflect the pharmacovigilance system that is in place. This may also be appropriate for triggered inspections, depending on the scope of the inspection.

In addition, any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with, the MAH may be inspected, in order to confirm their capability to support the MAH’s compliance with pharmacovigilance obligations.

This document gives an outline of the aspects of a pharmacovigilance inspection, which may be followed to achieve the objectives of the inspection.

2 RESPONSIBILITIES

Each inspectorate has the responsibility to ensure that any pharmacovigilance inspections conducted on behalf of the EMEA are performed in accordance with this procedure.

3 DEFINITIONS

Abbreviations used in the document:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>ASR</td>
<td>Annual Safety Report</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
</tbody>
</table>
4 DESCRIPTION OF PROCEDURE/REQUIREMENTS, INCLUDING RESPONSIBILITIES

The objectives for a pharmacovigilance inspection may vary according to the criteria under which it is decided to perform the inspection.

The criteria for conducting pharmacovigilance inspections will result from a request from the CHMP as detailed in EMEA SOP INS/PhV/1 (Procedure for co-ordinating pharmacovigilance inspections requested by CHMP).

The coordination of pharmacovigilance inspections should be in accordance with EMEA SOP INS/PhV/1.

4.1 Preparation for a pharmacovigilance inspection

The scope of the inspection will depend on the nature of the inspection (routine/triggered) and on the requirements of the inspection request.

Preparation of a pharmacovigilance inspection should involve collaboration with the inspectorate and the pharmacovigilance departments of the competent authority delegated to conduct the pharmacovigilance inspection. The preparation may also involve the assessors of a particular product or other specialist, e.g. IT specialist, depending on the scope of the inspection. The composition of the inspection team may also include such experts.

An inspection plan should be prepared in line with the scope and objectives of the inspection and should cover all the relevant aspects described in section 4.2.2. of this procedure.

MAHs and their subcontractors/co-marketing organisations may have distributed pharmacovigilance and safety evaluation tasks to more than one country (both EU and non-EU). It is important to ascertain (from the Detailed Description of the Pharmacovigilance System or by obtaining additional information, organisational charts, contracts/agreements and SOPs) how pharmacovigilance responsibilities are divided within the company and with marketing partners/contractors. It is also important to ascertain where the required information resides when
planning the pharmacovigilance inspection. As a result, several sites may need to be visited in order to obtain a complete picture of the pharmacovigilance activities of the MAH.

Access to the global pharmacovigilance database, and provision of MAH resource to conduct searches on the database, should be arranged with the MAH prior to the inspection.

The Detailed Description of the Pharmacovigilance System provided in the Marketing Authorisation application will provide the inspector(s) with information relating to the MAH. However, prior to the inspection, it should be confirmed that there have been no significant changes in the system that will have an impact on inspection planning.

The data and documentation review that should be performed as part of the pharmacovigilance inspection, (general sampling or with respect to a particular product or therapeutic area), shall be determined prior to the inspection and should address the scope and objectives of the inspection. Additional data and documentation for review may also be identified during the inspection. An adequate sample of data and documentation to undergo review shall be determined, and may be requested to be provided to the inspector(s), as part of the preparation. The basis for selecting the sample size may depend on the following factors:

- The organisation of the MAH and the distribution of the pharmacovigilance and safety evaluation tasks,
- The number of products with a marketing authorisation,
- The types of products and therapeutic areas,
- The specific questions raised by the CHMP which need to be addressed during the inspection,
- The clinical trial and pharmaco-epidemiological studies conducted by the MAH,
- The different possible origins of the reports (i.e. local, other EU, non-EU, licensing partner, distributor, spontaneous reports, clinical trials),
- Issues of non-compliance identified during previous inspections.

The sample should give a good representation of the conduct of pharmacovigilance at the marketing authorisation site.

The data and documentation request should be performed in a timely manner in order to allow inspectees to provide all the requested documents for review by the inspection team prior to the inspection.

4.2 Conduct of a pharmacovigilance inspection

4.2.1 Opening Meeting

Before the start of the inspection, an opening meeting must take place between the inspector(s) and the inspectee(s), for the purpose of introduction and to discuss the arrangements for the inspection.

In particular, the following points should be covered where relevant:

- The Lead Inspector should describe the purpose and the scope of the inspection,
- The Lead Inspector should outline the inspection references (e.g. regulations and guidelines that provide the basis for the inspection, see §6 for Community texts), and summarise the methods and procedures to be used to conduct the inspection,
- The activities and personnel to be interviewed that are described in the Pharmacovigilance Inspection Plan should be re-confirmed and inspection logistics should be discussed,
The Lead Inspector should re-confirm that the resources, documents and facilities required by the inspector(s) are available,

Confirm the time and date for the closing meeting and any interim meetings,

Appropriate site personnel should provide background information about the MAH and/or supporting contractor(s). This would normally include an overview of the organisation and links with other commercial organisations relevant to pharmacovigilance/drug safety, the systems used for the collection, collation, evaluation and reporting of adverse drug reactions, a summary of significant changes since the previous inspection (where applicable) and a summary of significant changes that are planned for the future.

4.2.2 Conduct of the inspection/collecting information and recording observations

The inspection activities should be detailed in the inspection plan. Nevertheless, during the inspection, the inspector(s) may amend the plan to ensure that the inspection objectives are achieved.

Sufficient information to fulfil the inspection objective(s) should be collected through examination of relevant documents and computer systems, as well as through the conduct of interviews.

If access to records or copying of documents is refused for any reason or there is any withholding of documents or denial of access to areas to which the inspector has a legal right of access, these refusals should be documented and included in the inspection observations.

The following items should be reviewed as part of the pharmacovigilance inspection:

4.2.2.1 Legal and administrative aspects

- Documentation of the responsible parties for pharmacovigilance/drug safety activities
- Identifying the QPPV at the MAH’s site
- Availability of information on all suspected ARs at least at a single point within the community
- Contractual documentation with respect to any pharmacovigilance/drug safety responsibilities being out-sourced by the MAH
- Documentation regarding the delegation of responsibilities for pharmacovigilance/drug safety with respect to co-marketing agreements,
- Commitments for AR reporting to the EMEA and Member States in relation to Centrally Authorised Products
- Special requirements for reporting of ARs to the competent authorities or for monitoring safety i.e. post-authorisation commitments and follow-up measures for centrally authorised products; compliance with Risk Management Plans; compliance with Paediatric Investigation Plans, where applicable
- Preparation and submission of Periodic Safety Update Reports (including discussion relating to off-label use/paediatric use)/Annual Safety Reports/SPCs (including revisions)/Clinical Investigator’s Brochure (including revisions)
- Documentation of responsibilities in relation to pharmacovigilance/drug safety of products undergoing clinical trials
- Collection and reporting of SAEs in clinical trials
- Collection and reporting of spontaneous ARs (see table for expedited reporting requirement in Volume 9A, part I, 4.3.2, p. 58)
- Collection, follow-up and reporting of pregnancy exposure
- Collection, follow-up and reporting of paediatric population exposure
- Provision to the competent authorities with any other information relevant to the evaluation of the risks and benefits of a medicinal product, particularly information concerning post-authorisation safety studies (including studies included in RMPs and PIPs)
4.2.2.2 Organisational structure

(i) Quality system and Standard Operating Procedures (SOP) for pharmacovigilance activities

- Documentation of SOPs and instructions to cover all aspects of pharmacovigilance/drug safety. These SOPs and instructions should include, but are not limited, to the following activities:
  - Collection and management of pharmacovigilance data (from consumers, healthcare professionals, medical information departments, medical representatives, quality complaint departments, regulatory affairs departments, legal departments, manufacturing sites, sub-contractors, co-marketing organisations, etc.) and of SAEs in clinical trials:
    - Causality assessment
    - Determination of seriousness and listedness/expectedness and whether AR reports are expeditable
    - Coding
    - Avoidance of duplicate reporting
    - Ensuring reporting compliance
    - Identifying and tracking initial and follow-up reports
    - Ensuring an adequate and complete follow-up
    - Handling of reports to and from other organisations (e.g. licensing partners, co-developers and CROs)
    - Handling of reports relating to comparator, product or placebo
    - Ensuring completeness of the information contained in database(s).
  - Review, validation and follow-up of suspected ARs
  - Data Management (accurate storage and retrieval of information, tracking of reports and ensuring timeliness, compliance with national requirements of confidentiality)
  - Expedited reporting to competent authorities (for national, mutual recognition and centralised procedures), investigators and MECs/IRBs
  - Monitoring of worldwide scientific literature
  - Collation and submission of Periodic Safety Update Reports/Annual Safety Reports
  - Management of requests for information by competent authorities
  - Management of urgent safety restrictions and type II variations
  - Updating of core safety information/developmental safety information/SPCs (including relevant results of paediatric studies)
  - Signal detection/trend analysis activities
  - Management of communications with competent authorities as necessary
  - Production of Risk Management Plans
  - Organisational charts to identify the key personnel
  - Control of SOPs and other procedural documentation, including writing, review, approval, updating, distribution and implementation
  - Review of Quality Control processes and documentation
  - Review of corrective and preventive action processes and documentation
  - Auditing of the pharmacovigilance system:
    - Determine that audits of key pharmacovigilance/drug safety activities are being carried out and which organisation is in charge
    - The processes for communicating and addressing audit findings
    - Audit of contractors/sub-contractors (if applicable)
    - Qualification and training of auditors

(ii) Qualified Person (QPPV)

- Documentation identifying the QPPV along with qualifications and training
- Documentation of QPPV and contact details in the quality system
- Verification that the QPPV has adequate (direct, timely) access to all relevant pharmacovigilance/drug safety information
- Verification that the same QPPV has been notified to all relevant competent authorities
- Verification that the QPPV has sufficient authority within the company to make amendments to the pharmacovigilance system in order to ensure compliance
- Documentation for delegation of tasks
- Verification of the back-up process when the QPPV is absent

(iii) Resources and training of Personnel.
- Interview of personnel involved in any pharmacovigilance activity, including medical representatives, medical information, regulatory affairs, legal, clinical trial and product quality personnel
- Documentation of job description, qualifications and training of individuals involved in any stage of pharmacovigilance/safety evaluation process
- Documentation on policies and procedures for training of personnel
- Allocation of deputies to key personnel

4.2.2.3 Facilities and computer systems
- Computer systems in use (administration, use and hardware/software specifications and validation). Please refer to the PIC/S document “Good Practices for Computerised Systems in Regulated “GxP” environments” (PI 011-2)
- Migration of data and legacy system, where relevant
- System for the archiving and retrieval of documents
- Archiving and filing facilities
- Controlled access to the archives

4.2.2.4 Safety Information from Clinical Investigations
- Identification of the responsible staff related to the clinical trials being undertaken by the MAH (qualifications and training)
- Documentation of the medical review of the SAE/AR
- Documentation of emergency unblinding procedures
- Serious Adverse Event Notification by investigators
- Procedures for the notification to investigators, MECs/IRBs and the competent authorities in accordance with (local) legal requirements of any information which may affect the health, safety and rights of patients
- Compliance of reporting with ICH/E2A and GCP Guidelines
- Production and submission of Annual Safety Reports
- Documentation of contractors/sub-contractors
- Mechanisms for informing trial subjects of new safety information which may affect their willingness to participate in a trial
- Methods used to ensure that all new safety information from clinical trials, on medicinal products with a market authorisation, is incorporated into reports to authorities
- Links between the post-marketing pharmacovigilance activities and clinical trial activities (people, procedures, departments, computer systems, organisations)
- Methods used for updating the IB
- Reconciliation of information in clinical trial and pharmacovigilance databases
4.2.2.5 Safety information from other departments: quality defects, medical information, legal information etc.

To be considered but not limited to:

- Quality defects and complaints should be examined to determine what procedures and links exist to establish whether there are quality defects that could lead to ARs or whether there may be a quality defect reported that could be the cause of actual or potential ARs and vice versa. Reconciliation of these data should be organised,
- Handling of medical information and legal information should also consider the potential for AR identification,
- Information collected by Marketing and Regulatory Affairs Departments.

4.2.2.6 Data/documentation review

The following are examples of testing that may be performed. However, this is not an exhaustive list and the strategies used will depend on the objectives of the inspection.

- Confirmation that potential ARs from any source, e.g. product complaints, medical information enquiries, medical representatives, EEA, third countries, co-marketing, post-marketing studies, etc. have been processed appropriately. This may include a review of compliance reports
- Determination of seriousness
- Determination of listedness/expectedness
- Causality assessment
- Consistency and correctness of coding with terminologies used and internal procedures
- Quality and completeness of the medical review
- Quality of the information included in case summaries
- Adequacy of follow-up measures taken
- Adequacy of follow-up information collection and reporting
- Any specific questions raised in the inspection request
- Submission of expedited and periodic reports to authorities. Have all relevant reports been submitted within the correct timeframes?
- Have all relevant cases (all serious ARs and all non-serious, unlisted spontaneously reported ARs) been discussed or included in the line listings of the PSUR covering the relevant time period?
- Have qualifying serious reports from clinical trials been reported in an expedited manner and included in PSURs and ASRs?
- Have specific requests in Assessment Reports e.g. for the presentation and submission of data, been appropriately addressed?
- Can serious ARs/AEs be identified in the listings of non-serious ARs/AEs?
- Has the output from literature searches been appropriately reviewed?
- Can specific literature cases be retrieved from the database?
- Have new safety issues arising from post-authorisation studies, conducted worldwide, been reported promptly to competent authorities?
- Adequacy of quality control process and follow-up measures taken (corrective action process)

4.2.2.7 Recording inspection observations

All inspection observations should be documented. If appropriate, copies should be made of records containing inconsistencies or illustrating non-compliance.
At the end of the inspection, the inspector(s) should review all observations to determine which are to be reported as non-compliance and/or as quality system deficiencies. The inspector(s) should then ensure that these are documented in a clear, concise manner and are supported by objective evidence. All reported observations (findings) should be identified with reference to specific requirements of the regulations or other related documents against which the inspection has been conducted. The names and titles of persons interviewed or present during the inspection meetings and the details of the inspected organisation should be documented.

If required by local regulations, the inspection observations may be collected in a minute (or similar) to be written by the inspector(s) at the end of the inspection.

4.2.3 Closing Meeting with the inspectee(s)

At the end of the inspection, the inspector(s) should conduct a closing meeting with the inspectee(s). The QPPV, his deputy or other responsible persons for pharmacovigilance activities should attend the meeting. The purpose of the closing meeting is:

- To summarise inspection findings and observations to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by either the inspector(s) or the inspectee(s),
- To provide the inspected party with an opportunity to correct any misconceptions made by the inspector(s) or to supply additional information in response to the findings. However, all efforts should be made during the inspection in order to minimise the misconceptions and discussion during the closing meeting,
- To clarify the procedures for the distribution of the inspection report, for the production of responses to the inspection report and for inspection follow-up (as appropriate), in accordance with the “Procedure for reporting of Pharmacovigilance inspections requested by the EMEA (EMEA SOP INS/PhV/4),”
- To request copies of any documents that may be required by the inspector, e.g. to assist with the preparation for other activities associated with the inspection.

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

4.3 Preparation of inspection report

The Lead Inspector, in agreement with the inspection team, shall prepare an inspection report in accordance with EMEA SOP INS/PhV/4 (Procedure for reporting of Pharmacovigilance inspections requested by the CHMP).

5 FORMS NEEDED FOR THIS PROCEDURE

Not applicable.

6 REFERENCES AND RELATED DOCUMENTS

• Commission Regulation (EC) No. 540/95.
• CPMP/ICH/135/95: “Note for Guidance on Good Clinical Practice”.
• Eudralex Volume 10, Chapter II: “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use”.
• Eudralex Volume 10, Chapter II: “Detailed guidance on the European database of suspected unexpected serious adverse reactions (Eudravigilance – Clinical Trial Module)”.
• CPMP/ICH/377/95: (E2A) “Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting”.
• CPMP/ICH/288/95: (E2C) “Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs” plus E2CA (Addendum).
• CPMP/ICH/3945/03: (E2D) “Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting”.
• CPMP/ICH/5716/03: (E2E) “Pharmacovigilance Planning”.
• Procedure for co-ordinating Pharmacovigilance inspections requested by the EMEA (EMEA SOP INS/PhV/1).
• Procedure for reporting of Pharmacovigilance inspections requested by the EMEA (EMEA SOP INS/PhV/4).
• PIC/S Good Practices for Computerised Systems in Regulated “GxP” environment (PI 011-2).
APPENDIX I

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.