European Medicines Agency
Inspections

London, 20 April 2009
EMEA/INS/PhV/85058/2008
Procedure no: INS/PhV-V/2

PROCEDURE FOR CONDUCTING PHARMACOVIGILANCE INSPECTIONS REQUESTED BY THE CVMP

Ad Hoc PhV 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 CVMP.	
Keywords: Conduct, PhV inspection, QPPV	**Public**
Supersedes: N/A	

Finalisation	**Date**
Adoption by Ad Hoc PhV Inspectors Working Group	11 March 2009

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1 PURPOSE

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

The legal basis for the conduct of PhV inspections is detailed in Article 57 (1) of Regulation (EC) No 726/2004 and Article 80 (1) of Directive 2001/82/EC. In addition, further details relating to the co-ordination and conduct of EU PhV inspections are given in Volume 9B, Guideline on monitoring of compliance with PhV regulatory obligations and PhV inspections for veterinary medicinal products, section 5 “Pharmacovigilance Inspections”.

The focus of these inspections is on the MAH’s systems for management of PhV data as well as on the conduct of the PhV for selected centrally authorised products in order to complete the assessment performed by the CVMP 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 studies, which are subject to expedited reporting, PSURs. In addition, the MAH’s ability to identify and report to competent authorities, as applicable, all important safety information from clinical studies and post-authorisation safety studies 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 targeted 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 PhV system that is in place. This may also be appropriate for targeted inspections, depending on the scope of the inspection.

In addition, any party carrying out PhV 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 PhV obligations.

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

2 RESPONSIBILITIES

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

3 DEFINITIONS

Abbreviations used in the document:

AE	Adverse Event
CVMP	Committee for Veterinary Medicinal Products
EC	European Community
EEC	European Economic Community
EMEA	European Medicines Agency

EU	European Union
IB	Investigator's Brochure
VICH	Veterinary International Conference on Harmonisation
IT	Information Technology
MAH	Marketing Authorisation Holder
PhVWP	Pharmacovigilance Working Party
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics

4 DESCRIPTION OF PROCEDURE/REQUIREMENTS, INCLUDING RESPONSIBILITIES

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

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

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

4.1 Preparation for a PhV inspection

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

Preparation of a PhV inspection should involve collaboration with the inspectorate and the PhV departments of the competent authority delegated to conduct the PhV 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 PhV 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 PhV 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 PhV inspection. As a result, several sites may need to be visited in order to obtain a complete picture of the PhV activities of the MAH.

Access to the global PhV 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 PhV 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 PhV 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 CVMP which need to the addressed during the inspection,
- The clinical studies and post-authorisation safety 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 studies),
- Issues of non-compliance identified during previous inspections.

The sample should give a good representation of the conduct of PhV 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 PhV 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 PhV/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 Pharmacovigilance 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 PhV inspection:

4.2.2.1 Legal and administrative aspects

- Documentation of the responsible parties for PhV/drug safety activities
- Identifying the QPPV at the MAH's site
- Availability of information on all suspected AEs at least at a single point within the community
- Contractual documentation with respect to any PhV/drug safety responsibilities being out-sourced by the MAH
- Documentation regarding the delegation of responsibilities for PhV /drug safety with respect to co-marketing agreements
- Commitments for AE reporting to the EMEA and Member States in relation to Centrally Authorised Products
- Special requirements for reporting of AEs 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, where applicable
- Preparation and submission of Periodic Safety Update Reports (including discussion relating to off-label use/ SPCs (including revisions)
- Documentation of responsibilities in relation to PhV/drug safety of products undergoing clinical studies
- Collection and reporting of SAEs in clinical studies
- Collection and reporting of spontaneous AEs
- 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

4.2.2.2 Organisational structure

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

- Documentation of SOPs and instructions to cover all aspects of PhV/drug safety. These SOPs and instructions should include, but are not limited, to the following activities:
    - Collection and management of PhV data (from animal owners, healthcare professionals, medical information departments, veterinary representatives, quality complaint departments, regulatory affairs departments, legal departments, manufacturing sites, sub-contractors, co-marketing organisations, etc.), and when applicable, of SAEs in clinical or post-authorisation safety studies:
        - Causality assessment
        - Determination of seriousness and whether AE 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)
        - Handling of reports relating to comparator, product or placebo in clinical studies or post-authorisation safety studies
        - Ensuring completeness of the information contained in database(s)
    - Review, validation and follow-up of suspected AEs
    - 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)
    - Monitoring of worldwide scientific literature
    - Collation and submission of Periodic Safety Update Reports
    - Management of requests for information by competent authorities
    - Management of urgent safety restrictions and type II variations
    - Updating of core safety information, if available
    - Signal detection/trend analysis activities
    - Management of communications with competent authorities as necessary
    - Production of Risk Management Plans, when applicable
- 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 PhV system to include whether audits are being conducted and if so, the processes for communicating and addressing audit findings

(ii)Qualified Person (QPPV)

- Documentation identifying the QPPV along with qualifications and training
- Documentation of QPPV and contact details in the PhV system
- Verification that the QPPV has adequate (direct, timely) access to all relevant PhV/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 PhV 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 PhV activity, including veterinary and or technical representatives, regulatory affairs, legal, clinical trial and product quality personnel if appropriate
- Documentation of job description, qualifications and training of individuals involved in any stage of PhV/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 Studies for products with a Marketing Authorisation or Post Authorisation Safety Studies

The following items may need to be considered if identified or established in the study protocol, and in consideration of national, study- or product-specific requirements, if available.

- Identification, qualifications and training of the responsible staff related to the clinical studies being undertaken by the MAH
- Documentation of the medical review of the AE
- Documentation of emergency unblinding procedures
- Serious Adverse Event Notification by investigators to sponsor
- Procedures for the notification to investigators, and the competent authorities in accordance with (local) legal requirements of any information which may affect the animal and user safety
- Documentation of contractors/sub-contractors
- Mechanisms for informing owners of new safety information which may affect their willingness to maintain their animal in the study
- Methods used to ensure that new safety information from clinical studies on medicinal products with a market authorisation that might influence the evaluation of benefits and risks of the authorised product, is reported to authorities in accordance with national or product-specific requirements
- Links between the post-authorisation PhV activities and clinical studies activities (people, procedures, departments, computer systems, organisations)
- Methods used for updating the IB
- Reconciliation of information in clinical trial and PhV databases, if appropriate

4.2.2.5 Safety information from other departments: quality defects, veterinary 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 AEs or whether there may be a quality defect reported that could be the cause of actual or potential AEs and vice versa. Reconciliation of these data should be organised.

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 AEs from any source, e.g. product complaints, product information enquiries, veterinary representatives, EEA, third countries, co-marketing, post-authorisation studies, etc., have been processed appropriately. This may include a review of compliance reports
- Determination of seriousness
- Causality assessment
- Consistency and correctness of coding with terminologies used and internal procedures
- Quality and completeness of the veterinary 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 Safety Update Reports to authorities. Have all relevant reports been submitted within the correct timeframes?
- Have all relevant cases (all serious AEs and all applicable non-serious spontaneously reported AEs) been discussed or included in the line listings of the PSUR covering the relevant time period?
- Have qualifying serious reports from clinical or post-authorisation safety studies been reported in an expedited manner and included in PSURs?
- Have specific requests from the NCAs been appropriately addressed?
- Can serious AEs be identified in the listings of non-serious AEs?
- Have literature searches been conducted and reviewed appropriately?
- Can specific literature cases be retrieved from the database?
- Have new safety issues arising from post-authorisation safety studies, conducted worldwide, been reported promptly to competent authorities if appropriate?
- Adequacy of quality control process and follow-up measures taken (corrective action process)
- Has the correct format for the Sender Report Identification Number and the Unique Case Registration Number been used when reporting into EudraVigilance Veterinary?

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 not being compliant with EU legislation and/or guidelines and/or as PhV 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 PhV 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 discuss them 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 PhV inspections requested by the EMEA (EMEA SOP INS/PhV-V/3)",
- 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-V/3 (Procedure for reporting of PhV inspections requested by the CVMP).

5 FORMS NEEDED FOR THIS PROCEDURE

Not applicable.

6 REFERENCES AND RELATED DOCUMENTS

- 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 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Official Journal L 311, 28/11/2001 p. 1- 66). As amended.
- Commission Regulation (EC) No. 540/95.
- CPMP/PhVWP/1618/01: "Position Paper on Compliance with Pharmacovigilance Regulatory Obligations", Adopted 5 December 2001.
- Volume 9B- Guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products, March 2007.
- EMEA/CVMP/893/04-UK: "Guideline on EU veterinary suspected adverse reaction report form for veterinarians and health professionals".
- Procedure for co-ordinating PhV inspections requested by the EMEA (EMEA SOP INS/PhV-V/1).
- Procedure for reporting of PhV inspections requested by the EMEA (EMEA SOP INS/PhV-V/3).
- PIC/S Good Practices for Computerised Systems in Regulated "GxP" environment (PI 011-2).