



How Inspection-ready Are You? Routine PV Activities in the EU

Vicky Edwards
Monika Pietrek

In 2001 the CHMP published a position paper¹ on the compliance with pharmacovigilance (PV) regulatory obligations. Since then, the EMEA and some national EU Regulatory Agencies have begun to conduct inspections of pharmaceutical companies. At least two Authorities now have statutory inspection program in place. In addition, EMEA and FDA² agreed on a mutual exchange of inspection findings and cross-country inspections.

Regulatory inspections have a history for manufacturing of medicinal products (Good Manufacturing Practice) and conduct of clinical trials (Good Clinical Practice). In preparation for inspection, companies started to perform audits of their own facilities and investigational sites to ensure that their quality systems were effective. Quality assurance (QA) developed specific, distinct expertise in those two areas. In the area of pharmacovigilance, inspections have therefore presented a novelty. Since then, parties, regulators, and pharmaceutical companies, as well as involved specialties QA and PV, have experienced a learning curve. In addition, inspection findings have identified the need for clarification of PV regulatory obligations which are either to be addressed by the new legislation or detailed guidance on specific issues, such as the role of the EU Qualified Person (QP) for PV.

As inspections have become an integral part of PV activities, representatives from the pharmaceutical and CRO industries have developed the following inspection checklist to assist in being prepared. Key objectives of this checklist follow:

- The location of necessary documentation
- The review of material
- The identification of required updates and/or missing documentation processes
- The review of organizational boundaries.

Before beginning to prepare for an inspection the company needs to identify the owner of this procedure. Any independent control procedure should be guided by Quality Assurance in collaboration with a functional representative. For pharmacovigilance the QP PV would be first choice; however, depending on company size and organization (affiliate, headquarters) the operational

head of PV of the respective office may be involved in an audit/inspection preparation. In large organizations this task may be delegated to another competent PV representative. Ideally, both operational head and QP PV should be involved in the planning, presentation of the findings and the actions following the audit/inspection.

The inspection checklist addresses the PV organization, the EU QP for PV, roles and responsibilities, training, the quality system (policies and procedures), case management, periodic reports, product complaints, safety issue management, medical information, regulatory affairs, QA, IT systems, record retention, and archiving.

Depending on the volume of the company PV activities, additional questions may refer to distinct products such as biologicals or devices or organizational aspects; e.g. for co-licensed products, to address transition plans in M&A situations or outsourcing of drug safety activities. Overall, an inspection checklist list will not replace the inspection; however, it should provide appropriate guidance to get inspection ready.

The following questions are designed to help in the preparation of an EU Regulatory Authority pharmacovigilance inspection. It is by no means exhaustive but focuses on the main areas in which inspection findings have indicated problems are most likely to occur.

Pharmacovigilance Organization

Do you have documentation that clearly describes the pharmacovigilance organization within your company?

You should be able to provide the following:

- Brief description of PV activities and where they occur globally
 - Contact details of interfaces
 - Organizational charts
 - List of employees (names and functions)
 - Job descriptions
 - CVs to be commented for responsible area
 - Training records

If you are in an affiliate, you will need to describe distinct roles and responsibilities of your PV department as well as of the central PV department in HQ.

European Qualified Person

Do you have one suitably qualified European Qualified Person (QP) for pharmacovigilance?

The role of the QP will be a focus of any inspection. You need to be able to show that you have notified the relevant authorities of the name and contact details of the individual concerned. A job description, updated CV, and training record should be available for inspection.

Do you have a suitably qualified deputy for the Qualified Person?

A suitably qualified deputy should be in place. This individual must be resident within EU as for QP. Supporting documentation as for QP should be available.

Are the roles and responsibilities of the Qualified Person clearly documented?

A company must be able to clearly demonstrate how the appointed QP actually fulfills the regulatory requirements.

Can QP access PV system for collection of ADRs at least at one point in the Community and can they perform database searches?

If unable to conduct searches themselves, the QP must at all times have access to someone who can.

Can the QP demonstrate that appropriate procedures exist to ensure single serious adverse drug reactions are reported to the competent authorities in accordance with regulations? Comprehensive procedural documents will suffice here.

Does the QP have awareness/oversight of all PSURs?

The QP does not necessarily need to sign off on PSURs but he/she should at least have oversight. You will need to demonstrate that such a procedure exists and is followed.

Is the QP aware of all company-sponsored postauthorization safety studies (PASS) and their reports?

You need to be able to demonstrate how the QP gets access to information related to PASS and can track compliance activities.

Does the QP participate in regular safety reviews?

You need to be able to demonstrate how the QP becomes aware of, or is involved in, safety reviews.



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Does the company have an escalation procedure for safety issues?

You need to be able to show that a process exists that describes QP involvement.

Is the QP aware of all requests for information received from competent authorities and of all responses?

This requires close liaison with Regulatory Affairs, and processes that describe how the QP is kept informed of these requests must be in place.

Is the QP aware of all signal generation activities and ongoing safety issues?

This is a key area of focus at inspection. Procedures must be in place that clearly describe the signal detection approach within your organization and how the QP is involved/informed.

Do you have a list of ongoing safety studies?

You will need to be able to provide an updated list and describe the process that ensures QP always has the most up-to-date information available.

Is the QP aware of arrangements with co-marketing/contractor agreements for meeting pharmacovigilance obligations?

The QP should have access to any safety data exchange agreements and must be able to demonstrate how these agreements are monitored and updated.

Does the QP have access to global compliance information?

QP needs to address/to be empowered to ensure global compliance. You need to be able to demonstrate timely access to company PV compliance metrics.

Does the QP receive audit/inspection findings of PV relevant departments?

You need to be able to demonstrate the process that gives the QP appropriate access to audit and inspection reports. Inspectors do have a legal right to request such reports if they believe there is a need, but generally they just want to see that the QP is actively involved in the process.

If not medically qualified does the QP have access to suitably qualified medical personnel at all times?

You must be able to show how the QP can get access to medical personnel at all times.

Do you have comprehensive out-of-hours procedures for contacting the QP or deputy 24 hours/day, 365 days/year?

You must have a process in place that outlines the contact procedures, but

you must also be able to demonstrate that the process works by providing evidence of periodic testing.

Roles, Responsibilities and Training of PV Staff

Do all members of staff involved in pharmacovigilance activities have training records?

Up-to-date training records are essential for all staff involved in PV activities. Typically they should contain the following:

- An up-to-date job description
- An up-to-date CV – signed & dated
- Documentation of knowledge of all relevant SOPs and related processes and their updates.
- A record of all training received with evidence of attendance
- Evidence of level of competence achieved in key activities
- Certification of competence to train others

Do you have a training SOP?

It is important that you can demonstrate the process for training for new starters and continuous training for all relevant personnel. The process should describe criteria for selecting staff for training and the frequency of training required.

Do you have a training program/schedule?

This is a useful document to have in place, as it should define training requirements for different roles within PV and will form the basis of an individual's training record.

How are PV employees trained on any new legislation?

It is important that you can demonstrate knowledge and training of new legislation to appropriate personnel. You should be able to show how PV works with Regulatory Affairs to ensure timely exchange of knowledge around new legislation.

Are organograms for all functions who may be involved up to date?

Inspectors may select individuals for interview from organograms and will expect them to be current. It is helpful to have a process whereby functional organograms are reviewed and signed on a regular basis.

Could you provide evidence of how you train your receptionist, clinical research, marketing representatives, security, and other personnel to handle phone calls related to poten-

tial adverse events or other product complaints?

It is important to retain records and training materials for all PV training delivered to company personnel. You may need to provide evidence of training delivered during an inspection. You are expected to be able to show that you have trained all company personnel in their responsibilities on learning of an adverse event report.

Policies and Procedures

Do you have a defined document hierarchy that covers numbering, version control, and training requirements?

This is essential. If you do not have this you must make it a priority action. You need to be able to describe your quality system hierarchy including relevant SOPs, Working Instructions, templates, metrics, and corrective action plans. You will also need to be able to describe how you modify existing processes, introduce new procedures, and implement them.

If hard copy documentation is used, do you have a procedure for ensuring no out-of-date procedures are utilized?

Inspectors are always very hot on valid procedural documents. If you utilize an electronic document retrieval system, you need to have a contingency plan in the event that the system goes down.

Record Retention and Archiving

Do you have a system in place to document, log, and distribute all incoming documents?

Logging and tracking documents is essential to ensure nothing gets lost.

Do you have a system in place to archive all documents (in- and outgoing documentation)?

You need to be able to demonstrate appropriate measures to protect your documentation throughout the period of its retention.

How do you define access rights and to whom (database and documentation)?

Access rights should be well controlled, and you must be able to demonstrate this.

Where do you keep treatment codes and how do you guarantee restricted access?

You must have procedural documents that describe the process and be able to show evidence of documented code break activities.



If you keep original paper copies, do you have a fire protection, water damage protection, and a pest control system in place?

All archived documentation should be appropriately stored in approved archive facilities.

How long do you retain records (what is the company policy)?

You should be able to show a company policy that defines how long safety data need to be retained.

How do you ensure security (of the building, PV department, archive, records)?

You must be able to demonstrate that all data stored are appropriately secure.

If your organization uses an offsite archiving facility, do you regularly inspect the offsite premises to ensure appropriate storage, retrieval and environmental monitoring?

If you use a third-party archiving company, you should conduct regular audits to ensure your documentation is properly protected and can be retrieved within the pre-agreed timeframe.

Do you have a list of individuals authorized to retrieve documents from an offsite archive facility?

It is important that you maintain a list of authorized individuals with the third-party archiving company. You will need to be able to show a copy of this list.

How do you ensure that retrieved documents are returned?

Your procedure for archiving should outline responsibilities for document return.

Product Complaints

In the event of a product quality complaint with associated adverse event, do you have a procedure for handling technical and product complaints that describes the link between Manufacturing and Drug Safety (and Medical Information)?

You need to be able to show that information is shared and tracked between all parties. You may need to provide evidence of reconciliation between the complaints database and the adverse event database.

Type II Variations

Do you have a procedure for submitting type II variations?

You need to have a procedure that defines roles and responsibilities of all involved. Be prepared to provide doc-

umentary evidence of a safety request from a Regulatory Authority resulting in a type II variation, with timeframes.

Medical Information

Do you have a process that describes how adverse event information received by Medical Information is transferred to Drug Safety?

You need to be able to demonstrate that all adverse event information is sent to Drug Safety in a timely manner. You may need to demonstrate a reconciliation process between Medical Information and Drug Safety to ensure that all cases received by MI are entered onto the global Drug Safety database.

Do you have a procedure that describes how an adverse event would be handled if received out of office hours?

This procedure should be tested regularly.

Regulatory Affairs

Does your Regulatory Affairs function track all requests and responses for information received from Regulatory Authorities?

Inspectors will expect tracking of requests and may ask for an example.

Does your Regulatory Affairs function have a formalized procedure for contacting appropriate personnel should an urgent request for safety information from a Regulatory Authority be received outside normal working hours?

An out-of-hours contact procedure should be in place and should give contact details of EU QP in addition to other key personnel.

Quality Assurance

Does your organization have a formalized program for global PV systems audits?

If you do not have such a routine system you should make this a priority. If you do not have the in-house resources or experience, you should consider using an external group who can provide the expertise to you.

Could you provide a schedule for internal PV audits for both global PV sites and subsidiaries?

Inspectors will rarely ask for audit reports but will seek evidence of an audit program.

IT Systems

Do you have full validation documentation for your safety database?

Adverse event safety information should always be stored in a fully validated system with an identifiable database administrator.

Have you done any system updates since last validation?

Documentation must be available.

Does the database have an audit trail?

Evidence may be required.

Does your database have a disaster recovery plan?

Such a plan is essential. You should also have contingency plans in place to support all aspects of the PV system in case of physical disasters.

Can you provide evidence of regular testing of the plan?

You should be able to supply documentation of testing, findings, actions and re-testing.

Single Case Processing

Do you have a process that defines how adverse event reports from all sources are processed and reported, if required, to appropriate competent authorities?

You should have SOPs in place that describe your process. You need to be able to demonstrate a consistent process across all sites involved in case processing and at the affiliate level. For literature cases you must be able to show which publications are routinely scanned, who is responsible, how often the literature is scanned and how quickly cases will be processed. You may also have to describe how local language publications are handled within the affiliates.

Are you able to demonstrate due diligence in obtaining follow-up information?

You need to be able to show all attempts to follow up a case and the outcome. This should be documented at the individual case level. Additionally a procedure that defines which cases should be followed up, how often, and when a case can be considered closed, would be advisable. Follow-up of pregnancy cases should be given particular consideration.

Can anyone delete a case from your database?

It is advisable that only authorized individuals can delete a case, and the database audit trail must be able to track all deletions.

Expedited Reporting of ICSRs

Do you routinely monitor compliance with expedited reporting requirements for ICSRs?

You must be able to demonstrate compliance tracking and monitoring

of any action plans implemented as a result of instances of noncompliance. Affiliates should be tracking submission to local competent authorities at a local level. Reasons for nonsubmission of reports should be recorded at the individual case level.

Aggregate Safety Information

Do you use validated search tools to create line-listings for inclusion in PSURs?

You must be able to show how you identified cases for inclusion and how you made sure that no valid cases were excluded.

Do you have a formal procedure for PSUR production?

An SOP should be in place to describe the process, timelines, and responsibilities.

Can you demonstrate compliance with regulatory submission timelines for PSURs?

Affiliates should be tracking submission to local competent authorities.

How do you ensure that assessment comments are addressed in future PSURs?

Your PSUR SOP should require that assessment reports are considered during compilation of the next PSUR.

Agreements

Do you have any licensing agreements with other organizations?

If so, you must have a documented safety exchange agreement in place for each product/company. This agreement should define responsibilities for expedited reporting, PSUR production, literature searching, signal detection, timelines for exchange of information, reconciliation of information exchanged. All agreements must be regularly reviewed and updated. ■

References

1. Committee for Proprietary Medicinal Products, Position paper on Compliance with Pharmacovigilance Regulatory Obligations London, 15 November 2001, CPMP/PhCWP/1618/01
2. Letter between EMEA and FDA dated 12 September 2003

Vicki R. Edwards, BPharm (HonS) is Director, European Pharmacovigilance, Abbott Laboratories. Monika Pietrek, MD, MSc, is Executive Vice President, Global Scientific and Medical Affairs, PRA International.