



PIPA Special Interest Group on Adverse Reactions

UK Standards in Pharmacovigilance 2005

Introduction

European legislation [1, 6-8] requires that Marketing Authorisation Holders (MAH) should have an appropriate system of pharmacovigilance in place. The obligations are the same whether the MAH is an innovative pharmaceutical company or a generic company. No guidance is given in the regulations as to what constitutes an 'appropriate system', and although the CHMP concept paper on compliance with pharmacovigilance regulations [2] outlines the principles of the pharmacovigilance system, it does not give any practical guidance into how this may be achieved.

These Standards on Pharmacovigilance have been developed in consultation with key stakeholders and aim to provide guidelines and practicable standards for all companies performing pharmacovigilance activities. Whilst adherence to these guidelines is voluntary they are recommended to all companies, regardless of company size or structure.

Regulatory Compliance

Standard Operating Procedures

All pharmacovigilance activities must be carried out in compliance with the requirements of relevant regulatory authorities. Companies must put in place standard operating procedures (SOPs) to describe activities relating to pharmacovigilance. These SOPs should describe how employees carry out specific activities relating to pharmacovigilance and should be written with due consideration to the requirements of relevant legislation and guidelines.

It is essential that these reference documents are sufficiently detailed to the level of, for example, the company definition of an “identifiable patient” to achieve clear consensual approaches to case handling on items that are not always internationally harmonised.

All SOPs should be reviewed at regular, pre-defined intervals (e.g. every 2 years) and should always be reviewed in response to any changes in relevant legislation or company organisation.

SOPs should cover each of the pharmacovigilance interfaces including, but not limited to;

- Processing of spontaneous adverse event reports (including literature reports, legal cases and cases from Registries and Post-marketing studies)
- Processing of clinical trial serious adverse event reports
- Preparation and submission of expedited reports (including timescales)
- Materiovigilance requirements (if applicable)
- Crisis management and issue communications (e.g. the handling of SmPC safety variations and urgent safety restrictions)

- On-going signal detection and risk benefit assessment
- Periodic safety report production (e.g. PSURs, Periodic Safety Summaries, Annual Safety Reports)
- Business/ Disaster recovery plan
- Document retention/archiving
- Training
- Exchange of safety information with a third party (if applicable)
- Quality checks
- Coding of medical terms

The complexity and detail of these SOPs will vary depending on the complexity and size of both the pharmacovigilance system and the pharmaceutical company.

The use of a “Summary of Pharmacovigilance Systems” or similar document to describe the working of the pharmacovigilance system is recommended. This file should describe how the pharmacovigilance systems functions as a whole, and should cover points such as contact details, details of sites involved in pharmacovigilance, lists of products authorisations, systems descriptions, Qualified Person and deputy details, quality-control procedures. It should succinctly identify what pharmacovigilance activities are conducted in what countries, at what site, and by which parties.

Qualified Person

All MAHs must appoint a Qualified Person (QP) for Pharmacovigilance, who takes personal responsibility for the pharmacovigilance system. This individual must be appropriately trained and aware of their responsibilities, and whilst not necessarily a qualified physician, they must have adequate access to a medically qualified safety expert. The name and contact details of the QP for Pharmacovigilance must be communicated to the authorities.

Audit & Inspection

Audits of the pharmacovigilance system and support activities (e.g. IT, archiving, medical information, QA etc) must be carried out at regular intervals. The frequency of audits should be defined internally and should take account of the significance of the area to be inspected. Since pharmacovigilance is a global activity, it is recommended that these audits be cross functional whenever possible to test the robustness of the whole system.

Audits must be carried out by appropriately trained individuals with relevant knowledge and experience, who are independent of the area to be inspected. Consideration should be given to the use of external consultants for audits in smaller companies, where appropriate expert resource may be limited.

Sharing of Safety Information

Systems must be in place to ensure the swift passage of safety information between the pharmacovigilance department and other relevant departments (e.g. marketing, medical information, regulatory, quality assurance), and to ensure the timely update of regulatory documentation (e.g. SmPCs) as necessary.

All staff must be aware of how to recognise a potential adverse event and the importance of collecting the right type and amount of information upfront (including permission to seek more information from a third party e.g. a treating physician), and transmitting it clearly and promptly to the pharmacovigilance department. Staff should also be aware of the implications of the Data Protection Act.

Documentation practices

Good documentation is an essential part of the pharmacovigilance system. Good documentation practices include the following [3]:

- Alterations made to an entry on a document should be signed and dated, and the alteration should permit reading of the original information.
- Where documents require the entry of handwritten data these entries should be made in clear, legible, indelible handwriting.
- No amendments should be made to source documentation (e.g. healthcare professional reports)
- Documents should be regularly revised and kept up-to-date. When a document has been revised, systems should ensure superseded documents are no longer used.
- A retention period for pharmacovigilance documentation (e.g. lifetime of product licence plus shelf life) should be defined

Good case-management practices ensure complete and proper collection and categorisation of data. Useful details can be found in the report of the CIOMS working group V [4]. These include, for example, advice on translation issues, case follow-up approaches, and recommendations on using the Internet for pharmacovigilance.

Qualifications & Training

Drug Safety/Pharmacovigilance Staff

Pharmacovigilance professionals, who undertake key activities such as adverse event seriousness/expectedness assessments, causality assessments, regulatory reporting decisions, PSUR writing, risk/benefit assessments, etc., should have suitable qualifications or experience. This may be a medical degree, a degree in pharmacy, nursing, pharmacology or a life science, or an appropriate equivalent qualification or experience

All pharmacovigilance and support staff must receive ongoing training appropriate to the level of their responsibilities. This should include training in relevant pharmacovigilance legislation and guidelines, corporate or local pharmacovigilance SOPs and the use of local and global databases. Update training should also be undertaken if any of these documents are revised.

In addition all pharmacovigilance professionals should have an up-to-date working knowledge of the following subjects if they have not been covered in previous training, academic studies or job experience:

- Drug development
- Areas of medicine, pharmacy and pharmacology related to products for which they are responsible
- Information sources and information technology

- Evaluation of information
- Communication skills and written presentation of information
- Regulatory affairs
- Health economics and evidence-based medicine
- Customer care and customer roles
- Public relations and marketing of medicines

All training and assessment must be documented for each individual working in pharmacovigilance and made available to any Company or Regulatory auditor for review.

Any training documentation, together with the individual's *curriculum vitae* and job description should demonstrate to an auditor that the person is suitably qualified and trained to undertake their role within pharmacovigilance.

Pharmacovigilance staff have a professional and ethical obligation to remain up-to-date with best practice standards in drug safety. Individuals should be able to provide evidence that they continue to maintain their professional competence through systematic improvement and broadening of knowledge and skills e.g. by attending educational courses, seminars and through company self-developed competency systems.

Courses leading to post-graduate qualifications in pharmacovigilance are available at a number of institutions. In addition, conferences and seminars on relevant topics are regularly run by commercial organisations and non-profit making groups such as PIPA and DSRU.

Training for Non-Pharmacovigilance Staff

All company employees are required to understand their responsibilities for reporting adverse event information to the pharmacovigilance department. The level of training required will differ, depending on their role within the Company.

Training provided to non-pharmacovigilance staff must be routinely updated and documentary evidence retained for review by Company or Regulatory Auditors.

All employees who have regular contact with customers (e.g. sales representatives, customer services, medical information, call centre representatives etc.) must have a documented procedure for forwarding information on adverse events to the pharmacovigilance department without delay. Each employee working in such a role must have documented evidence that they have received training in this procedure.

Investigators and other clinical research staff participating in Company-sponsored clinical trials must document that they have understood their responsibilities for reporting appropriate safety information to the Company.

Pharmacovigilance Liaison

Health Care Professionals

The company should have in place an appropriate system to cover dealing with healthcare professionals providing information on adverse events. The system should include the timing and method of requests for further information by the company. Where adverse event information is incomplete, the system should address the follow-up of adverse event reports. The follow-up procedure should prioritise obtaining information based on criteria of seriousness and expectedness; with serious unlisted/unexpected cases taking highest priority and non-serious expected cases the lowest priority. High priority should also be given to cases of special interest such as those requested by regulatory authorities or that may result in a labelling change.

These priorities will also define the amount of detail sought for specific cases. CIOMS V [4] and ICH E2D [5] provide guidance on the data elements that should be collected depending on the seriousness and expectedness of a case and provide further recommendations for follow-up of cases.

Follow-up information may be obtained via a telephone call, a written request, or a site visit. The method of follow-up and number of attempts made will depend upon the nature of the case, and follow up practices should be documented in company procedures. Written requests for follow-up should be made by providing partially completed forms or questionnaires to the reporter. These forms should be easy to complete and the cover letter should identify the key information sought. The use of a reply paid envelope is encouraged. In the event that the reporter states that no further follow-up attempts be made, this request must be respected and documented in the case records.

All follow-up attempts (both written and verbal) should be appropriately documented.

Regulators

The method of interaction between the MAH and the regulatory authorities will depend upon the nature of the issues under discussion. Initial telephone discussions may be appropriate but should be followed by a confirmatory letter. Liaison with Regulators regarding potential safety issues may involve extensive discussions and provision of information and it is important that the Company maintains a professional attitude in both verbal and written communications with Regulators at all times.

Patients / Consumers

When reports are received directly from non-healthcare professionals, permission should be sought from the patient to contact their primary healthcare provider in order to obtain relevant additional medical details. Such permission should be documented together with permission to retain their details in accordance with the Data Protection Act.

Licensing Partners

The pharmacovigilance responsibilities of MAHs when entering into licensing agreements are specified in Volume 9 of the Rules Governing Medicinal Products in the European Union [1].

In order to fulfill these obligations close collaboration is required between partner companies. Detailed safety data management agreements should be drawn up, including as a minimum:

- Agreed definitions
- Timelines (including clock start time), formats and methods for exchange of individual case safety reports (including language of exchange)
- Responsibility for:
 - regulatory reporting
 - individual case assessment and follow up
 - literature reviews
 - PSUR preparation and signal detection
 - Maintenance of core safety data
- Which company will hold the global safety database
- How enquiries from Regulatory Authorities will be handled
- How product complaints will be handled
- Contact personnel at each company
- How the companies will audit each other
- How often the reconciliation between two companies will be performed
- Frequency of periodic meetings
- How the licensing agreement will be terminated and reviewed

Clinical Research Organisations (CROs) and/or consultancies

Where Pharmacovigilance activities are contracted to a third party company companies should have detailed contracts and ways of working in place to ensure that all Pharmacovigilance obligations are fulfilled.

References

1. European Commission. Rules Governing Medicinal Products in the European Union June 2004; Volume 9: http://pharmacos.eudra.org/F2/eudralex/vol-9/pdf/Vol9_10-2004.pdf
2. CHMP. European Concept Paper on Compliance with pharmacovigilance Regulations 2001; CPMP/PhWP/1618/01
3. EC Guide to Good Manufacturing Practice
4. CIOMS Working Group V. Current Challenges in Pharmacovigilance: Pragmatic Approaches 2001
5. ICH E2D. Post Approval Safety Data Management 2003; ICH Step 5
6. Consolidated Directive 2001/83/EC
7. UK Statutory Instrument 1994 No 3144: The Medicines for Human Use (Marketing Authorisation Etc) Regulation 1994
8. UK Statutory Instrument 2004 No 1031: The Medicines for Human Use (Clinical Trials) Regulation 2004

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Useful links:

MHRA web site: <http://www.mhra.gov.uk/index.htm>

International Society of Pharmacovigilance: <http://www.isoonline.org/>

PIPA web site: <http://www.pipaonline.org>

EMA web site: <http://www.emea.eu.int/>