European legislation (Directive 2010/84/EU; Regulation (EU) No 1235/2010) requires that Marketing Authorisation Holders (MAH) should have an appropriate system of Pharmacovigilance in place. Since the introduction of the updated legislation in July 2012, a set of guidelines for the conduct of Pharmacovigilance (PV) has been developed, known as Good Pharmacovigilance Practices (GVPs). The obligations are the same whether the MAH is an innovative pharmaceutical company or a generic company. Limited guidance is given in the guidelines as to what constitutes an ‘appropriate system’.

These Standards on PV have been developed in consultation with key stakeholders and aim to provide practical guidelines for all UK pharmaceutical companies. The Standards are focused on postmarketing requirements, rather than for those working in clinical trials. They must not be read or implemented in isolation. All PV departments must act in line with the formal European Legislation and the GVPs.

While targeted for PV departments, these Standards may also prove useful to inform associated functions of the legal PV requirements (including Medical Information, Medical Affairs, Customer Services, Regulatory, Commercial, Research and Development).

Adherence to these PIPA Standards is voluntary. However, they are recommended to all companies, regardless of company size or structure.
Regulatory Compliance

2.1 Procedures

Procedures should be clearly defined within a range of documents such as: Standard Operating Procedures, Working Practices, Job Aids, Forms and Templates. These documents should be cross-referenced and linked as appropriate. Sufficient detail should be given to ensure robust and consistent management of PV processes in line with the legislation.

All procedural documents must 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. A sufficient period for training should be incorporated into the timeline between issue date and implementation.

Procedures should be in place to cover activities including, but not limited to:

- Processing spontaneous adverse event reports and suspected transmission of infectious agents, including literature reports, health authority reports, legal cases and solicited cases (e.g. from registries, market research/post-marketing studies and patient compliance programmes)
- Processing other safety data reports - including unsolicited reports regarding use in pregnancy, lactation, paediatrics, overdose, drug abuse, misuse, medication errors, lack of efficacy, occupational exposure
- Processing adverse event reports originating from compassionate use programmes
- Preparation and submission of expedited reports to health authorities (including timescales)
- Medical devices vigilance 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 management
- Periodic safety report production and submission (e.g. PSURs, Periodic Safety Summaries)
- Handling ad hoc safety requests from health authorities and Direct Healthcare Professional Communications (DHPCs)

2.2 Qualified Person for Pharmacovigilance

All Companies must appoint a QPPV who resides within the European Economic Area – this role must be formally documented in a written agreement and/or their job description. They take personal responsibility for the PV system. This individual must be appropriately trained 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 QPPV must be communicated to the authorities. They must serve as the single contact point and ensure 24 hour availability.

2.3 Audits

Internal independent company audits of the PV system and support activities (e.g. IT, archiving, Medical Information, Regulatory Affairs, quality assurance etc.) must be carried out at regular intervals. The frequency of audits should be defined internally considering the significance of the function to be audited. Audit planning must take a risk based approach, involving a strategic approach covering 2-5 years (GVP Module IV). Since PV 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, independent of the function to be audited. Audit planning must take a risk based approach, involving a strategic approach covering 2-5 years (GVP Module IV). Since PV 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, independent of the function to be audited. Consideration should be given to the use of external consultants for audits in smaller companies, where appropriate expert resource may be limited. In companies that have undergone inspection by the Regulatory Authorities, findings and corrective actions should fall into the scope of any internal audit.

2.4 Sharing of Safety Information

Company staff must be aware of how to recognise a potential adverse event and their obligation to collect essential information (including permission to seek more information from a third party e.g. a treating physician), and transmit it clearly and promptly to the PV department. Staff should also be aware of the implications of the UK Data Protection Act of 1998 (e.g. patients’ full names should not be taken from Healthcare Professionals, permission should be sought from consumers prior to contacting their GP, etc.).

Systems must be in place to ensure the secure and timely passage of safety information between the PV department and other relevant departments (e.g. Medical Information, Quality Complaints, Regulatory Affairs, Marketing), and to ensure the efficient updating of regulatory documentation (e.g. SmPCs) as necessary. Reconciliation of all relevant information should take place and this process should be documented.

2.5 Periodic Safety Update Reports (PSURs)

PSURs must be written in accordance with the detailed guidance within GVP Module VII.

Medical products authorised through national, mutual and decentralised procedures, with the same active substance, should follow the same PSUR submission scheme in all EU Member States. Submission dates should be determined by the EU harmonised birth date (HBD) and corresponding data lock point (DLP) of the concerned medicinal product. The latest version of the list of adopted EU HBDs and related DLPs for the forthcoming PSURs and allocated PSUR Reference Member State (P-RMS = Member State in charge of making the PSUR assessment report) can be found on the Heads of Medicines Agencies (HMA) website. Marketing Authorisation Holders of generic medicinal products are also expected to use the EU HBDs and related DLPs, where applicable.

All PSURs must be submitted to the EMA for single assessment. For nationally authorised products, they should also be submitted according to the CMDh/317/2014, Rev. 1, requirements until submission via the EMA portal becomes mandatory.
2.6 Signal Detection

Processes should be implemented to ensure that:
- All sources of relevant information are screened systematically and regularly to identify any potential signals (GVP Module I, PIPA Guidelines for Signal Management).
- Appropriate action is taken in response to new information that may change a product’s risk-benefit balance.
- Competent Authorities, Healthcare Professionals and patients are informed of changes in the risk-benefit balance.

All aspects of these processes should be documented in formal procedures, including the roles and responsibilities of the staff undertaking them. Product specific activities should also be described in risk management plans, as appropriate. These should be seen as supporting routine activities.

The methods used to achieve this will vary depending on the products and volume of reports received, and may be specific to an individual product. It is therefore good practice to document considerations used in the choice of approach. See PIPA Signal Detection Standards for further information.

2.7 Documentation Practices

Good documentation is an essential part of the PV system and includes:
- Alterations made to an entry on a report document should be signed and dated, and the alteration should permit reading of the original information.
- Where report documents require the entry of handwritten data these entries should be made in clear, legible, indeleble handwriting.

Procedures should be regularly revised and kept up-to-date. When a document has been revised, systems should ensure superseded documents are no longer used and are archived.

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.

The document management system should be described in a document management policy (see GVP Module I).

3 Qualifications & Training

3.1 Pharmacovigilance Staff

PV 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 PV and support staff must receive ongoing training appropriate to the level of their responsibilities. This should include training to ensure staff understanding and competence in relevant PV legislation and guidelines, corporate or local PV procedures and the use of local and global databases.

Update training should also be undertaken when any of these documents are revised.

In addition, all PV professionals should have an up-to-date working knowledge of other disciplines that have an impact on their role. Examples may include safety aspects of marketing (ABPI Code of Practice) and licensing procedures.

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

Training documentation, together with the individual’s curriculum vitae and job description, should be appropriately signed, dated and retained to demonstrate that the person is suitably qualified and trained to undertake their role.

PV 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 PV 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.

3.2 Non-Pharmacovigilance Staff

Company employees and contractors are required to understand and take full responsibility for reporting adverse event information to the PV department. The scope and level of training should be tailored to their role.

The requirement for further training must be fully considered and documented within company policy. This may vary in style, frequency and content depending upon need. All update training should be fully documented as above.

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 PV department without delay.

Each employee working in such a role must have documented evidence that they have received training in this procedure. This should be updated whenever there is a change in legislation. Refresher sessions are required to ensure ongoing compliance with the procedure.
Pharmacovigilance Liaison

4.1 Healthcare Professionals

All Companies should have a clear process to interact with Healthcare Professionals providing information on adverse events. This should include obtaining the appropriate information, the frequency, timing and method of contact and prioritisation of cases.

Consideration should be given to the use of follow-up forms. These should be easy to complete and 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.

4.2 Regulatory Authorities

The method of interaction between the company and the Regulatory Authorities will depend upon the nature of the issues under discussion. Initial telephone discussions may be appropriate but should be documented and followed by a confirmatory letter or email.

4.3 Patients / Carers

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 UK Data Protection Act. It is important that any discussion does not compromise the patient/doctor relationship and should follow the ABPI Code of Practice.

4.2 Third Party Agreements

PV responsibilities should be clearly defined within third party agreements and systems descriptions such as the PSMF. For example, co-licensing, co-marketing and service provider agreements such as outsourced Medical Information, Clinical Research Organisations and Contract Safety Organisations. The agreements should include:

- Agreed definitions
- Timelines (including clock start time), formats and methods for exchange of individual case safety reports
- Responsibility for:
  - Regulatory reporting
  - Individual case assessment and follow up
  - Literature reviews
  - Periodic report preparation/submission and signal detection
  - Maintenance of core safety data
- Which company will hold the global safety database and retain PV records
- How enquiries from Regulatory Authorities will be handled
- How product complaints will be handled
- How urgent safety alerts and product recalls will be managed
- Contact personnel at each company
- How the companies will audit each other
- How often the reconciliation between two companies will be performed
- How the agreement will be reviewed or terminated

Regulatory Inspections

The impact of a regulatory inspection cannot be underestimated. Due to the often intensive nature of regulatory inspections, it is wise to prepare early and to include inspection preparation activities in all aspects of PV.

Each MAH is subject to a formal PV inspection at regular intervals. The frequency of inspections is dependent on a number of factors including the size and complexity of the PV system operated by the MAH.

The MHRA have developed a Risk Based Approach to Inspections for all areas of good practice, such as Good Clinical Practice (GCP) and Good Pharmacovigilance Practice (GPhP). Self Assessment Questionnaires are sent out usually biennially requesting completion and return to the Medicines and Healthcare Products Regulatory Agency (MHRA) within a defined timeframe. The information provided by the MAH will be used by the MHRA to help prioritise their inspection programme and identify companies which may be at higher risk of non-compliance with the regulations. It is not a legal requirement to complete this questionnaire although it is anticipated that failure to do so is likely to give that company a higher risk score, therefore making it more likely to be inspected sooner rather than later.
References

- EC Guide to Good Manufacturing Practice

- CIOMS Working Group V. Current Challenges in Pharmacovigilance: Pragmatic Approaches (2001)

- Consolidated Directive 2001/83/EC

- UK Statutory Instrument 1994 No 3144: The Medicines for Human Use (Marketing Authorisation Etc) Regulation

- ABPI Code of Practice
  http://www.pmcpa.org.uk/media/Documents/PMCPA%20Code%20of%20Practice%202015.pdf

- UK Data Protection Law

- EMA Good Pharmacovigilance Practices (GVP)

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