PHARMACOVIGILANCE AND RISK MANAGEMENT

PHARMACOVIGILANCE Playbook (Part–1 of 2)

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**INTRODUCTION**

Pharmacovigilance (PV) is an extension of the science of Safety Pharmacology in clinical practice or therapeutics.

World Health Organization defines Pharmacovigilance (PV) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Over the years the definition and scope of activities related to drug safety have evolved into a global enterprise keeping pace with the expanding markets and a support offered by information technology and statistical tools towards a larger data mining and predictive analytic models.

All stakeholders of the pharmaceutical and healthcare industry have become risk averse and rightly so; be it drug safety or business sustainability both of which are interlinked, compounded by the complexities and compulsions of keeping the regulators aware of the accrued safety data in clinical practice. It has thus become essential for pharmaceutical companies to build systems and processes to proactively identify and expeditiously manage emerging safety risks.

**RISK IN GENERAL CONTEXT**

ISO 31000:2009 defines risk as the *effect of uncertainty on objectives* and an effect is a positive or negative deviation from what is expected. Uncertainty prevails whenever the information, knowledge, awareness or understanding of an occurrence, consequence, or likelihood is deficient or incomplete.

Any organization, system or network can have indigenous risks which can have potential adverse consequences for its sustainability, economic performance, as well as larger environmental, safety and societal effects. Thus managing risk efficiently and ethically helps improve performance and pulls an organization, system or network out of the red ocean back to the blue ocean of sustenance and viability.

**ISO 31000:2009**


Organizations using ISO 31000:2009 can draw a comparison of their risk management standards and practices with a valid and internationally recognized benchmark thus providing a robust quality structure for efficient management and corporate governance.

**Related General Standards**

A number of other general standards also relate to risk management.

ISO Guide 73:2009 (Risk management - Vocabulary) contains the definitions of generic terms related to risk management. It provides a guideline to support establishment of a consistent and relevant understanding of, and a logical approach to, the description of activities relating to the management of risk, and the use of uniform risk management terminology in processes and frameworks dealing with the management of risk.

ISO Guide 73:2009 is intended to be used by:

- those involved in managing risks,
- those who are involved in activities of ISO (International Organization for Standardization) and IEC (International Electrotechnical Commission), and
- developers of national or region-specific standards, guides, procedures and codes of practice relating to risk management.

ISO/IEC 31010:2009 (Risk management - Risk assessment techniques)

IEC 31010:2009 is a 'dual logo' IEC/ISO, single prefix IEC, general standard which supports ISO 31000 and provides guidelines on selection and application of systematic techniques for risk assessment. This standard is not intended for certification, regulatory or contractual use.

ISO/IEC 31010:2009 does not deal specifically with safety. It is a general risk management standard and any references and applications to safety are entirely of an informative nature. Guidance on the introduction of safety aspects into IEC standards is detailed in ISO/IEC Guide 51 as is also described in ICHQ9 (Quality Risk Management)

Pharmacovigilance (PV) Operations

The safety data sources with which the pharmacovigilance operations begin include clinical trial data, safety call centers, spontaneous reporting, literature surveys, and lately inputs from unconventional data sources like social media discussions. All the data sources give rise to information which can be defined as an individual case which is evaluated and processed by the pharmacovigilance department. Pharmacovigilance experts perform a causality assessment and report it to relevant stakeholders like the regulatory authorities in the form of either expedited reports or aggregate safety reports. The accrued safety data becomes a part of the safety dataset of the drug and creates opportunities for detailed analysis if needed.

Analysis of the aggregate data is performed for safety signals and a risk benefit assessment conducted.

Throughout the product life cycle PSURs (periodic safety update reports) are prepared and submitted to regulatory authorities as per applicable guidelines and standards.

In clinical trials safety is continuously assessed to mitigate risk by modifications of clinical trial designs, product labeling, maintaining risk registries based on risk management plans, and even discontinuation of clinical development or market withdrawal of the product if needed.

Summary of the major pharmacovigilance activities are shown in the Figure 1.
Figure 1: Illustration Of The Major Activities Associated With Pharmacovigilance

SAE: Serious Adverse Event; QC: Quality Control

**Holistic Pharmacovigilance (PV) System**

Pharmacovigilance has a very wide scope and differences in the system are inevitable, however there are a few basic components which are necessary irrespective of the organizational structure of a company.

These include:

- Safety Systems (database)
- Safety Case Processing and Medical Review
- Safety Medical Writing and Aggregate Reporting
- A Robust Quality Management System (QMS) with meticulously designed standard operating procedures (SOPs), quality standards, metrics, and training
- Risk Analysis and Safety Signal Detection
- Global Safety Reporting
- Qualified person for pharmacovigilance (QPPV) (Europe)

Depending on the organizational structure in a company activities may be allocated to different department, e.g., Safety regulatory reporting may be performed by Regulatory Affairs department, Medical Writing department may be in-charge of Aggregate Report Writing.
There is an increasing trend towards outsourcing most of the activities to contract research organizations (CROs), business process outsourcing companies (BPOs), Business Process as a Service (BPaaS) companies or niche safety service providers. However, activities like signal detection and risk management are usually performed in-house in most pharmaceutical companies.

**Figure 2:** A Holistic Pharmacovigilance System

**QPPV:** Qualified Person For Pharmacovigilance; **EU:** European Union; **SOP:** Standard Operating Procedure

**Pharmacovigilance (PV) Guidelines, Policy Statements and Regulatory Directives**

Pharmacovigilance systems are highly developed and regulated in countries or regions where the drug development and healthcare industries collaborate in developing new and innovative medicines. The other regions of the world are also increasingly becoming cognizant of the need to continuously monitor drug safety.
Pharmacovigilance systems and their functioning are influenced by regulations, policies, and directives. Multiple Pharmacovigilance tools have been created to meet the expectations of regulators and ethically collect data for evidence based decision making regarding the long term drug/device safety.

The three major regulatory agencies which have taken a lead in defining global pharmacovigilance guidelines and approached to analyzing drug safety are the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA).

In the USA, the Code of Federal Regulations (CFR) is legally binding, as are the European national laws and ordinances. Directives contain the current thinking and opinions on a topic and bind member states to common objectives, which must be implemented into national law within a stipulated timeframe. The guidance documents, guidelines, and recommendations are not legally binding, but should be applied and play an important role in real practice.

Global pharmacovigilance principles have been harmonized through the International Conference on Harmonization (ICH). ICH E1eE2F focuses primarily on clinical safety principles. General direction is provided in ICH E2AeC (Clinical Safety Data Management), E2D (Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting), E2E (Pharmacovigilance Planning), and E2F (Development Safety Update Report).

ICH E6 (Good Clinical Practice) describes the responsibilities and expectations of all major stakeholders in the conduct of clinical trials.

ICH member states are working towards implementing global harmonization best practices in the areas of drug safety and risk management. Most nations have agreed to major concepts related to pharmacovigilance, however regional differences in interpretation do still exist.

There is incomplete harmonization in global reporting formats, clinical trial reporting requirements, and label safety standardized information.

**ADVERSE EVENT REPORTING**

**A Few Important Definitions**

Identification of an adverse event by the end users of a drug forms the first event of importance of pharmacovigilance and triggers a cascade of activities towards understanding, documenting and reporting the event. Reporting the event forms the core of the pharmacovigilance system. Regulatory authorities closely monitor the reporting process and periodically audit and inspect the adverse event evaluation processes.

ICH E2A defines and distinguishes between the following terms

- Adverse events (AEs)
- Adverse drug reactions (ADRs), and
- Serious adverse events (SAEs)
**Adverse event (AE) (or adverse experience)**

Any untoward medical occurrence in a patient or clinical investigative subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can thus be any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a therapeutic or diagnostic product, whether or not considered related to the therapeutic or diagnostic product.

**Adverse drug reaction (ADR)**

In the clinical development stages the experience with a new therapeutic or diagnostic product or its new usages, particularly when the therapeutic dose(s) may not be established: all noxious and unintended responses to a therapeutic or diagnostic product related to any dose should be considered adverse drug reactions.

The phrase “responses to a therapeutic or diagnostic product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

In the post-marketing stage of a therapeutic or diagnostic product, a well-accepted definition of an adverse drug reaction (ADR) is found in WHO Technical Report 498 (1972) and reads as follows:

*Unexpected adverse drug reaction:*

An adverse reaction the nature or severity of which is not consistent with the applicable product information (e.g. the Investigator Brochure for an unapproved investigational medical product).

Adverse events are classified as “serious” based upon patient outcome or applicable criteria usually associated with events that pose a threat to a patient’s life or functioning. The regulatory reporting of an adverse event is guided by its seriousness (not severity).

A serious adverse event (experience) or reaction is any untoward medical occurrence at any dose which:

- results in death
- is life threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect.

Appropriate Medical and Scientific evaluation should be performed before deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may endanger the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Such events should also usually be considered serious.

Regional or country specific differences in reporting serious adverse events (SAEs) may exist, for example, the latest amendment to Schedule Y (2013) in India mandates even the investigators to report SAEs directly to the regulatory agency (DCGI).
Timelines of Adverse Event Reporting

ICH E6 guidelines recommend that all SAEs should be reported to the sponsor immediately, except for those known and listed in the protocol or other document and not needing immediate reporting. Fatal or unexpected adverse drug reactions (ADRs) occurring in clinical trials need to be reported to the regulatory authorities as soon as possible, but no later than seven calendar days after knowledge of the adverse event by the sponsor, followed by as complete a report as possible within eight additional calendar days.

Serious unexpected reactions (ADRs) which are not fatal or life threatening must be reported as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

Adverse events not meeting the criteria for expedited reporting are reported at the end of the clinical trial as part of the marketing application or in Periodic safety update reports (PSURs).

Unblinding – European Directive

The Volume 10 of the guidance document “The Rules Governing Medicinal Products in the European Union” provides guidelines on un-blinding of the treatment allocation in a clinical trial when suspected unexpected serious adverse reactions (SUSARs) occur. In the European Union (EU) suspected unexpected serious adverse reactions (SUSARs) must be un-blinded before submission to the regulatory authorities; this may not be mandatory for other regulatory authorities in Asia or the USA. Recently, the FDA has acknowledged the increasing need for un-blinding some expedited safety reports, but suggests alternatives to un-blinding be undertaken as far as possible; this rule came into effect on March 28, 2011.

It is essential that access to un-blinded data be available to only the reviewers and all other personnel involved in a clinical trial remain blinded to the treatment allocation. This preserves the integrity of the clinical study.

Standard Operating Procedures (SOPs), Study-Specific Procedures (SSP’s), and Drug Safety Plans (Pharmacovigilance Plan)

Depending on the scope and complexity of activities undertaken by a company, the number of SOPs may from a few to an extensive list. Companies may follow a system of writing very generic SOPs and further develop study-specific procedures (SSPs) based on those SOPs in accordance with the scope of work. Such SSPs provide a robust framework weaved around a particular project or specific product under clinical development.

Some companies may bundle together all the pharmacovigilance procedures into a single drug safety plan, or pharmacovigilance plan, which forms a summary of all of the processes to be followed by the pharmacovigilance department together with the clinical trial personnel. In Europe, a detailed draft of the pharmacovigilance system must be included in the marketing authorization application.
For a general framework of the Pharmacovigilance department the following SOPs/SSPs should be made functional:

- Serious adverse event reporting
- Safety case processing (intake, process flow, assessment, medical review, documentation, archiving)
- Safety database
- Safety data conventions
- Review of patient (clinical/laboratory) data
- Aggregate data review and report writing
- Safety signal detection
- Un-blinding
- Regulatory reporting of safety information and 24x7 safety coverage *(pharmacovigilance call center support)*

Other SOPs/SSPs are designed as applicable to a particular product or therapeutic area. At the initiation of any clinical trial, safety reporting timelines should be reviewed, the timeframes for ongoing review and assessment of patient data should be defined, and the assignment of any un-blinded staff should be finalized. Studies utilizing a drug safety monitoring board (DSMB) or Clinical Endpoint Committee (CEC) may require additional SOPs/SSPs or guidelines created to explicitly define the roles, responsibilities and processes to be performed.

To substantiate the written procedures in the form of SOPs/SSPs, regular teleconferences and/or meetings should be held to ensure adequate communication of information, undertake necessary modifications in best practices as needed during the study, and maintain compliance and audit readiness. Training is an essential component of maintaining a pharmacovigilance and risk management framework.

**Pharmacovigilance Quality Management System (QMS)**

Pharmacovigilance departments should include a robust quality management system (QMS) for safety analysis and reporting, data review, and documentation. The purpose of a quality management system (QMS) is to ensure that all pharmacovigilance activities are executed to the highest ethical standards and comply to applicable regulatory requirements and contractual obligations to any licensing partners. Key elements of the quality management system include a standard quality policy, an approved documented library of standard operating procedures (SOPs), quality control (QC) procedures, key performance indicators (KPIs), job descriptions, and training plans.

A quality management system (QMS) is an integral part of continuous process improvement. Within the quality management system each process is reviewed via quality control steps within the processes. The end results of the quality control (QC) are measured against defined key performance indicators (KPIs). Deviations from the defined processes are identified, and those suggesting a deviation from the SOPs/SSPs or master quality plan signify a quality issue and are addressed through a root cause analysis (RCA) followed by the creation of a corrective action and preventive action (CAPA) plan. Quality assurance (QA) can then monitor to ensure that quality is being managed within the pharmacovigilance department and that all quality issues are being addressed in a timely manner.
Pharmacovigilance Department – Organizational Structure (Basic Organogram)

Organization of a Pharmacovigilance Department

The core functional unit within the pharmacovigilance department is essentially comprised of the drug safety physician (DSP), drug safety associate (DSA), and medical assistant. A team may comprise of several drug safety physicians, a single physician conducting medical review, and a few medical assistants for administrative support. Depending on the size of the company and the number of employees, pharmacovigilance teams may be organized by a project, product or by therapeutic area, or may be specialized into pre-marketing and post-marketing groups. The matrix structures are essentially similar. On a larger scale global pharmacovigilance departments may exist in a limited number of regional hubs, with each hub managed by a senior pharmacovigilance professional who provides oversight. A basic example of a pharmacovigilance organizational chart is depicted in Figure 3.

Figure 3: A Representative Organizational Structure Of A Mid-Sized Pharmacovigilance (PV) Department

RM: Risk Management; DSMB: Drug Safety Monitoring Board; CEC: Clinical Endpoint Committee; IT: Information Technology
Collaborative Pharmacovigilance activities on Global Clinical Trials

Success in pharmacovigilance objectives requires a cross-functional, cross-regional, and cross-cultural collaborative effort. For example, within the pharmacovigilance system, safety case processing and medical assessment may occur in several locations, particularly if some steps in the process are outsourced at offsite locations. Global pharmacovigilance capability can allow round-the-clock pharmacovigilance, but can only be fruitful with validated global systems, consistent processes and workflows, focused and continuous training, and efficient communication across regions.

Pharmacovigilance staff works closely with the clinical development teams and may interact regularly with clinical site investigators, clinical research associates (CRAs), clinical project managers (CPMs), clinical data managers (CDMs), biostatisticians, and medical writers. In addition, for projects using drug safety monitoring board (DSMB) or Clinical Endpoint Committee (CEC), pharmacovigilance staff may work independently with the committees to explain and clarify the safety information required for clinical endpoint review or for periodic DSMB meetings.

For Part 2 of this Playbook:

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