CHAPTER 13

Pharmacovigilance and Risk Management

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DEFINITION OF PHARMACOVIGILANCE AND RISK MANAGEMENT

The World Health Organization (WHO) defines pharmacovigilance as the science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems. The definition and scope of pharmacovigilance have evolved to recognize the importance of a systems approach for monitoring and improving the safe use of medicines.\(^1\)

A simpler definition describes pharmacovigilance as the processes and science of monitoring the safety of medicines and taking action to reduce risk and increase benefit.\(^2\) Therefore, the assessment of benefit versus risk must begin during the preclinical evaluation of a medicinal product and must extend throughout its full life cycle.

As a result, there is now added focus on safety and risk assessment after a product has received regulatory approval, when it is placed on the market and prescribed to large populations. Although there is no international standard that dictates the components of an adequate pharmacovigilance system or the processes to be engaged in risk management, there is consensus among the major regulators that pharmacovigilance is necessary and important in the development and commercialization of medicinal products.

Therefore it is essential in building capacity for clinical trials to understand the components, the functions, and the processes required for full and effective pharmacovigilance and risk management.

THE IMPORTANCE OF IMPLEMENTING A SYSTEMATIC PHARMACOVIGILANCE APPROACH IN GLOBAL CLINICAL TRIALS

The amount and variety of safety-relevant data gathered from different patient populations in global clinical trials are enormous; therefore it is crucial that a concise and systematic approach to pharmacovigilance be implemented. Systematic safety monitoring is needed to identify previously recognized and unrecognized adverse drug reactions and to evaluate the safety and efficacy of medicinal products during clinical trials and in the postmarketing period.

It is important that pharmacovigilance not be perceived as a burden put upon the pharmaceutical product development industry by the regulating bodies. Ongoing pharmacovigilance should be understood as essential to the only appropriate way to develop safe medicines, introduce them into the market, and have them survive in the market once approved. Not only does the failure to perform ongoing safety assessment activities increase the chances of placing subjects at risk unnecessarily, it also increases a company’s risk of investing in the development of the wrong molecules.

The following example illustrates the value of ongoing systematic pharmacovigilance. Figure 13.1 displays aggregate alanine aminotransferase (ALT) data reported during a clinical trial performed to evaluate a new oncology compound. The product was dosed cyclically, administered intravenously every 21 days. Review of aggregate data from the initial eight patients suggested that the product caused a transient hepatitis, particularly apparent after the first dose, as shown by the spiking ALT levels. It was thus advisable to re-evaluate the initial dosing and the dosing intervals, and closely monitor liver function in all patients to avoid unacceptable toxicity and to better assess the benefit/risk value and the appropriate population for the drug. Because the review was part of ongoing pharmacovigilance during the clinical trial, the safety issue was identified and addressed early in clinical development. Such laboratory trend analysis yields maximum benefit when part of a systematic approach to safety monitoring.

Capacity building for pharmacovigilance and medicine safety should address all processes for developing individual and system capacity and enable achievement of sustainable ability to
manage effectively the safety of patients and health products. Performing systematic pharmacovigilance requires a full understanding of the scope of pharmacovigilance, which includes both active safety reporting and postmarketing surveillance. It involves the ongoing processes of risk identification, risk assessment, and risk mitigation. All of these processes are equally important to the pharmaceutical company, the regulatory authorities, the investigator, and the patient.

There are many ways of building pharmacovigilance capability, and many differences in how pharmacovigilance systems are created. Historically, companies created pharmacovigilance functionality as the need arose to assess their products under development. Since there are variations in the required sample size of studies, geographical site distribution, adjuvant or comparator products used, and in the definition of “standard treatment” in different countries, differences naturally evolved. Global pharmacovigilance is an ongoing process of harmonization. Currently, there are many national, cultural, and regulatory differences among countries in how pharmacovigilance is implemented. The goal is always the accurate assessment of the benefit versus the risk of a product in the populations who receive it, and mature pharmacovigilance systems are able reach accurate conclusions despite different types of data.

**OPERATIONAL OVERVIEW OF PHARMACOVIGILANCE**

An operational overview of pharmacovigilance begins with safety information coming from a variety of sources, including clinical trials data, safety call centers, spontaneous reports, and literature searches, each of which has the potential to create an individual case. Within the pharmacovigilance department each case is processed, assessed as to its relationship (causality) to the investigational product, and reported to the regulatory authorities and other stakeholders, either as an expedited report or as part of an aggregate report, based upon pharmacovigilance policies, regulations, and guidance documents. In addition, each case becomes part of the total safety dataset for that medicinal product.

Aggregate data are systematically analyzed for safety issues and assessed for benefit versus risk, and periodic safety update reports (PSURs) are submitted to the regulatory authorities as additional safety information is collected. This continues throughout the product’s life cycle. Safety findings are addressed in order to mitigate risk. This may include modification to a clinical trial design, changes in proposed labeling, implementation of a risk mitigation plan,
or discontinuation of development or use of a marketed product. A flow diagram summarizing the major activities associated with pharmacovigilance is shown in Figure 13.2.

**COMPONENTS AND CAPABILITIES OF A COMPLETE PHARMACOVIGILANCE SYSTEM**

Based upon the intent and scope of pharmacovigilance, there are certain components and capabilities that are essential to a fully functioning pharmacovigilance system, regardless of how a company's safety department is constructed (Figure 13.3). These include:

- a qualified person for pharmacovigilance (QPPV) (Europe)
- safety systems (database) support.
- safety case processing and review
- medical writing and aggregate reporting
- a sound quality management system including standard operating procedures (SOPs), quality standards, metrics, and training
- signal detection and risk analysis
- global safety reporting

**FIGURE 13.2**
Summary of the major activities associated with pharmacovigilance. SAE: serious adverse event; QC: quality control. (Please refer to color plate section)
In some companies some activities may be performed by different departments, for example, safety regulatory reporting may be part of regulatory affairs, or aggregate report writing may be done within a company’s medical writing department. Some activities may be outsourced to contract research organizations (CROs) or safety niche providers, while others are kept in-house, but all must be covered for complete pharmacovigilance capacity.

PHARMACOVIGILANCE POLICIES, REGULATIONS, AND GUIDANCE DOCUMENTS

In the major regions of the world where medicinal products are developed, pharmacovigilance is highly regulated. Structures, systems, and roles are determined by laws, regulations, guidances, and guidelines; it is within this context that the department’s organizational structure is established, the individual roles and the systems required are defined, the skill sets necessary are determined, and the tools to perform pharmacovigilance effectively are created.

The major regulatory stakeholders driving the formation of global pharmacovigilance regulation 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 is legally binding, as are the European national laws and ordinances. Directives reflect current thinking on a topic and bind member states to common objectives, which must be implemented into national law within a given timeframe. Guidance documents, guidelines, and recommendations are not legally binding, but should be respected and play an important role in actual practice.

Global principles are harmonized through the International Conference on Harmonisation (ICH). ICH E1–E2F focus on clinical safety. Direction is provided in ICH E2A–C (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 stakeholders in the conduct of clinical trials.

However, even as efforts to harmonize pharmacovigilance processes continue, companies must still comply with national laws and local regulations. As in other areas of development, companies should have SOPs around pharmacovigilance processes in order to ensure consistency, compliance, and quality.

**Adverse Event Reporting**

**DEFINITIONS**

Reporting of adverse events is the cornerstone of pharmacovigilance, and therefore closely supervised by regulatory authorities. ICH E2A defines the following adverse events (AEs), adverse drug reactions (ADRs), and serious adverse events (SAEs) as follows:

*Adverse event (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 therefore be an unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse drug reaction

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

The phrase “responses to a medicinal 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.

Regarding marketed medicinal products, a well-accepted definition of an ADR in the post-marketing setting 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 defined as “serious” based upon patient event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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

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

Medical and scientific judgment should be exercised in 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 jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

ADVERSE EVENT REPORTING TIMELINES

According to ICH E6, all SAEs should be reported to the sponsor immediately, except for those identified in the protocol or other document as not needing immediate reporting.

Fatal or unexpected ADRs occurring in clinical investigations should be reported to the regulatory authorities as soon as possible, but no later than seven calendar days after knowledge of the 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 filed 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 that do not meet the requirements for expedited reporting are reported at the end of the clinical trial as part of the marketing application or in PSURs.

EUROPEAN DIRECTIVE ON UNBLINDING

Volume 10 of the publication “The Rules Governing Medicinal Products in the European Union” provides guidance on unblinding the treatment allocation when suspected unexpected
serious adverse reactions (SUSARs) occur. In the European Union (EU) SUSARs must be unblinded prior to submission to the regulatory authorities; this is not required by other regulatory authorities in Asia or the USA. Recently, the FDA acknowledged the potential need for unblinding some expedited safety reports, but recommends alternatives to unblinding be undertaken if possible; this rule came into effect on March 28, 2011.

Procedures related to unblinding must ensure that only those who need to review unblinded data have access to them, and that everyone else involved in the trial remains blinded as to treatment assignment. This is required to preserve the integrity of the study.

Standard Operating Procedures, Study-Specific Procedures, and Safety Plans

The number of SOPs related to pharmacovigilance may vary from few in number to many, depending upon the length and complexity of the processes involved. Companies with few SOPs may write individual study-specific procedures (SSPs) consistent with their SOPs, but which provide more detail in relation to a specific product under development. Sometimes all of the pharmacovigilance procedures are combined into a safety plan, or pharmacovigilance plan, which becomes a summary of all of the processes to be followed by the assigned staff in conjunction with the clinical trial or across trials. In Europe, a detailed description of the pharmacovigilance system must be included in the marketing authorization application.

At a minimum, SOPs/SSPs should cover the following activities:

- serious adverse event reporting
- safety case handling (intake, process flow, assessment, documentation, archiving)
- safety database
- safety data conventions
- review of patient (clinical/laboratory) data
- aggregate data review
- signal detection
- unblinding
- regulatory reporting of safety information and 24 hour safety coverage.

Other SOPs/SSPs are developed as relevant to the specific product or therapeutic area. At the beginning of each trial safety reporting timelines should be reviewed, the timeframes for ongoing review and assessment of patient data should be agreed upon, and the assignment of any unblinded staff should be determined. Studies utilizing a drug safety monitoring board (DSMB) or clinical endpoint committee (CEC) will have additional SOPs/SSPs or charters created to clearly define the roles and processes to be performed by these groups.

In addition to written procedures, regular teleconferences and/or meetings should be held to ensure adequate communication of information, make modifications in best practices as needed during the study, and maintain compliance and audit readiness. Because processes may change during a clinical trial, training is an important part of pharmacovigilance and risk management.

Quality Management System

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

A QMS is part of continuous process improvement. Within the QMS each process is reviewed through quality control steps within the process. The result of the quality control is measured
against defined KPIs. Deviations from defined processes are identified, and those suggesting a quality issue are addressed through a root cause analysis followed by the creation of a corrective action and preventive action (CAPA) plan. Quality assurance can then check to ensure that quality is being managed within the pharmacovigilance department and that all quality issues are being addressed.

**ORGANIZATIONAL STRUCTURE OF A PHARMACOVIGILANCE DEPARTMENT**

**Departmental Organization**
The basic functional “unit” within the pharmacovigilance department is comprised of the drug safety physician (DSP), drug safety associate (DSA), and medical assistant. A “team” may consist of several DSAs, a single physician providing medical review, and one or two medical assistants for administrative support. Depending on the size of the company and the number of employees, pharmacovigilance teams may be organized by product or by therapeutic area, or may be separated into premarketing and postmarketing groups. Matrix structures are common. Global pharmacovigilance departments may exist in a limited number of regional hubs, with each hub having a senior pharmacovigilance member who provides oversight. An example of a pharmacovigilance organizational chart is depicted in Figure 13.4. Figure 13.5 shows an example of a matrix structure within pharmacovigilance.

**Collaboration and Teamwork on Global Clinical Trials**
Successful pharmacovigilance requires cross-functional, cross-regional, and cross-cultural collaboration. For example, within the pharmacovigilance department itself, safety case processing and assessment may occur in several locations, particularly if some steps in the...
workflow are provided in low-cost centers. Global pharmacovigilance capacity can allow round-the-clock pharmacovigilance, but can only be successful with global systems, consistent processes and workflows, adequate and ongoing training, and excellent communication across regions.

As members of the clinical development team, pharmacovigilance staff also interact regularly with site investigators, clinical research associates (CRAs), clinical project managers (CPMs), clinical data managers (CDMs), biostatisticians, and medical writers. In addition, for projects using DSMBs or CECs, pharmacovigilance staff independent of the clinical team may work with the committee members to provide or clarify the safety information needed for clinical endpoint review or for periodic DSMB meetings.

**ROLE OF THE MEDICAL MONITOR**

ICH-GCP does not define or describe the responsibilities of a medical monitor. A practical definition might be “a physician or other qualified individual, separate from the principal investigator, who is responsible for medical and safety monitoring of research subjects for conditions that may arise during the conduct of a clinical trial”.

The role of the medical monitor is to be the clinical team’s advocate for subject safety and well-being. This extends beyond individual patient safety monitoring and may include medical assessment of the clinical study protocol for feasibility, upfront risk analysis, input into decisions on study design, treatment regimens, comparator selection, medical interpretation of data, and input into data analysis and report generation.

During the study the medical monitor is an important member of the clinical project team. Responsibilities include interaction with site investigators to provide them with known information on the product under study, ongoing assessment of the medical and safety aspects of the medicinal product, serving as the medical consultant to the project team by providing

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**FIGURE 13.5**
Sample matrix structure in pharmacovigilance (PV) by product. DSPM: drug safety product manager; DSA: drug safety associate; IT: information technology.
medical and therapeutic area expertise, participating in data review and interpretation, and helping to ensure overall project success. Despite regular interaction with clinical site personnel, the medical monitor should not interfere with the investigator’s responsibility for medical assessment and treatment of individual subjects, but should provide the investigator with all medical information known by the company to ensure that the best assessment and treatment decisions may be made.

In essence, the medical monitor plays a unique role that bridges the site, the pharmacovigilance department, and the rest of the clinical development team.

**ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM**

In different regions of the world, job titles vary for similar roles on the pharmacovigilance team. The titles drug, or product, safety associate or safety specialist may be used interchangeably with pharmacovigilance associate; the title drug safety physician is commonly used when referring to the physicians providing pharmacovigilance.

**Head of Pharmacovigilance**

The head of pharmacovigilance plays a critical role in the pharmacovigilance department, and is the person ultimately responsible for all of the safety and risk management activities performed within the department. Typically, he or she will have many years of experience in pharmacovigilance and be an authority on pharmacovigilance regulations and reporting requirements. In addition to providing leadership and oversight within the department, the head of pharmacovigilance acts as a senior resource throughout the company on matters such as safety strategy, regulatory and safety risk management, safety compliance, and safety quality assurance. The head of pharmacovigilance may be identical with the QPPV in smaller European companies. However, typically the role is separate from the QPPV to ensure the independence of the QPPV from the daily operational tasks.

**Drug Safety Physician/Directors of Drug Safety**

It is frequently necessary for the medical monitor to remain blinded as to the medicinal product causing an adverse reaction in a clinical trial. Knowledge of the treatment arm may bias the medical monitor in decisions affecting other aspects of the study. In such cases, a physician not otherwise associated with the study will be assigned to assess adverse events, possibly as an unblinded medical reviewer. In large, global pharmaceutical companies, these DSPs exist in the pharmacovigilance department completely separate from the medical monitors on the clinical team. In smaller companies where physicians may play multiple roles, it is important to firewall blinded and unblinded medical staff in order to protect the integrity of the clinical data.

Other responsibilities of the DSPs include medical review of aggregate data and reports. More experienced DSPs or directors of drug safety are involved in signal detection and analysis. Some may be responsible for creating and implementing development risk minimization plans (Europe) or risk evaluation and mitigation plans (USA), which are now required by many regulatory authorities.

**Qualified Person for Pharmacovigilance in Europe**

The QPPV is a required role for all pharmaceutical companies in Europe, but not yet required in other regions of the world. A named person is responsible for all aspects of pharmacovigilance for a medicinal product. The QPPV must be a physician or someone acting under the supervision of a qualified physician. He or she ensures the adequacy of the pharmacovigilance system and full compliance with meeting regulatory obligations and timelines for safety.
reporting. Therefore, the QPPV must be very experienced in clinical trial safety as well as safety regulations, compliance, and policy. The QPPV oversees the pharmacovigilance plan development and proactive risk minimization strategies. He or she is the single point of contact for safety with the regulatory authorities.

Pharmacovigilance/Drug Safety Product Manager

The pharmacovigilance or drug safety product manager (DSPM) is an experienced member of the pharmacovigilance department assigned to oversee specific safety products, usually when large numbers of safety staff are required. Examples of projects requiring a DSPM include studies with large numbers of SAEs, case reports, studies with clinical endpoints that are also SAEs, projects involving a number of different safety functions (e.g. case reporting and regulatory submission, literature review, and aggregate reporting), and other safety projects of special interest. A DSPM may also organize and coordinate DSMBs and CECs, utilizing key opinion leaders and medical and statistical experts.

Drug Safety Associate

The role of a DSA is to monitor and track SAEs, serious and non-serious ADRs, and other medically related product information. It is paramount to ensure the timely processing and reporting of such information in accordance with company and regulatory reporting timelines. The DSA usually has an educational background in one of the life sciences; it is also advantageous to have a working knowledge of medical terminology. Many DSAs are nurses, pharmacists, or other allied health professionals. The DSA works under the supervision of the DSPM, director of drug safety, QPPV, or medical monitor.

Some of the other functions performed by the DSA include, but are not limited to, developing safety plans and other SSPs; providing input to and reviewing study safety tracking reports for accuracy and quality; maintaining electronic and paper files; assisting the medical monitor with the documentation and processing of routine exceptions and rescreen approvals; performing safety review of clinical [case report forms (CRFs)] and patient laboratory data; liaising with sponsors, investigational sites, and/or reporters regarding safety issues; and participating in project team meetings and teleconferences.

Medical Assistant

The medical assistant plays an important role in maintaining efficient and accurate organization of documents and information within the department by providing administrative support to the pharmacovigilance team. Duties of the medical assistant include filing; faxing; assisting with the planning and organization of meetings, teleconferences, and training sessions; maintaining meeting minutes; handling mailing activities; answering SAE hotline and other departmental telephone lines; documenting contacts and submitting to appropriate personnel; maintaining office supplies and equipment; creating, maintaining and auditing work tracking systems; and ensuring accuracy and audit readiness of the departmental files and file room. In some cases, medical assistants may be trained as data entry personnel and can assist in the data entry of safety information into appropriate safety databases.

Safety Systems Specialists

Owing to the large amounts of data involved, numerous databases and technology systems are required to manage the daily workflow associated with pharmacovigilance, including individual case management and aggregate data analysis. This requires staff who have backgrounds in information technology (IT). In some cases, these staff are further specialized in the creation, validation, and maintenance specifically of safety systems. In smaller companies, the safety systems specialist may be part of the IT department, assigned as needed to support pharmacovigilance.
Pharmacovigilance Trainer

In the current dynamic environment surrounding pharmacovigilance and risk management, ongoing training for pharmacovigilance staff is essential to maintain awareness of current global and local regulations, policies, and guidelines. Pharmacovigilance training includes subject matter training on the therapeutic area of the product under development and specific training on the science related to the investigational product. Often the medical monitor or an expert in another therapeutic area supplies this training. Training related specifically to pharmacovigilance is continuous, with more senior staff reviewing and mentoring the junior staff. Beyond a certain size, however, staff specifically dedicated to performing pharmacovigilance training is usually necessary. All training should be documented and filed appropriately. Pharmacovigilance staff should be "audit ready” in terms of their knowledge of the rules, regulations, SOPs, and confidentiality requirements surrounding the specific protocol or project, as well as safety reporting requirements and general confidentiality requirements regarding clinical research subjects and their data.

APPROPRIATE FACILITIES FOR PHARMACOVIGILANCE

No specific requirements exist for the physical structure of a pharmacovigilance department. However, it is imperative that all subject data be kept confidential, and that there is adequate storage area with appropriate security, limited data access, and adequate disaster recovery. Infrastructure that enables documenting receipt and forwarding of time-sensitive safety information must be in place. It is crucial that unblinded safety information is not accessible to staff who must remain blinded during the clinical trial. This may be achieved through physical separation or through appropriate security measures for system and data access.

Although not required by regulation in most countries, many pharmacovigilance departments maintain a 24 hour emergency telephone system to allow prompt interaction with the investigative sites in fatal or life-threatening situations and to facilitate expedited case assessment and reporting. In the EU, a QPPV must be readily available at all times for any crisis situation.

SAFETY DATABASES

A safety database allows the pharmacovigilance department to monitor, assess, and report to the regulatory authorities serious safety information. The utilization of any specific safety system is not a direct legal requirement. However, under most circumstances, a more powerful database is needed, therefore the use of safety databases is currently standard. Specifically developed commercial safety databases are available. The database owner may maintain the system on their servers or install the full system on a company server and allow access through licenses. Alternatively, access to a safety database can be provided though a CRO or safety niche provider. This may be a more attractive solution financially for limited case volumes.

The database must be validated (e.g. CFR 21 compliant) and acceptable to all regulatory authorities on the global level. A recently established requirement is to have the capability for reporting expedited cases electronically. The specifications for electronic reporting are detailed in ICH E2B. Such an “E2B compliant” gateway allows direct export of such expedited cases to the authorities’ databases such as EudraVigilance in Europe. For smaller companies not having their own safety database, expedited cases may be entered directly (manually) into any authority database. In the USA, electronic safety reporting is not yet mandatory.

SAFETY CASE PROCESSING AND REVIEW

Most commercial safety databases provide the functionality of a paperless workflow, allowing all case processing steps to be performed within the system. The company’s process should be
described in an SOP available to auditors. Even if no safety database is used, the case processing workflow should always be detailed in an SOP, SSP, or safety plan to ensure clear assignment of roles and responsibilities. This is especially important when various steps in the workflow are distributed among different global locations. Updating cases as new information is obtained requires a clear audit trail to all prior information.

An example of such a workflow is depicted in Figure 13.6.

**Steps in Serious Adverse Event Case Processing**

1. When an investigator, healthcare provider, or clinical site monitor identifies a potential SAE, the event is reported to the sponsor immediately.

2. Upon receipt of an SAE at the pharmacovigilance department, the report is assessed as to whether it fulfills the minimum requirements for reporting.

3. A valid case is checked for duplication, i.e. whether the same case was previously reported, or whether this is follow-up information on a previously opened case.

4. If the case is identified as valid for initial data entry, it will undergo a triage step, being reviewed for expectedness, relatedness, and seriousness, with special attention as to whether the case is fatal or life threatening. This determines the appropriate timeline for processing and reporting to the regulatory authorities.

5. The case then undergoes data entry, a case narrative is created and the case undergoes medical review. Any missing or unclear information is queried and added to the case.

6. Once all of these activities are completed and quality checked, the case is finalized within the allotted timeframe and if expedited reporting is required the information is sent to the appropriate recipients.

7. The process is repeated as additional information becomes available until the event is resolved or no further information can be obtained.

**GLOBAL SAFETY REPORTING**

Since the main objective of pharmacovigilance is the identification of information that may affect the safety of patients, once a potential risk is noted, it must be communicated to all stakeholders. The distribution follows well-defined rules described in ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. According to ICH E2A,

All adverse drug reactions (ADRs) that are both serious and unexpected (SUSARs = Suspected Unexpected Serious Adverse Reactions) are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose.
Initial reports should be submitted within the prescribed timeframe providing the following minimum criteria are met:

- an identifiable patient
- a suspect medicinal product
- an identifiable reporting source, and
- an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship.

During global clinical trials, a SUSAR that occurs in one country may require expedited reporting to regulatory authorities, institutional review boards/ethics committees, and investigators in all participating countries. This must be done in accordance with each country’s local laws and regulations. Unfortunately, countries vary in their requirements as to the format and timeframe for the reporting of cases. In addition, reporting requirements are frequently changing at the country level.

Keeping aware of the reporting requirements in various countries is a time-consuming task, which requires staff that fully understand the global pharmacovigilance reporting requirements. There are commercial databases available to provide up-to-date regulatory reporting intelligence. In some companies staff within the pharmacovigilance department perform safety regulatory reporting; this may be part of the electronic workflow. In other companies a team that is part of the regulatory department may perform this activity.

SAFETY DATA REVIEW AND ASSESSMENT

During a clinical trial, safety data will be collected from a number of different sources. These include the subject CRF, laboratory reports, SAE reports, and information specific to a particular study or therapeutic area such as electrocardiographic or radiographic imaging data. All safety data should be reviewed in an ongoing manner with the intent of minimizing risk to the participating and future subjects, and determining whether the benefit exceeds the risk if the product becomes commercially available (i.e. whether the product is safe enough for general use). This is done through the combined processes of individual subject data assessment and aggregate data review and assessment.

**Individual Subject Data**

The scope of individual data review begins with information on the subject CRFs. Screening and baseline information such as demographics, significant past medical history, concomitant diseases and medications, and prior treatment regimens are recorded and become part of the clinical database for the study. Laboratory and other ancillary information are also collected. Prior to the start of each study, alert triggers are determined in order to flag potential safety issues, and criteria for withholding or discontinuing treatment due to adverse events are written into the study protocol. When a subject experiences a serious adverse event or a safety alert is triggered, all available safety information on that subject should be reviewed in order to minimize harm to the subject under study.

**Subject Profiles**

Reviewing individual subject data effectively requires that either repetitive data cuts be reviewed or the pharmacovigilance staff must be able to look at cumulative data in real time. Commercial tools are available which enable cumulative data to be reviewed for each individual subject as well as in aggregate. Figure 13.7 shows an example of a subject profile depicting temporal information between an adverse event (vertigo), the receipt of medications, and selected laboratory results. An individual subject’s safety parameters can be reviewed in context throughout his participation in the study. This helps to ensure maximum safety monitoring of individual subjects.
Review of Aggregate Data

The scope and timing of aggregate data review activities vary among clinical trials. These should be determined before the start of the study. Parameters to be determined include the objectives of the review; data fields to be reviewed; the frequency of the review; the process for raising, monitoring, and resolving queries generated; and how the review and any findings will be documented.

The main safety objective of ongoing review is the timely identification of potential safety issues. Other objectives may include identifying subjects included in a study inappropriately who may be placed at unintentional risk, or other systemic protocol violations that may be recurring. Aggregate data review may also identify training needed at sites or by the clinical study team in order to minimize subject risk, which may occur owing to unclear or misinterpreted direction in the protocol.

Review of aggregate data may be done in-house or by an external and independent team of experts such as a DSMB or data monitoring committee (DMC). If a DSMB or DMC is used, pharmacovigilance staff are often involved in the organization of the data along with an assigned (unblinded) statistician. Figure 13.8 shows an example of a decision tree for the use of a DSMB for a clinical trial.

Signal Detection and Analysis

The WHO defines a safety signal as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. When a signal is detected, further investigation is warranted to determine whether an actual causal relationship exists.

Signal detection uses data imports from the safety database or other clinical, laboratory, or epidemiological databases, as well as regulatory data sources. A compliant and suitable safety database should be able to process data related to signal detection. Signals can be suggested by alerts or trends in incoming data.
Signals can also be identified by major statistical algorithms and advanced analysis in conjunction with biostatistics. Commercial tools are also available for data mining and signal detection and analysis. Signal detection consists of several activities:

- **Signal detection tools:**
  - single case evaluation, including literature surveillance
  - aggregate report creation
  - software tools for large case volumes and trend analysis

- **Signal generation/detection procedure:**
  - permanent monitoring of single case reports/report series
  - periodic report review
  - ad hoc analysis of reports from external sources, e.g. literature reports, requests from competent authorities (CAs) on report/reports

- **Signal work-up and documentation:**
  - quality of the information
  - other risk factors (e.g. natural history of the underlying disease/severity, specificity and outcome)
  - biological and pharmaceutical plausibility
  - class effect
  - epidemiological context
  - frequency
  - drug utilization/population exposure/age, gender and indication

- **Signal assessment and documentation:**
  - QPPV or other senior pharmacovigilance involvement/decision
    - signal not confirmed (no further actions, only documentation)
    - signal doubtful (special scrutiny for future cases)
    - signal confirmed.

Upon confirmation of a safety signal, the subsequent course will be variable but may involve action by company executives and/or the regulatory authorities, depending on the magnitude of risk. It is important that action is taken promptly in order to avoid any unnecessary harm; therefore, an ongoing and systematic approach is essential.
For safety findings that have low or minimal safety impact, these will be reported in the clinical study report (clinical trials), in updates to the investigator brochure, in the core data sheet, or in periodic safety update reports required by the regulatory authorities. The conclusion of any update report must comment on any new safety issue. Reports may be written within the pharmacovigilance department or by a medical writing team, with input from pharmacovigilance staff. In the case of marketed products, changes to labeling may be required. All of this is part of the communication of any safety risk to those who might use the product.

**MANAGING RISK**

Consequences of finding a significant safety issue may include any of the following activities:

- Amending the protocol
- Temporarily suspending enrollment
- Discontinuing the study
- Discontinuing development of the medicinal product
- Implementing a development risk management plan (RMP) or risk evaluation and mitigation strategy (REMS).

Risk management represents the top of the pharmacovigilance activity pyramid (Figure 13.9). These activities are the culmination of the processing and review of individual adverse events and other safety data, the review and assessment of aggregated data, and the identification, analysis, and interpretation of safety signals.

**Risk Management Plans and Risk Evaluation and Mitigation Strategies**

The RMP (EU) and the REMS (USA) are now a standard part of pharmacovigilance planning. ICH E2E (Pharmacovigilance Planning) was originally created to achieve consistency and harmonization, particularly during the early postmarketing period of medicinal products. Within the past few years, the US and European regulatory agencies have increased their guidance on benefit risk assessment and risk minimization.
The intent of both the RMP and the REMS is to minimize risks related to a medicinal product through interventions and to communicate those risks to patients and healthcare providers. Elements may include medication guides or patient package inserts, a detailed communication plan about safety issues, specific elements to assure safe use of a product such as required laboratory testing or prescriber training, an implementation plan and a timetable for assessment.

Currently, the RMP or REMS may be created at any time during clinical development, but most often they are submitted as part of the marketing application. In the EU, RMPs are routinely required as part of the detailed description of the pharmacovigilance system. In the USA, the regulatory authorities can request a plan if there is a reason to suspect that one may be necessary, based upon non-clinical data, early use data, class data for the medicinal compound, or other factors.

If new safety information becomes available after regulatory approval, the regulatory authorities may request a REMS or an updated RMP. Additional pharmacovigilance such as active surveillance, other clinical or epidemiological trials, specialized training, or restricted access may be included in the plan. The activities must be sufficient to minimize the likelihood of harm so that benefits still outweigh risks, and to ensure that the risk reduction procedures are communicated and implemented.

OUTSOURCING WHILE BUILDING PHARMACOVIGILANCE CAPACITY

Large, global pharmaceutical companies usually have well-established pharmacovigilance systems. In countries where pharmacovigilance is not well established there may be a need to build pharmacovigilance capacity. For example, some companies only have medical affairs departments whose function is mainly to provide medical input to marketing strategy and ensure that product literature and marketing brochures meet legal and ethical requirements. They lack the capacity for complete, product life-cycle pharmacovigilance and risk management. To have a complete and systematic approach to pharmacovigilance requires the ability to perform all of the defined pharmacovigilance activities. Outsourcing some aspects of pharmacovigilance to a CRO or safety niche equivalent while building internal capacity may be an option.

Worldwide pharmacovigilance can be centralized in a few regions, or hubs, if the systems are global and there is good communication and process flow between regions. Some of the functions may be competently performed in low-cost regions. If outsourcing, sponsors must ensure that any vendors performing pharmacovigilance and risk management have the experience and capacity to perform those services, and that they are sufficiently knowledgeable in the regulations associated with pharmacovigilance.

Outsourcing those functions best performed by pharmacovigilance experts such as signal detection, aggregate data interpretation, and risk evaluation and mitigation, requires careful selection of vendors. Many CROs are able to provide complete safety services and resources, acting as a smaller company’s pharmacovigilance department permanently or until such time as the company is able to manage the expense on its own. These services include performing safety audits; creation of SOPs and SSPs; medical and safety monitoring; individual case management; creating and maintaining pharmacovigilance databases; signal detection; trend analysis; organizing and managing DSMBs, DMCs, and CECs; and reporting of expedited and periodic safety reports to regulatory authorities, principal investigators, and institutional review boards.

GENERAL CONSIDERATIONS AND CONCLUSIONS

Pharmacovigilance and risk management are an essential part of pharmaceutical product development and commercialization, the activities of which are highly regulated in many parts
of the world. Rare adverse events may not be identified until large numbers of patients receive
the product, so pharmacovigilance and risk management must extend throughout the prod-
uct’s life cycle. Benefit and risk must be continually assessed as more is learned about the
product through its use. Building pharmacovigilance and risk management capacity requires
a systematic approach to ensure that all safety aspects are monitored and addressed properly.
Since capacity building takes time and resources, outsourcing of certain activities may enable
capacity building to proceed before all capabilities can be done in-house. The use of a limited
number of safety centers is a viable and cost-effective option, provided there are good
processes, good tools, and good communication of responsibilities and events.

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