PHARMACOVIGILANCE

INTRODUCTION

- 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 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.

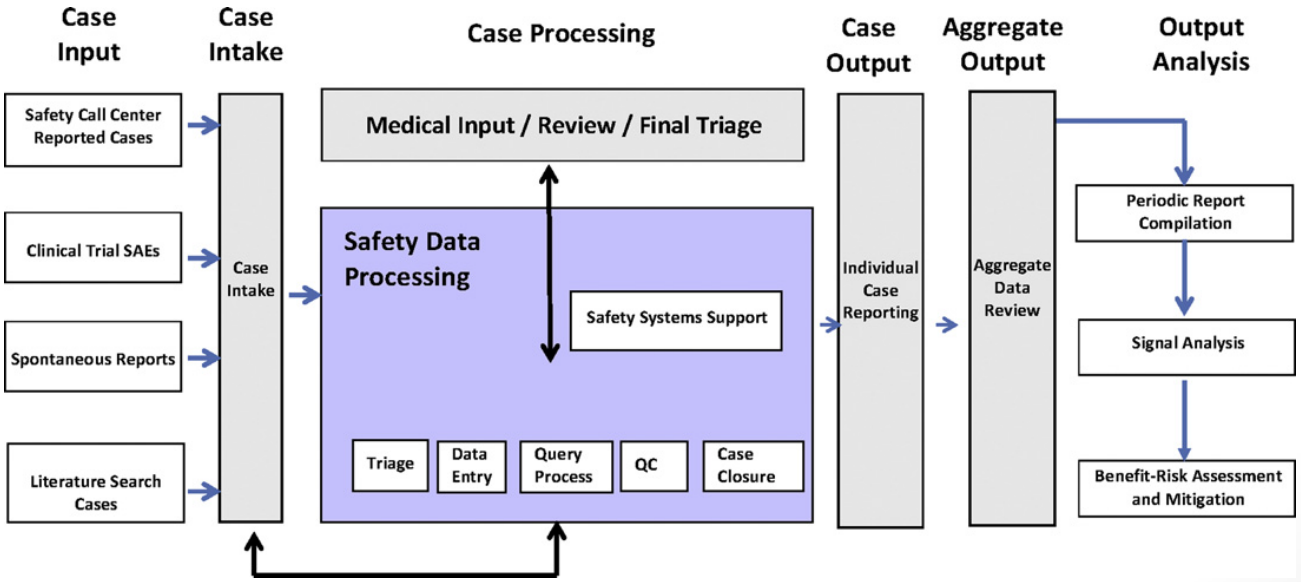
- Capacity building for pharmacovigilance and medicine safety should address all processes for developing individual and system capacity and enable achievement of sustainable ability to manage effectively the safety of patients and health products.
- Performing systematic pharmacovigilance requires a 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.

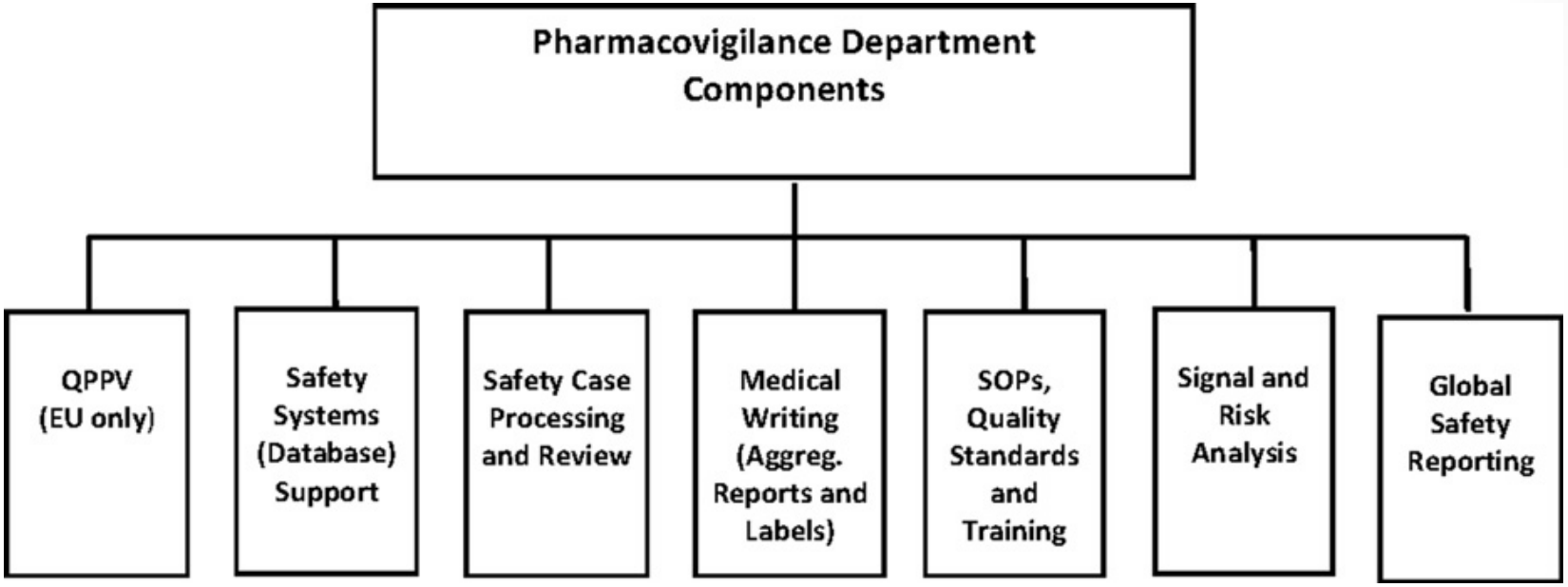
OPERATIONAL OVERVIEW OF PHARMACOVIGILANCE

- 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.



COMPONENTS AND CAPABILITIES OF A COMPLETE PHARMACOVIGILANCE SYSTEM



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 inhouse, but all must be covered for complete pharmacovigilance capacity.

PHARMACOVIGILANCE POLICIES, REGULATIONS, AND GUIDANCE DOCUMENTS

- 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.

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 Event Reporting

- **DEFINITIONS**
- 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.

Adverse Event Reporting

- 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 definitionabove. 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

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.
- Global pharmacovigilance departments may exist in a limited number of regional hubs, with each hub having a senior pharmacovigilance member who provides oversight

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.

ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM

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.

ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM

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.

ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM

- **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

ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM

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 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, 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;
- participating in project team meetings and teleconferences.

ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM

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; 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.

ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM

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.

ROLES AND RESPONSIBILITIES OF THE PHARMACOVIGILANCE TEAM

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.

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.

- 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 product'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.