

**KNOWLEDGE AND PERCEPTION ON PHARMACOVIGILANCE
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Author****Susanta Kumar Rout**
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Research Centre,
Bangalore, Karnataka.**ABSTRACT**

India market has mostly seen the launch of only those products that have been already approved and marketed in the regulatory markets of USA, Europe, Japan or other countries. For accessing the benefit-risk profile of a drug and to take appropriate corrective actions. Pharmacovigilance is not new to India, and has in fact been going on from 1998 when India Decided to join the Upsala centre for Adverse Event Monitoring and already 16 years have passed. Something has been achieved during this period, but much more still needs to be done in this field in India. The occurrence of active pharmaceutical

substances in the environment is of growing concern. Certain classes of biological medicinal products, however, are associated with specific safety issues. The importance of Pharmacovigilance is increasing day by day, and people became more aware about the benefit and risks of medicines. Ascertaining the causality of suspected adverse drug reactions (ADRs) still remains a challenge in resource-limited settings. With the increasing and ever-more stringent regulations in pharmacovigilance, the regulatory authorities face greater demands for patient welfare and safety. In this review we focuses on strategies and current scenario of pharmacovigilance sector in India along with recent guideline for Safety Specification and Pharmacovigilance Plan that might be submitted at the time of licence application.

KEYWORDS: Pharmacovigilance, adverse drug reactions, pharmaceutical product.**INTRODUCTION**

India has more than half a million qualified Doctors and 15,000 hospitals having bed strength of 6,24,000. It is the fourth largest producer of pharmaceuticals in the world. It is emerging as an important Clinical trial hub in the world. Many new drugs are being introduced in our

country.^[1] Product safety implies patient safety, Pharmacovigilance is more than spontaneous reporting alone and the evaluation of medicines is more than pharmacovigilance.^[2] The World Health Organization defines pharmacovigilance as 'the pharmacological science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'. The goal of pharmacovigilance is the safer use of medicines and this is usually achieved by dissemination of accurate, timely and clinically relevant information. Early detection of safety signals from clinical trials and proactive postmarketing surveillance is necessary to identify the risks associated with the products. Number of recent high profile drug withdrawals point towards this fact. Information collected during the pre-marketing phase of drug development may not detect rare ADRs. Adverse drug reactions (ADRs) are common causes of morbidity and mortality in both hospital and community settings. ADRs are responsible for about 5% to 20% of hospital admissions.^[3, 4] The roles of pharmacists have moved from traditional aspects of preparing and dispensing medicines to a more vital role that includes many aspects of pharmaceutical care, such as preventing ADRs and medication errors, improving patient satisfaction and quality of life, and improving economic outcomes.^[5-7] Pharmacists can play a crucial role in both ADR reporting and pharmacovigilance activities.^[8] Due to the increase in the number of expiring patents on biological products during the last three years, the interest and investment of private and public national producers in the biological market has increased. A large number of national / International producers have started projects to develop and produce biological products in India. The aim is to produce new products as well as re-creating biological products that are not innovations. The use of a drug during a clinical trial is under controlled conditions, also, limited and selected numbers of patients are enrolled in the clinical trials. Drug use in special situations and population or drug interactions may not be studied. Therefore, the post-marketing surveillance of drugs is important. Need for a Pharmacovigilance Plan and sets out its principles of good practice for the design and conduct of observational studies.^[9] The new guidelines is mainly adapted from the newly-established international Good Pharmacovigilance Practice, composed of 16 different modules together with some product/population specific considerations, as well as annexes and templates of submission. The Guidelines were published in March 2014 and the effective date will be 1st July 2015. Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline. There is an immense need to understand the importance of Pharmacovigilance and how it impacts the life cycle of the product. This will enable integration of good Pharmacovigilance practice in the process and procedures to help

ensure regulatory compliance and enhance clinical trials safety and post marketing surveillance.

Background

Historical Background

The word pharmacovigilance has derived from the Greek word *pharmacon* means „drug“ and the Latin word *vigilare* means „to keep awake or alert, to keep watch.“ Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. Recently, the concerns of pharmacovigilance have been widened to include herbal, traditional and complementary medicines, blood products, biological, medical devices and vaccines. Several disasters led to an awareness that drugs not only can heal but also can harm including sudden death caused by chloroform anaesthesia in 1877 and fatal hepatic necrosis due to arsenicals in 1922. In the United States a tragic mistake in the formulation of a children's syrup in the late 1930s was the trigger for setting up the product authorization system under the Food and Drug Administration (FDA). FDA had the authority to review new drugs for safety, by scrutinizing animal studies and small human volunteer trials for any signs of serious hazards ^[10]. Child deaths after diethylenglycol was mistakenly used to solubilise sulphanilamides in 1937 led to the first enactment of legislation on adverse reactions (Federal Food, Drug and Cosmetic Act, 1938). Following 100 deaths in France in 1952 after diethyl tin diiodide and the thalidomide tragedy of the 1960s, in England and in Germany with reports of foetal abnormalities (phocomelia and micromelia) in relation with the use of a new sleep-inducing thalidomide, there was a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. In the summer of 1962 a new bill amending the 1938 Food, Drug and Cosmetic Act, the Kefauver-Harris Amendments, gave the FDA the power to approve or disallow the introduction of new drugs and the continued marketing of established compounds based on substantial evidence of their therapeutic efficacy as well as safety. Around 1980 it became compulsory to record side effects (adverse drug reactions) by the regulatory authorities in many countries to allow for a continual monitoring of the risk and benefit of products both in the investigational phase before authorization and as postmarketing surveillance when the product is commercialised as an authorized product. Many national authorities have identified the need for developing an organizational plan for managing risks and for communication and action during crises. Regulators themselves often react under duress in a drug safety

crisis within a legislative or administrative framework that is inadequate or excessively restrictive.

Summary

The development of a new drug typically takes about 10 to 12 years and can cost as much as \$ 1.5 billion. Each year, worldwide, only about 26 new chemical entities drugs enter the market.^[11-12] Pharmacovigilance is an important and integral part of clinical research.^[13] Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product lifecycle. Pharmacovigilance is “defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines.” Medicines have led to major improvement in the treatment and control of diseases; they also produce adverse effects on the human body from time to time. Many drugs are precisely targeted to the causes and mechanisms of disease, they may also have minor or distressing effects on other parts of the body, or interact negatively with the systems of the particular individual or with other drugs or substances they are taking, or not work well or at all for some, many or all of those who take them for illness.^[14] There are risks in any intrusion into the human body, wheather chemical or surgical. Nothing in this field is entirely predictable as the interaction between chemicals and the human body may produce surprise. Efficacy is used to express the extent to which a drug works under ideal circumstances.

“Surveillance” comes from old French, *sur* means over and *veiller* means to watch. The transitive verb from “surveillance” is the back-formation “surveil”, “to exercise surveillance over”. The original Indo-European root of “veiller” is UEG, from which the Latin word *vigor* and *vigilare* (to watch or stay awake) derive, with their connotations of watchfulness and liveliness; indeed, “watch” and “wake” have the same root. Metathesis of *vigilare* gives *velox*, speedy, from which we derive “velocity”. Thus, “vigilance” and “surveillance” have the same etymology; their origins imply both watchfulness and speedy action. “Monitoring” derives from the Latin word *monere*, to bring to the notice of, remind, advice.

Pharmacovigilance highlights

1. Adequacy of current PV methods and the appropriateness of current regulatory systems.
2. The role of regulators, industry and academia in collecting evidence.
3. Use of evidence in decision-making.
4. Communication of decisions; as well as.

5. The need for transparency and information sharing.

Terms commonly used in Pharmacovigilance

Benefits

These are commonly expressed as the proven therapeutic good of a product, but should also include the patient's subjective assessment of its effects.

Risk

It is the probability of harm being caused, usually expressed as a percent or ratio of the treated population; the probability of an occurrence.

Harm

It is the nature & extent of actual damage that could be caused. It should not be confused with risk.

Effectiveness

It is used to express the extent to which a drug works under real world circumstances, i.e., clinical practice (not clinical trials).

Efficacy

It is used to express the extent to which a drug works under ideal circumstances (i.e., in clinical trials).

Adverse Drug Reaction

A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. Montastruc et al, have been studied to characterize the profile of adverse drug reactions (ADRs) reported with selegiline, a monoamine oxidase B (MAO-B) inhibitor used in the treatment of Parkinson's disease.

Adverse Event

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Side Effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

Serious ADRs

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: Results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, is a congenital anomaly/birth defect.

Unexpected Adverse Reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

Adverse Reactions

Intrinsic factors of the drug Pharmacological, idiosyncratic, carcinogenicity, mutagenicity, teratogenicity.

Signal

Reported information on a possible causal relationship between an adverse event and a drug - the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Causality

Causality (also referred to as causation) is the relationship between an event (the *cause*) and a second event (the effect), where the second event is understood as a consequence of the first. In common usage, causality is also the relationship between a set of factors (causes) and a phenomenon (the *effect*). Anything that affects an effect is a factor of that effect. A direct factor is a factor that affects an effect directly, that is, without any intervening factors. (Intervening factors are sometimes called "intermediate factors".) The connection between a cause(s) and an effect in this way can also be referred to as a causal nexus.

Extrinsic Factors

Adulterants, contamination, underlying medical conditions, interactions, wrong usage.

Innovator Products

Limited information available at time when drug is first marketed. Conduct intensive monitoring to identify new, unlabeled adverse reactions, monitor for 'rare' reactions. Provide updates to prescribers on new findings, labeling changes, safety issues.

Generic Products

Monitor efficacy, monitor adverse effect profile to study differences in ADR pattern with respect to innovator products. Help in improving quality of generics used whether the problem arose due to ADR or quality defects.

Day zero

Day zero should be considered the day on which the minimum criteria for a reportable adverse reaction report becomes available.

Medication Errors

Medication errors are mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Examples of medication errors include misreading or miswriting a prescription. Medication errors that are stopped before harm can occur are sometimes called "near misses" or "close calls" or more formally, a potential adverse drug event. Not all prescribing errors lead to adverse outcomes. Some do not cause harm, while others are caught before harm can occur ("near-misses"). Medication errors are more common than adverse drug events, but result in harm less than 1% of the time. About 25% of adverse drug events are due to medication errors.

Misuse

This refers to situations where the medicine is intentionally and inappropriately used not in accordance with the authorised PI or the directions for use on the medicine label.

Drug Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicine, which is accompanied by harmful physical or psychological effects.

Summary Product Characteristics (SPC)

Product information as approved by the TFDA. The SPC serves as the basis for production of information for health care providers as well as for consumer information on labels and leaflets of medicinal products.

Vigiflow

A web based data management tool used to manage ADR database. All data are stored on a database server in Uppsala, Sweden.

What should be reported

New drugs. Report all suspected reactions including minor ones. For established or well known drugs. If serious, unexpected, unusual ADRs Change in frequency of a given reaction ADRs to generics not seen with innovator products, ADRs to traditional medicines. All suspected drug-drug, drug-food, drug-food supplement interactions. Statement highlighting marine source of supplements such as glucosamine so that can be avoided by those with allergy to sea food. ADRs associated with drug withdrawals, ADRs due to medication errors. ADRs due to lack of efficacy or suspected pharmaceutical defects.

Pharmacovigilance activities in the guidelines

- a) Pharmacovigilance systems and their quality systems.
- b) Pharmacovigilance system master file.
- c) Pharmacovigilance inspections.
- d) Pharmacovigilance audits.
- e) Risk Management Systems.
- f) Management and reporting of adverse reactions to medicinal products.
- g) Periodic safety update report (PSUR).
- h) Post authorization safety studies.
- i) Signal management.
- j) Additional monitoring.
- k) Public participation in pharmacovigilance.
- l) Continuous pharmacovigilance, on-going benefit-risk evaluation, regulatory action and planning of public communication.
- m) International cooperation.
- n) Safety communication.
- o) Risk minimization measures: selection tools and effectiveness indicators.

Important role of Pharmacovigilance

Serve public health, and to foster a sense of trust among patients in the medicines they use that would extend to confidence in the health service in general.

- a) Ensure that risks in drug use are anticipated and managed.

- b) Provide regulators with the necessary information to amend the recommendations on the use of the medicines.
- c) Improve communication between the health professionals and the public.
- d) Educate health professionals to understand the effectiveness/risk of medicines that they prescribe.

Regulated guidelines

This guideline is intended to aid in planning pharmacovigilance activities, especially in preparation for the early post marketing period of a new drug. The main focus of this guideline is on a Safety Specification and Pharmacovigilance Plan that might be submitted at the time of licence application. The guideline can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the Safety Specification and Pharmacovigilance Plan into the Common Technical Document (CTD).

Industry and regulators have identified the need for better and earlier planning of pharmacovigilance activities before a product is approved or a license is granted. This ICH guideline has been developed to encourage harmonization and consistency, to prevent duplication of effort, and could be of benefit to public health programs throughout the world as they consider new drugs in their countries.

The guideline is divided into different sections^[1]

- 1) Safety specification.
- 2) Pharmacovigilance Plan.
- 3) Annex – Pharmacovigilance methods.

Safety specification

In safety issue the Pharmacovigilance Plan is a separate in different documents i.e. Important identified risks, Important potential risks, Important missing information.

Pharmacovigilance Plan

Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a Pharmacovigilance Plan. The Plan for each Important safety issue should be presented as.

- a) Objective of proposed actions.

- b) Actions proposed.
- c) Rational for proposed actions.
- d) Monitoring by the sponsor for safety issue and proposed actions.
- e) Evaluation and reporting.

Pharmacovigilance Methods

The best method to address a specific situation can vary depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, sponsors should employ the most appropriate design.

The FDA Approach^[15]

The FDA identifies risk management as an iterative process designed to optimize the benefit-risk balance for regulated medicines throughout the product life cycle.

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (CDER, CBER)

This document provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required. Identifying and describing safety signals: From Case Reports to Case Series.

Good Reporting Practice

Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts

and subsequent follow-up, especially for serious events and encourages sponsors to use trained health care practitioners to query reporters.

Characteristics of a Good Case Report

Good case reports include the following elements.

- a) Description of the adverse events or disease experience, including time to onset of signs or symptoms.
- b) Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications.
- c) Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors.
- d) Documentation of the diagnosis of the events, including methods used to make the diagnosis.
- e) Clinical course of the event and patient outcomes (e.g., hospitalization or death).
- f) Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate.
- g) Information about response to dechallenge and rechallenge; and any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).
- h) Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container).
- i) Sequence of events leading up to the error.
- j) Work environment in which the error occurred and Types of personnel involved with the error, type(s) of error, and contributing factors.

Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS) or Vaccine Adverse Events Reporting System (VAERS), using thorough

database search strategies based on updated coding terminology (e.g., the Medical Dictionary for Regulatory Activities (MedDRA)).

Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following.

- a) The clinical and laboratory manifestations and course of the event.
- b) Demographic characteristics of patients with events (e.g., age, gender, race).
- c) Exposure duration.
- d) Time from initiation of product exposure to the adverse event.
- e) Doses used in cases, including labeled doses, greater than labeled doses, and overdoses.
- f) Use of concomitant medications.
- g) The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment.
- h) The route of administration (e.g., oral vs. parenteral).
- i) Lot numbers, if available, for products used in patients with events.
- j) Changes in event reporting rate over calendar time or product life cycle.

Use of Data Mining to Identify Product-Event Combinations

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or so-called data mining, can provide additional information about the existence of an excess of adverse events reported for a product.

Safety Signals That May Warrant Further Investigation

The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, numbers treated, etc.

- a) New unlabeled adverse events, especially if serious.
- b) An apparent increase in the severity of a labeled event.
- c) Occurrence of serious events thought to be extremely rare in the general population.
- d) New product-product, product-device, product-food, or product-dietary supplement interactions.

- e) Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities).
- f) Confusion about a product's name, labeling, packaging, or use.
- g) Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment).
- h) Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal).
- i) Other concerns identified by the sponsor or FDA.

Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population.

European Union^[16]

Regulation (EU) No. 1235/2010 and Directive 2010/84/EU were approved in December 2010 by the European Parliament and Council. All pharmaceutical companies, regulatory agencies, and other stakeholders had 18 months to implement these requirements, with an implementation deadline of July 2012. The Regulation and Directive were supported by Commission Implementing Regulation (EU) No 520/2012, published in June 2012. This provides additional information and includes transitional time frames for several elements of the new legislation through 2016. The pharmacovigilance obligations apply to all medicinal products authorised in the EU, including those authorised before 1 January 1995 and whatever procedure was used for their authorisation. The principle guidance documents are summarised in Volume 9A of “The rules governing medicinal products in the European Union – Pharmacovigilance” (Volume 9A) and in the pharmacovigilance related guidelines of ICH (E2 series) which incorporates international agreements reached within the framework of the International Conference on Harmonisation (ICH).

Volume 9A explains the role and responsibilities of the various parties involved, i.e. the Marketing Authorisation Holder (MAH), the Competent Authorities of the Member States, the EMEA, the CHMP Pharmacovigilance Working Party and the European Commission.

Volume 9A also describes the requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections, Risk Management Plan (RMP) and especially points out the responsibilities of the qualified person responsible for pharmacovigilance.

Marketing Authorization Holder (MAH)

The Marketing Authorisation Holder (MAH) must ensure that he has an appropriate system of pharmacovigilance and risk management in place in order to assure responsibility and liability for his products on the market and to ensure that appropriate action can be taken, when necessary. Specifically, the MAH Provide information to TFDA on all adverse Drug reactions, Submit report on adverse reactions occurring outside Tanzania, Submit a "null" six monthly report for the first two years and annually for the following three years if there is no ADR report submitted to them, Inform TFDA on any significant safety issue(s) or action(s) taken by foreign agency, including the basis for such action(s), and Provide periodic safety update report(s) (PSURs) for the marketed product Submit risk management plans including risk-benefit assessment reports to TFDA.

Council Health Management Team (CHMT)

The Council Health Management Team (CHMT), Appoint a District Pharmacist or any other designated person to become the focal person for pharmacovigilance activities in the respective council, Supervise the implementation of pharmacovigilance activities within the council, Communicate all relevant safety information to health care providers and patients in the council, Conduct further investigation of signals and other risk factors, Organize and conduct training and sensitization of health care providers and patients within the council, Plan and budget for pharmacovigilance activities within the council, and Ensure pharmacovigilance related reports are submitted to TFDA on quarterly basis.

Timelines

The investigator has to immediately report to the sponsor all serious adverse events with the exception of those that are identified as not requiring immediate reporting in the protocol or the investigator's brochure ('IB').

Immediate reporting and follow-up report

Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the

investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event.

The follow-up report should allow the sponsor to determine whether the serious adverse event requires a reassessment of the benefit-risk balance of the clinical trial, if the relevant information was not already available and provided in the initial report.

Non-immediate reporting

In cases where reporting is not required immediately the investigator shall report within the appropriate time frame, taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the protocol or the IB.

WHO Programmed for International Drug Monitoring

Started 1968 Located in Uppsala, Sweden Collaborating center for maintaining global ADR database.

Roles of WHO Collaborating Centre

Identify early warning signals of serious adverse reactions to medicines. Evaluate the hazard. Undertake research into the mechanisms of action to aid the development of safer and more effective medicines.

Need for Pharmacovigilance

- a) Insufficient evidence of safety from clinical trials, Animal experiments, Phase 1-3 studies prior to marketing authorization.
- b) Medicines are supposed to save lives, Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable.
- c) ADR-related cost to the country exceeds the cost of the medications themselves.
- d) Promoting rational use of medicines and adherence.
- e) Ensuring public confidence.
- f) Ethics, to know of something that is harmful to another person who does not know, and not telling, is unethical.

Pharmacovigilance in India

India is becoming a hub for clinical research activities due to its large population, high enrolment rate and low cost.^[17] Signals can arise from post marketing data and other sources, such as pre clinical data and events associated with other products in the same

pharmacological class.^[18] “Surveillance” appeared at the end of the 18th century, meaning “watch or guard kept over a person; supervision for the purpose of direction or control, superintendence”. Pharmacovigilance is fastest emerging as an important approach for the early detection of unwanted effects of the drugs and to take appropriate regulatory actions if necessary. National Pharmacovigilance Centre CDSCO has initiated a country-wide Pharmacovigilance program under the aegis of DGHS, Ministry of Health and Family Welfare Government of India. India is becoming a hub for clinical research activities due to its large population, high enrolment rate and low cost 3. Moreover, the lag period when a drug is placed for the first time on the market in USA, Europe, and Japan or somewhere in the world and its subsequent availability in India has decreased considerably. As a result, for such drugs the long term safety data is not available and the time of their marketing in India. This is clear by the fact that all the high profile drugs that have been recently withdrawn were available in Indian market. In such cases, the Indian regulatory agencies cannot count on the experience of other market to assess benefit risk balance of a drug. The term “postmarketing surveillance” first appeared in the 1960s and was attributed to Bill Inman, who defined it as “techniques for detecting and measuring the incidence of adverse drug reactions [including] all kinds of schemes for generating or testing hypotheses”. It has also been defined as the systematic surveillance and scientific study of all intended and unintended effects of medicines on human health, after their release for marketing”, which in effect circularly defines “surveillance” as “surveillance”.^[19] Postmarketing surveillance refers to analysis of data accumulated typically for the purpose of detecting adverse effects after a medicinal product has been given a marketing authorization by a regulatory body. The term normally refers to the processes of signal detection and signal evaluation, but it may be confused with the term “pharmacovigilance”, which first appeared in French in the late 1960s, when the term “pharmacovigilance intensive” and “pharmacovigilance spontanée” In fact, the World Health Organization’s definition of pharmacovigilance is “the science and act adverse effects or any other possible drug-related problems”.

Resources For Pharmacovigilance Centres

National Centres have to maintain high standards of data protection when information has been received on patients who have not given their informed consent. Patients should also be helped to understand that the information they provide is likely to contribute to an international understanding of drug safety.^[20]

The National Pharmacovigilance Centres

At present, post-marketing surveillance of medicines is mainly co-ordinated by national pharmacovigilance centres. In collaboration with the Uppsala Monitoring Centre (UMC) the National Centres have achieved a great deal in.

- a) Promoting the reporting of adverse reactions.
- b) Collecting case reports of adverse reactions.
- c) Clinically evaluating case reports.
- d) Collating, analyzing and evaluating patterns of adverse reactions.
- e) Distinguishing signals of adverse reactions from “noise”.
- f) Recommending or taking regulatory action in response to findings supported by good evidence.
- g) Initiating studies to investigate significant suspect reactions.
- h) Alerting prescribers, manufacturers and the public to new risks of adverse reactions and
- i) Sharing their reports with the WHO Programme for International Drug Monitoring.
- j) The number of National Centres participating in the WHO International Drug Monitoring Programme has increased from 10 in 1968 when the Programme started to 67 in 2002. The centres vary considerably in size, resources, support structure, and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity. The following books shall be provided to various centres as identified by the NPAC.

1. Meyler's Side Effects.
2. AHFS Drug Information hand book.
3. Martindale/online.
4. Davies Text Book of ADR.
5. Physician's Desk reference.
6. British National Formulary.

National Pharmacovigilance Programme

The Program aims to foster the culture of ADR notification in its first year of operation and subsequently aims to generate broad-based ADR data on the Indian population. Sponsored and coordinated by the country's central drug regulatory agency (CDSCO). Peripheral Pharmacovigilance Centre (PPCs). Regional Pharmacovigilance Centers (RPCs). Zonal Pharmacovigilance Centre (ZPCs). Monitor clinical status of patients, identify the correct

ADRs not side effects, get more information, investigate at hospital level, help doctors to fill-up the forms, keep patient's record if more information needed.

Valid Report

The Individual Case Safety Report (ICSR) is a Health Level Seven standard for the capture of the information needed to support the reporting of adverse events, product problems or consumer complaints associated with the use of FDA regulated products or a report received by a company or agency which describes an adverse event. Reports, describing serious adverse drug reactions that needed to be exchanged in pharmacovigilance between the various parties in accordance with community legislation, are referred to as ICSRs or safety reports. An ICSR has to contain the data elements as defined in the related guidance documents adopted at International level. Any supporting information related to the Case must be sufficiently described within the ICSR with the reference to the documents that are held by the sander, which may need to be provided on request, it is recognised that it is often difficult to obtain all details on specific Case, However the complete information related to an individual case, that is available to the sender, has to be reported in accordance with the legal requirements as set out in the community legislation. This may also include Causality assessment if requested by competent authorities. It is the responsibility of the sender to structure all information available in accordance with the elements as defined with in ICH E2B specifications. In addition, whenever more recent information on an individual case to be provided and not only partial information e.g. Changes or Updates.

The minimum information needed for a Valid Report according to ICH E2B

- a) One identifiable patient.
- b) Identifiable reporter.
- c) One reaction / event &
- d) One suspected Drug.

It is important to harmonise the way to gather and, if necessary, to take action on important clinical safety information arising during clinical development. Thus, agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice standards in this area. The initiatives already undertaken for marketed medicines through the CIOMS-1 and CIOMS-2 Working Groups on expedited (alert) reports and periodic safety update reporting, respectively, are important precedents and models. The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new,

important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product). An "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

Expected adverse event/reaction

The following documents or circumstances will be used to determine whether an adverse event/reaction is expected.

1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country.
2. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be.
 - a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis
 - b) hepatitis with a first report of fulminant hepatitis. Whereas, Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase.

Objective Periodic safety updates reports

The main objective of a PSUR is to present a comprehensive and critical analysis of the risk benefit balance of the medicinal product taking into account new or emerging information, in the context of cumulative information, on risks and benefits. The PSUR is therefore a tool for post-authorisation evaluation at defined time points in the lifecycle of the product. For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicine in everyday medical practice and long term use in the post-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trials. A different benefit-risk profile may emerge as pharmacovigilance reveals further information about safety. The marketing

authorisation holder should therefore re- evaluate the risk-benefit balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance and risk management to facilitate optimization of the risk-benefit balance through effective risk minimization. The PSUR should not be used to provide the initial notification of significant new safety information or, as a general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted.

Table-1: List of ADR Monitoring Centres Under Pharmacovigilance Programme of India (PVPI).

S.No	Institute	Address
1	Department of Pharmacology, AIIMS	New Delhi
2	Department of Pharmacology, Therapeutic toxicology, Govt Medical College, Jammu	Jammu
3	Department of Pharmacology, R.G. Kar Medical College, Kolkata	West bengal
4	Department of Pharmacology, PGIMER,	Chandigarh
5	Department of Pharmacology, Lady Hardinge Medical College, New Delhi	New Delhi
6	Department of Pharmacology, Seth GS Medical College & KEM Hospital, Parel	Mumbai
7	Department of clinical & experimental Pharmacology, School of tropical Medicine, Chittaranjan Avenue	Kolkata
8	Department of Pharmacology, JIPMER	Pondicherry
9	Department of Pharmacology, medical college, guwahati	Assam
10	Institute of Pharmacology, SAIMS Medical College, Indore	Ujjain
11	Department of Pharmacology, GSVM Medical College, Swaroop Nagar, Kanpur	U.P,
12	Department of Pharmacology, Pandit Bhagwat Dayal Sharma, Post Graduate Institute of Medical Sciences, Rohtak	Haryana
13	Department of Pharmacology, Dayananda Medical college and Hospital, Ludhiana	Punjab
14	Department of Pharmacology, sheri Kashmiri Institute of Medical Sciences, Srinagar	J & K
15	Himalayan Institute of Medical Sciences, Dehradun	Uttarakhand
16	Department of Pharmacology, SMS Medical College, Jaipur	Rajasthan
17	Department of Pharmacology, Santosh Medical University, Santosh Nagar, Ghaziabad	New Delhi
18	Department of Clinical Pharmacology, Christian Medical College, Vellore	Tamil Nadu
19	Institute of Pharmacology, Madras Medical College	Chennai

Table-2:

Causality term	Assessment criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) Rechallenge satisfactory, if necessary
Probable/ Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations
Conditional / Unclassified	Event or laboratory test abnormality More data for proper assessment needed, or Additional data under examination
Unassessable / Unclassifiable	➤ Report suggesting an adverse reaction ➤ Cannot be judged because information is insufficient or contradictory ➤ Data cannot be supplemented or verified

CONCLUSION

The three major regulatory agencies including the US FDA, European medicine Agency (EMA) and Medicines and health care product regulatory Agency (MHRA) have started publication of drug safety news about selected post marketing drug safety reviews, important emerging drug safety issues and recently approved drugs safety products. Pharmacovigilance remains a dynamic clinical and scientific discipline. It continues to play a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines. When adverse effects and toxicity do appear especially when previously unknown it is essential that these are reported, analyzed and their significance communicated effectively to an audience that has the knowledge to interpret the information. Which carry an inevitable and some-For all medicines there is a trade-off between the benefits and the potential for harm. The harm can be minimized by ensuring that medicines of good quality, safety and efficacy are used rationally. Pharmacovigilance looks at all available information to assess the safety profile of a drug. Pharmacovigilance should also take the benefit of the drug in account.

Pharmacovigilance required for systematically identifying and correlating drugs and side effects and taking corrective actions, especially for the product launching first time in India.

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