



Detection, Assessment, Understanding and Prevention of Adverse Effects: Pharmacovigilance: A Review

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ABSTRACT

Pharmacovigilance is an important and integral part of clinical research. Despite its 40 years history, 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, analysed 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 and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. Taking medicines and prescribing them are among the commonest of activities of people who are unwell and of those who care for them. It makes sense that those medicines should be monitored to equally demanding standards as those evident in the development and evaluation of drugs and that prescribing habits and the extent of rational and cost-effective use should be reviewed. Responsibility for the holistic approach to drug safety that is encompassed in the science and practice of pharmacovigilance as reflected in this article has to be shared if ideal practice is to be achieved. The scientists, clinicians, pharmaceutical manufacturers, drug developers, regulators, public policy makers, patients and the general public all have their own complementary roles in achieving what is envisaged.

Keywords: Pharmacovigilance, National Pharmacovigilance Programme, Role of Pharmacovigilance, Risk Management, Good Pharmacovigilance Practice, Pharmacoepidemiologic Studies.

INTRODUCTION

Pharmacovigilance (abbreviated as PV or PhV) also known as drug safety, 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. Generally speaking, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological, herbalism and traditional medicines with a view to¹:

- Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure and
- Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.
- Identifying new information about hazards associated with medicines

Pharmacovigilance is therefore an activity contributing to the protection of patients and public health.

Pharmacovigilance starts from the clinical stage and continues throughout the product life cycle of the drug, mainly divided as pharmacovigilance during pre-

marketing (that is clinical phase) and post-marketing. The process of collection of such information about a drug begins in phase I of clinical trial, before approval of the drug, and continues even after approval, several post-market safety studies are conducted, with many made mandatory by drug regulatory agencies around the world.

The etymological roots are: *pharmakon* (Greek Word) means "drug" and *vigilare* (Latin Word) means "to keep awake or alert, to keep watch." Pharmacovigilance is gaining importance for doctors and scientists as the number of stories in the mass media of drug recalls increases.

Because clinical trials involve several thousand patients at most, less- common side effects and ADRs are often unknown when a drug enters the market. Even very severe ADRs such as liver damage are often undetected because study populations are small. Post marketing surveillance uses tools such as data mining of spontaneous reporting systems and patient registries, and investigation of case reports to identify the relationships between drugs and adverse events.

TERMINOLOGY²

Pharmacovigilance is particularly concerned with **Adverse Drug Reactions** (ADRs).

Adverse Drug Reactions are officially described as a response to a drug which is noxious and unintended including lack of efficacy of drug and which occurs at



doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. It also includes overdose, misuse and abuse of drug.

Adverse Effect

An appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment or alteration of the dosage regimen or withdrawal of the product.

This definition can include medication error which is a major cause of adverse effects due to drugs, it includes harm from counterfeit drugs, it includes accidental overdose, it includes all medicinal products (so it includes delivery systems such as inhalers) and it includes quality problems and excipients. This definition therefore includes adverse effects from a much broader range of causes. On the other hand the latter part of the definition focuses on the value of knowing about adverse effects: we want to know about those we can do something about in terms of prevention, diagnosis or treatment. 'Adverse reaction' and 'adverse effect' are interchangeable but adverse effect is more patient-centred and adverse reaction is more drug-centred.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

Adverse Event/ Adverse Experience

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.

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 information³.

This is considerably outmoded as a general definition. It retains some value in respect of signals from 'spontaneous reports', but it fails to include signals from published series or from examination of health care records, laboratory experiments, or from clinical trials or epidemiological studies. 'Incompletely documented previously' is also a statement which requires

interpretation. A single definition of a Signal is very challenging, because of the different types of information that might constitute a signal in different contexts. A basic difficulty is, what is new and to whom?

Aronson and Hauben considered all definitions they could find and then produced a new one:

"Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention and is judged to be of sufficient likelihood to justify verifiable and when necessary, remedial actions."

Serious Adverse Event or Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death or
- Requires inpatient hospitalisation or prolongation of existing hospitalisation or
- Results in persistent or significant disability/incapacity or
- Is life-threatening

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided:

The term "severe" is not synonymous with serious. In the English language, "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe), the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on patient/ event outcome or action criteria serves as guide for defining regulatory reporting obligation⁴.

This definition is used almost globally. One comment is important: the terms 'life threatening' and 'requires inpatient hospitalisation' are value judgement and context dependent, respectively. It is particularly important to reflect that whether or not a patient is admitted to hospital or not will vary from situation to situation.

IMPORTANCE OF PHARMACOVIGILANCE⁵

Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product lifecycle. Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline.

While major advancements of discipline of pharmacovigilance have taken place in the western countries not much has been achieved in India. 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.

Pharmacovigilance is not new to India and has in fact been going on from 1998, when India decided to join the Uppsala centre for adverse event monitoring. The importance of pharmacovigilance is withdrawals the regulatory agencies, media; consumers have become more aware about the benefit and risks of medicines. Spontaneous reporting of adverse drug reaction and adverse events is an important tool for gathering the safety information for early detection. In recent years many Indian companies are increasing the investment in research and development and are enhancing their capacity to develop and market new drugs with their own research efforts.

Further India is becoming a hub for clinical research activities due to its large population, high enrolment rate and low cost. 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 drug⁶.

There by stressing the importance of developing their own adequately designed pharmacovigilance system in India. For an effective pharmacovigilance system to be functional and efficient, all the stake holders need to be alert and attentive throughout the life cycle of a medicinal product in the market. The office of the Drugs Controller General of India (DCGI) has been making sincere attempts for the implementation the National Pharmacovigilance Programme (NPP) in India. To full fill the pharmacovigilance obligations for its marketed products, as per regulations, a generic company in India is mainly to carry out the following activities. Collection monitoring and reporting of spontaneous adverse reactions, including expedited reporting of serious unexpected adverse reactions and preparations. Pharmacovigilance help to prevent adverse drug effects: Medical science has grown in leaps and bounds since the days of Hippocrates. Modern day pharmaceutical drugs are really life saves. They have increased life expectancy and improved the quality of life for millions of people. But there is the other side of the coin as well; these drugs sometimes have very adverse effects that can even be life threatening⁷.

There is a need to monitor the effects of drugs before and after it's successfully tested and launched in the market. Pharmacovigilance involves the monitoring and assessing

the quality of drugs, detection and preventing of any adverse effects of drugs. Pharmacovigilance involves evaluating information provided by health care providers, pharmaceutical companies and patients in order to understand the risk and benefits involved with a particular drug. Pharmaceutical companies spend millions of dollars and a considerably long time in developing new drugs.

They again spend a lot of money in conducting clinical trials before the drugs are approved and launched in the market. It is recognized that information technology (IT) has entered and transformed the world of health care and clinical medicine in which the work of doctors and the care of patients proceed with higher quality, efficiency and lower costs. It is also no secret that IT has merged in to clinical safety practice and sparks the creation of worldwide pharmacovigilance systems for safety signal detection.

The IT transformative force and health it, adoption have fundamentally changed the conduct of clinical research, practice of medicines and medicinal safety monitoring. In today's world pharmacovigilance pushes new boundaries and it is no longer sufficient to simply report adverse events along with efficacy and quality requirements.

Regulators are demanding proactive surveillance programs that include comprehensive risk management plans and signal detection/ analysis throughout a clinical products life cycle.

- This addresses what exactly is pharmacovigilance?
- What do we know of its benefits and risks?
- What challenges are out there preventing its wide spread usage?
- And what does the future hold for pharmacovigilance in worldwide medicine?

It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post marketing phases through judgment as to whether and how this might happen lies with the regulators. The stronger the national systems of pharmacovigilance and adverse drug reaction (ADR) reporting, the more likely reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Careful safety monitoring is not restricted, however to new drugs or to significant therapeutic advances. It has a critical role to play in the introduction of generic medicines, and in review of the safety profile of older medicines already available as well, where new safety issues may have arises. While spontaneous reporting remains a corner stone of pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports are unable to determine the



frequency of an ADR attribution to a product or its safety in relation to a comparator.

More systematic and robust epidemiological methods that take in to account the limitations of spontaneous reporting or post marketing studies are required to address these key safety questions. They need to be incorporated in to post marketing surveillance programs. This includes the use of pharmacoepidemiologic studies⁸.

These activities are undertaken with the goal of identifying adverse events and understanding to the extent possible, their nature, frequency and potential risk factor. Pharmacovigilance in principle involves the identification and evaluation of safety signals. Safety signals refer to a concern about an excess of adverse events compared to what would be expected to be associated with products use.

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. Pharmacovigilance is particularly concerned with adverse drug reactions. Many other issues are also relevant to pharmacovigilance science are substandard medicines, medication errors, lack of efficacy reports, use of medicines for indications that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, assessment of drug related mortality, abuse and misuse of medicines, adverse interactions of medicines with chemicals, other medicines and food.

AIM OF PHARMACOVIGILANCE⁹

- Improve patient care and safety in relation to the use of medicines, all medical and Para medical interventions.
- Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.
- Pharmacovigilance keeps track of any drastic effects of drugs.
- Improve public health and safety in relation to the use of medicines.
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
- Promote understanding, education, clinical training in pharmacovigilance and its effective communication to the public.

These processes involved in the clinical development of medicines. Once put onto the market, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population. At this point most medicines will only have been tested for short-term safety and efficacy on a

limited number of carefully selected individuals. In some cases as few as 500 subjects, and rarely more than 5000, will have received the product prior to its release¹⁰.

For good reason, therefore it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions post release.

More information is generally needed about use in specific population groups, notably children, pregnant women and the elderly and about the efficacy and safety of chronic use, especially in combination with other medicines. Experience has shown that many adverse effects, interactions (i.e. with foods or other medicines) and risk factors come to light only during the years after the release of a medicine

KEY PLAYERS OF PHARMACOVIGILANCE

Key players of pharmacovigilance in national drug policy are: Government, Industry, Hospitals and Academia, Medical and Pharmaceutical Associations, Poisons and medicines information centres, Health professionals, Patients, Consumers, Media and World Health Organization. Key elements of pharmacovigilance in national drug policy are:

- Establishment of national pharmacovigilance systems for the reporting of adverse events, including national and, if appropriate, regional pharmacovigilance centres.
- Development of legislation/ regulation for medicine monitoring.
- National policy development (to include costing, budgeting and financing).
- Continuing education of health-care providers on safe and effective pharmacotherapy.
- Provision of up-to-date information on adverse reactions to professionals and consumers.
- Monitoring the impact of pharmacovigilance through process indicators and outcome.

The purpose of the programme is to collate data, analyse it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public⁹.

The management of the risks associated with the use of medicines demands close and effective collaboration between the key players in the pharmacovigilance. Sustained commitment to such collaboration is vital if the future challenges in pharmacovigilance are to be met and if the discipline is to continue to develop and flourish.

Those responsible must jointly anticipate, describe and respond to the continually increasing demands and expectations of the public, health administrator policy officials, politicians and health professionals. However there is little prospect of this happening in the absence of



sound and comprehensive systems which make such collaboration possible. The constraints typically include lack of training, resources, political support, and most especially scientific infrastructure. Understanding and tackling these are an essential prerequisite for future development of the science and practice of pharmacovigilance. The provision of good quality, safe and effective medicines and their appropriate use is the responsibility of national governments. The establishment of a national medicine regulatory agency and a designated centre for the study of adverse reactions are central to the achievement of these functions.

Multidisciplinary collaboration is of great importance, in particular, links need to be forged between various departments of the ministry of health and also with other stakeholders, such as the pharmaceutical industry, universities, nongovernmental organizations (NGOs) and those professional associations having responsibility for education on rational use of medicines and pharmacotherapy monitoring.

NATIONAL PROGRAMME OF PHARMACOVIGILANCE

Before a product is marketed, experience of its safety and efficacy is limited to its use in clinical trials, which are not reflective of practice conditions as they are limited by the patient numbers and duration of trial as well as by the highly controlled conditions in which Clinical Trials are conducted. The conditions under which patients are studied during the pre-marketing phase do not necessarily reflect the way the medicine will be used in the hospital or in general practice once it is marketed¹¹.

Information about rare but serious adverse drug reactions, chronic toxicity, use in special groups (e.g. pregnant women, children, elderly) and drug interactions is often incomplete or not available. Certain adverse drug reactions may not be detected until a very large number of people have received the medicine.

Pharmacovigilance is therefore one of the important post-marketing tools in ensuring the safety of pharmaceutical and related health products.

- Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use.
- Providing information to users to optimise safe and effective use of medicines.
- Monitoring the impact of any action taken.

PHARMACOVIGILANCE IN NATIONAL DRUG POLICY

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MILESTONES OF THE PROGRAMME

- **Short-Term Objectives:** To foster a culture of notification.
- **Medium-Term Objectives:** To engage several healthcare professionals and NGOs in the drug.
- Monitoring and information dissemination processes.
- **Long-Term Objectives:** To achieve such operational efficiencies that would make Indian.
- National Pharmacovigilance Programme a benchmark for global drug monitoring.
- Endeavours

OUTLINE OF THE NATIONAL PHARMACOVIGILANCE PROGRAMME^{11,12}

The National Pharmacovigilance Programme aims to provide adverse drug reaction data related to various drugs available in the country to the central drugs regulatory authority i.e. Central Drugs Standard Control Organisation (CDSCO). The programme will be coordinated by the National Pharmacovigilance Advisory Committee (NPAC) constituted by the Ministry of Health & Family Welfare. The Programme would comprise of the following steps:

Step 1- Identifying various centres across the country for capturing ADR related data

- 1) Set up 2 Zonal Pharmacovigilance Centres (ZPC) to coordinate the nationwide programme (AIIMS for North and East, KEM- Mumbai for South and West) Zonal Centres shall provide a room and other requisite infrastructure, e.g. a PC with internet facility, access to fax, telecom etc.
- 2) Identify 5 Regional Pharmacovigilance Centres (RPC) across the country.
 - Ideally medical colleges with interested and initiated pharmacologists.
 - Can provide a small area (approx. 100 sq. feet).
 - Can deploy a pharmacologist for the Programme.
- 3) **Identify Peripheral Pharmacovigilance Centres (PPC):** At least one teaching hospital in each state and union- territory and some other leading medical institutions, clinics or pharmacies in the area under each RPC.
 - Ideally centres that have internet facility



- Manned by doctors/ pharmacists who are enthusiastic about carrying out research activities e.g. monitoring ADRs
- Visited by not less than a total of 50 patients daily in any/ all of the following departments: Medicine, Gynaecology, Paediatrics, Orthopaedics, Cardiology and Oncology

Step 2- Training and Coordination

To ensure harmonized implementation of the Programme efforts shall be made to arrive at a uniform understanding of the operational systems along with standardized formats to document and analyse ADRs. An induction training programme shall be arranged for healthcare professionals participating in the NPP¹³.

Intensive interaction/ training sessions will be organized for all participants to:

- 1) Clearly define their individual and team roles and responsibilities.
- 2) Set operational benchmarks e.g. Each PPC to record at least 30 AEs (Adverse Events) each month (statistically speaking 30 AEs in about 1500 patients who visit each month would be quite easy to record). Completed AE forms shall be forwarded to the concerned RPC at the end of each month.

Each RPC

- To collate and scrutinize the data received.
- To perform the causality analysis of all 120 to 150 forms received every month.
- **To submit a monthly report-** Prepared in a specific form to be forwarded to National Pharmacovigilance Centre (NPC) every month.
- To report any alarming or critical ADRs to NPC along with supporting evidence.

Each ZPC

- To collate the data (approx. 1000- 1200 forms) received from RPCs.
 - To verify/ validate the causality analysis.
 - To prepare MIS reports for NPC in a specified format.
 - To pass on the final data to WHO Uppsala Centre for their global data pool.
 - To publish a periodic newsletter.
- 3) Evolve SOPs for generating and forwarding ADR data and for general conduct of the Programme (Zonal centres to prepare SOPs which must ensure that the Programme is conducted in compliance with this Protocol).
 - 4) Impart relevant skills for carrying out ADR data capture namely

- Appropriate communication skills to elicit ADR related information.
- For recording ADR information through hands on training.
- For meticulous collation and completeness of data.
- For fostering notification culture.

These training programs and interaction meetings shall be held every 6 months after the initial training. Besides, continuous communication through emails, carrying relevant information related to ADR monitoring methods shall be maintained among the participating centres.

BROAD OBJECTIVES OF THE PROGRAMME

- To foster the culture of AE notification and reporting to establish a viable and broad-based ADR monitoring program in India¹⁴.
- Specific objectives of the Programme.
- To create an ADR database for the Indian population to create awareness of ADR monitoring among people to ensure optimum safety of drug products in Indian market to create infrastructure for ongoing regulatory review of PSURs.

COORDINATOR'S ELIGIBILITY AT DIFFERENT TIERS OF NPP

- **PPC-** Any physician (primary- care or specialist), pharmacist.
- **RPC-** A pharmacologist, preferably not below the rank of an assistant professor, attached to a medical college.
- **ZPC-** A pharmacologist, not below the rank of a professor, attached to a medical college

NATIONAL PHARMACOVIGILANCE CENTRES ARE RESPONSIBLE FOR:

- Promoting the reporting of adverse reactions.
- Collecting case reports of adverse reactions.
- Clinically evaluating case reports.
- Collating, analyzing and evaluating patterns of adverse reactions.
- Distinguishing signals of adverse reactions from "noise".
- Recommending or taking regulatory action in response to findings supported by good evidence.
- Initiating studies to investigate significant suspect reactions.
- Alerting prescribers, manufacturers and the public to new risks of adverse reactions; and
- Sharing their reports with the WHO Programme for International Drug Monitoring.



National centres have played a significant role in increasing public awareness of issues relevant to the safety of medicines. As a result, in some countries, pharmacovigilance is increasingly being seen as much more than a regulatory activity as it also has a major part to play in clinical practice and the development of public health policy¹⁵. This development is partly attributable to the fact that many national and regional centres are housed within hospitals, medical schools or poison and medicine information centres and is in collaboration with a Medicines Regulatory Authority (MRA). The scope of activities of national centres has expanded to include communication of information about the benefits, harm and effectiveness of medicines to practitioners, patients and the public.

The Central Drugs Standard Control Organization (CDSCO) is initiating a country-wide pharmacovigilance programme under the aegis of DGHS, Ministry of Health & Family Welfare, and Government of India. The programme shall be coordinated by the National Pharmacovigilance Centre at CDSCO. The National Centre will operate under the supervision of the National Pharmacovigilance Advisory Committee to recommend procedures and guidelines for regulatory interventions.

The overall objective as per the National Pharmacovigilance Programme will be:

- To monitor safety of the drugs and provide structured inputs for appropriate regulatory interventions.
- To create awareness about ADR monitoring in India.

Regional centres will be the secondary pharmacovigilance centres under the National Pharmacovigilance Programme.

To carry out the functions as envisaged in the "Protocol for the National Pharmacovigilance Programme" a Coordinator will have to be designated who will be in-charge of the pharmacovigilance activities at the designated regional centre¹⁸.

By accepting to participate in the National Pharmacovigilance Programme all centres explicitly agree that all pharmacovigilance activities at their institutions shall be performed in strict consonance with the National Pharmacovigilance Programme appended here (Coordinators of the centres and heads of the institutions are advised to carefully go through the Protocol prior to joining the programme).

Outline of tasks to be carried out: The National Pharmacovigilance Programme encourages the reporting of all suspected adverse reaction to drugs and other medicinal substances including herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions would be important since it may highlight a wide spread prescribing problem.

Regional Centre is expected to carry out the following tasks: To maintain a log of all ADE notification forms received and forwarded To receive blank ADE forms and acknowledge receipt To fill or get filled the ADE forms Collect & collate Adverse Drug notifications from Peripheral as well as own centres Receive Adverse Drug Events (ADE) forms and maintain log of all ADE forms received and forwarded.

- Correspond with Peripheral Centres, provide them with general technical support, coordinate and monitor their functioning.
- Identify and delegate a pharmacologist for management of pharmacovigilance tasks.
- Carry out (and/ or review) data causality analysis of all ADEs.
- To forward all duly-filled ADE forms [those generated at the same centre and those received from immediate lower-level centre] as per pre-determined time line.
- Liaise with health care professionals in order to inculcate/ foster the culture of ADE reporting/ notification by acknowledging the cooperation by the notifier and share with the notifier relevant feedback from higher centre.
- Organize and attend training programmes/ interactive meetings for all peripheral centres falling under the respective regional pharmacovigilance centres.
- To provide updates, reports and such other information as may be required by the National Pharmacovigilance Advisory Committee and to attend their meetings.
- To conduct special pharmacovigilance projects on various drugs which may be of special concern or interest to CDSCO/ Government of India.
- To maintain account of the funds provided under this program as per your institution's systems; to review the account statement received from peripheral centres, and provide a consolidated statement to the zonal centre. Carryout audits to ensure compliance with the program, enlist non-compliance, establish corrective measures and implement them at regional centres and oversee their implications at peripheral centres

In line with the size & patient intake of the institutions where it is based, the regional centre shall ensure a minimum 50 adverse event reporting's every month and this number must be increased periodically. This number will be in addition to the number of reports generated by the peripheral centres falling under respective regional centres.



What to Report?

The National Pharmacovigilance Programme (NPP) shall encourage reporting of all suspected drug related adverse events, including those suspected to have been caused by herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions would be important since it may highlight a widespread prescribing problem.

The programme particularly solicits reports of:

- All adverse events suspected to have been caused by new drugs and 'Drugs of current interest' (List to be published by CDSCO from time to time).
- All suspected drug interactions.
- Reactions to any other drugs which are suspected of significantly affecting a patient's management, including reactions suspected of causing: Death, Life-threatening (real risk of dying), Hospitalisation (initial or prolonged), Disability (significant, persistent or permanent), Congenital anomaly and required intervention to prevent permanent impairment or damage.

What can Report?

Any health care professionals (Doctors including Dentists, Nurses and Pharmacists) may report suspected adverse drug events. The Programme shall not accept reports from lay members of the public or anyone else who is not a health care professional.

Where to Report?

After completion the form shall be returned/ forwarded to the same pharmacovigilance Centre from where it was received. Reporting can be done to any one of the country wide pharmacovigilance Centres nearest to the reporter (Complete list of pharmacovigilance Centres is available at www.cdsc.nic.in). In case of doubt the form may be sent to the national pharmacovigilance centre at: Central Drugs Standard Control Organisation, New Delhi.

What happens to the information submitted?

The information in the form shall be handled in strict confidence. Peripheral Pharmacovigilance Centres shall forward the form to the respective Regional Pharmacovigilance Centres who will carry out the causality analysis. This information shall be forwarded to the Zonal Pharmacovigilance Centres. The data will be statistically analysed and forwarded to the global Pharmacovigilance Database managed by WHO Uppsala Monitoring Centre in Sweden. The final report based on the analysed data will be periodically reviewed by the National Pharmacovigilance Advisory Committee constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with the responsibility to review data and suggest any regulatory interventions that may be required with respect to the drug/ drugs or class of drugs.

ROLES AND RESPONSIBILITIES^{16, 17}

Where established, the national pharmacovigilance centre will be responsible for the development of pharmacovigilance in the public health system will promote pharmacovigilance in the PHPs and sensitize professionals and public health staff to the reporting of adverse reactions and irrational use of medicines.

Role of Pharmacist

- Participate in spontaneous Reporting of Adverse Events, Also report (even if no adverse event).
- Medication errors.
- Exposure during pregnancy.
- 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.

Patients and the Public

Public awareness about adverse reactions, early reporting and management are essential for ensuring patient confidence, in and adherence to, pharmacotherapy. In some countries patient reporting is accepted and can add value, but this needs to be separate from involvement of patient interest groups can be sought while formulating the programme and should be part of the feedback-communication link.

Primary Health-Care Workers

It is the responsibility of the primary health-care provider to detect, investigate, manage and report ADRs. These staff will need training on the importance of adverse reactions, diagnosis, basic principles of causality assessment and the important elements of the adverse reactions reporting form.

Patient education is an important role of the primary health-care provider. Educating the public on ADRs is important for promoting adherence. Counselling and explanation about adverse reactions will promote patients' confidence and adherence.

The reporting of adverse reactions needs continuous stimulation. It is important to achieve a positive attitude towards pharmacovigilance. To encourage reporting, the following steps should be of help:

- Easy access to reporting forms and Training.
- Acknowledgement of receipt of a report and provision of feedback to the reporter.
- Participation of reporting staff in pharmacovigilance meetings, and of pharmacovigilance staff in professional meetings and



- Collaboration with the national pharmacovigilance centre.

Other Health-Care Workers

Health-care workers outside the government system should also report adverse reactions. These would include among others, nongovernmental organizations and charitable health facilities.

District Investigation Team

The district investigation team plays a central role in monitoring adverse reactions. The team should comprise a clinician in the district hospital, head nurse, pharmacist and district health officer or programme manager. The team is responsible for following up adverse reactions reported from all the health facilities within their district.

(In the case of vertical programmes the specific programme manager will be responsible for medicines pertaining to that programme.) The team will play an important role in collaboration with and encouragement of reporting by primary health centre staff and hospital staff. Their detailed follow-up of suspected ADRs will be used to assess causality.

When dealing with reports of ADRs, the district investigation team should:

- Seriousness (including all deaths).
- Severity; exposure to medicine during pregnancy.
- Apparent signals of new reactions and
- Patterns of suspected reactions which although not serious, may affect adherence and the success of the programme.

Refer all reports to the national pharmacovigilance coordinator for processing and review by the Expert Safety Review Panel (ESRP).

National Pharmacovigilance Coordinator

The coordinator, who should be on the staff of the national pharmacovigilance centre, should function as the focal point for the national pharmacovigilance system in the PHP.

Ideally this should be a full-time position. The responsibilities of the national coordinator would include coordination, communication, integration, training and supervision of the pharmacovigilance-related activities of the district investigation teams. This person would also serve as member or secretary of the national ESRP.

The coordinator should ensure that the ADR reports are processed appropriately for assessment by the ESRP. These would generally fall into one of three categories:

- Reports selected for investigation by the district investigation team, which should be considered in detail.

- Reports considered to be a signal of a new adverse reaction and
- All other reports, which may be presented in summary format, so that an overall reaction profile of the medicine can be obtained.

National Medicines Regulatory Authority

The regulatory authority will receive reports and recommendations from the ESRP. It will perform risk assessment and consider options for regulatory action which may involve requiring the manufacturers to make changes in the labelling of their product or may be a restriction in the use of the product, a temporary suspension or complete withdrawal. The regulatory authority may liaise with other national MRAs and it should always pass on the information on any action taken to WHO (World Health Organisation).

Pharmaceutical Industry and Marketing Authorization Holders

Pharmaceutical manufacturers are legally responsible for the safety and effectiveness of medicines while the product is available in the marketplace. They should provide medicines of good quality and have stewardship of their products. As essential players in the provision of medicines, they should be kept informed of the results of monitoring and relevant decisions. They also have a duty towards assessing the effectiveness and safety of a PHP and the benefits to patients. They should report adverse reactions both to the national pharmacovigilance centre (and in the absence of such to the MRA) or PHP and in countries with no MRA they should also report to WHO through the disease control PHP.

Media

It is important that the media are involved from the start of a PHP and that the need for the programme is publicized together with the need for pharmacovigilance. The pharmacovigilance programme should be explained and good lines of communication should be set up between the media and the ESRP or the designated liaison person, to ensure the availability of authoritative information. The need for good information should be anticipated so that potential crises can be dealt with quickly and effectively, and public confidence maintained¹⁹.

When communicating with the media, the following information should be available:

- A complete account of any event of concern and its appropriate context (in terms that will be understood by the lay public), e.g. a clear statement that an event is an isolated occurrence, to prevent concern that it may be widespread.
- The likelihood that there will be new cases linked to therapy with the medicine.

- An outline of actions taken or planned (depending on the stage, this will range from a plan of action to a completed investigation).
- The cause of the event (when identified with reasonable certainty).
- The corrective action that has been or will be taken.
- Guidance to the public on how to respond to concerns over the medicine including contact information for reporting further adverse events.

It is useful to assess the impact of media communications on public awareness and attitudes as this will assist the development of future communication strategies.

The roles of WHO and the International Advisory Committee:

At an international level WHO will play a key role. While supporting countries to conduct PHPs, WHO and its regional offices have a responsibility to promote the establishment and building of sustainable safety monitoring systems. WHO will take a lead role in supporting Member States in the safe use of medicinal products, WHO will serve as a repository for information from both pharmacovigilance programmes and PHPs, and will disseminate this information appropriately¹⁹.

WHO will identify areas requiring research and encourage and support initiatives to conduct operational research. It will assist countries to define and develop policy on monitoring the safe use of medicinal products and it will respond to controversial issues on the safety of medicines that threaten the use of medicines in a national or international PHP. It will promote and encourage uniformity of terminology and will promote and develop resource materials and provide leadership in training and capacity development.

Advisory Committee on Safety of Medicinal Products (ACSMP):

An Advisory Committee has been established by WHO to advise on issues that:

- Are important to national or international programmes and have the potential to affect them adversely if not resolved.
- Cannot be met by structures and/or institutions and/or systems that are already available.
- Respond to identified needs of a country that may be beyond the capability of the country or countries themselves; such responses should be made within an appropriate period of time, taking into account any existing information and the urgency of the issue²⁰.

WHO Programme for International Drug Monitoring

National pharmacovigilance centres are functioning as an international network coordinated by the WHO Programme for International Drug Monitoring. The

Programme has achieved much in improving the activities, support and recognition of individual national pharmacovigilance centres²¹.

It plays a key role as a communication and training centre and clearing-house for information on the safety of medicines. The WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden manages the international database of adverse reaction reports received from national centres. In 2005 this database held over 3.5 million case reports. The majority of contributing national centres has ready electronic access to these. The Centre has established standardized reporting by all national centres and has facilitated communication between countries to promote the rapid identification of signals. The terminologies developed within the WHO programme for coding adverse reactions to medicines have been widely adopted by national centres, manufacturers and medicine regulators.

GOOD PHARMACOVIGILANCE PRACTICES

The Premarketing Guidance and the Pharmacovigilance Guidance focus on premarketing and post marketing risk assessment respectively. The Risk MAP Guidance focuses on risk minimization²². Together risk assessment and risk minimization form what FDA calls risk management. Specifically risk management is an iterative process of

- 1) Assessing a product's benefit-risk balance.
- 2) Developing and implementing tools to minimize its risks while preserving its benefits.
- 3) Evaluating tool effectiveness and reassessing the benefit-risk balance and
- 4) Making adjustments as appropriate to the risk minimization tools to further improve the benefit-risk balance.

This four part process should be continuous throughout a product's lifecycle with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food Drug and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for routine risk assessment and risk minimization (e.g., FDA requirements for professional labelling and adverse event monitoring and reporting).

THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT²³

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore post marketing safety data collection and risk



assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

Pharmacovigilance principally involves the identification and evaluation of safety signals. Here safety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from post marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well documented case report can be viewed as a signal, particularly if the report describes a positive re challenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports also known as case reports. The reports are used to develop case series for interpretation.

1) 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. Computer- assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records as needed²⁴.

FDA suggests that the intensity and method of case follow- up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

2) Characteristics of a Good Case Report

Good case reports include the following elements:

- Description of the adverse events or disease experience, including time to onset of signs or symptoms.
- 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.
- 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 factors²⁵.
- Documentation of the diagnosis of the events including methods used to make the diagnosis.
- Clinical course of the event and patient outcomes (e.g., hospitalization or death).
- Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy including blood levels as appropriate.
- Information about response to de challenge and re challenge 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).

For reports of medication errors good, good case reports also include full descriptions of the following, when such information is available:

- Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container).
- Sequence of events leading up to the error.
- Work environment in which the error occurred and
- Types of personnel involved with the error, types of error, and contributing factors.

3) Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from post marketing 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). When available FDA recommends that



standardized case definitions (i.e., formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series. In general FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation (see section IV.F. for more details). As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports²⁶. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

- Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy).
- Absence of symptoms related to the event prior to exposure.
- Evidence of positive de challenge or positive re challenge.
- Consistency of the event with the established pharmacological/ toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury.
- Consistency of the event with the known effects of other products in the class.
- Existence of other supporting evidence from preclinical studies, clinical trials and/or pharmacoepidemiologic studies and
- Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event, no co- or pre- morbid medical conditions).

Confounded cases are common especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfined cases may be useful. For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the

potential association between a product and an adverse event²⁷.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. A number of references are available to assist sponsors in capturing a complete account of the event. FDA recommends that sponsors follow up to the extent possible with reporters to capture a complete account of the event, focusing on the medication use systems (e.g., prescribing/order process, dispensing process, administration process). This data may be informative in developing strategies to minimize future errors²⁸.

4) 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:

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

5) 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.

By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product-event combinations warranting further investigation. Data mining can be used to augment existing signal detection



strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event²⁹ (e.g., liver failure) for a specific drug (i.e., the “observed reporting fraction”) with (2) the fraction of reports for the same particular event for all drugs (i.e., “the expected reporting fraction”). This analysis can be refined by adjusting for aspects of reporting (e.g., the reporting year) or characteristics of the patient (e.g., age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease³⁰.

6) Safety Signals That May Warrant Further Investigation

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. 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. Safety signals that may warrant further investigation may include, but are not limited to, the following³¹:

- New unlabeled adverse events especially if serious.
- An apparent increase in the severity of a labelled event.
- Occurrence of serious events thought to be extremely rare in the general population.
- New product-product, product-device, product-food, or product-dietary supplement interactions.
- Identification of a previously unrecognized at risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities).
- Confusion about a product's name, labelling, packaging or use³².
- Concerns arising from the way a product is used (e.g., adverse events seen at higher than labelled doses or in populations not recommended for treatment).
- 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 Risk MAP goal) and
- Other concerns identified by the sponsor or FDA.

7) 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 context³³. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment. Limitations in national denominator estimates arise because:

- Accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available.
- It may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low and
- A product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events.

FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator. FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes³⁴.

To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). These background rates can be derived from:

- National health statistics,
- Published medical literature, or

- Using large automated databases or ongoing epidemiologic investigations with primary data collection.

FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria and duration of time at risk.

While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g., publicity, newness of product to the market) and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

PHARMACOEPIDEMIOLOGIC STUDIES³⁵

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control and case-crossover. The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests prespecified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the premarketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated prior to marketing. Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high. Because different products pose different benefit-risk considerations (e.g., seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be

made on a case-by-case basis. When an important adverse event-product association leads to questions on the product's benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest. When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding.

A protocol for a pharmacoepidemiologic study generally includes:

- 1) Clearly specified study objectives.
- 2) A critical review of the literature and
- 3) A detailed description of the research methods including:
 - The population to be studied, the case definitions to be used.
 - The data sources to be used (including a rationale for data sources if from outside the U.S.).
 - The projected study size and statistical power calculations and
 - The methods for data collection, management and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such as data from previously conducted clinical trials or large databases. In recent years, a number of pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO, Medicaid) that allow retrieval of records on product exposure and patient outcomes.

CONCLUSION

So it can be concluded that important role of pharmacovigilance is to:

- 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.
- Ensure that risks in drug use are anticipated and managed.
- Provide regulators with the necessary information to amend the recommendations on the use of the medicines.
- Improve communication between the health professionals and the public.
- Educate health professionals to understand the effectiveness/ risk of medicines that they prescribe.

Experience has shown that for a country to be able to rely on its own pharmacovigilance programme a number of elements need to be in place. These are as follows:

- A dedicated pharmacovigilance centre, independently funded (usually by the state), and staffed by a person or persons with expert knowledge of drug safety and of the evaluation of reports of adverse events.
- Links, electronic and personal between the pharmacovigilance centre and WHO, specifically with the Uppsala Monitoring Centre.
- Access to comprehensive and unbiased drug information relevant to the medicines available in the country.
- The national pharmacovigilance programme should have clinical underpinning and should be known to and be actively supported by the ministry of health, health professionals and the academic sector.

The programme should have ready access to sound and independent drug information (particularly information on drug safety) and it should serve as a robust and dependable reference centre. The public should know of its existence and have trust in the judgement and expertise of its professional staff. There should be adequate financial support from the state to enable the programme to perform these functions.

- The national pharmacovigilance centre may be based physically (but not necessarily so) at the ministry of health, within the national MRA, within a leading state hospital, or at an academic school of pharmacy, medicine or health sciences. Whatever arrangement is made, there should be close collaboration, exchange of information and mutual technical support between the centre and the MRA.
- A national medicines safety review committee (ESRP) for adverse reactions that advises both the MRA and the national pharmacovigilance centre and that has strong clinical representation in its membership, should provide support and focus for the work of the national centre and for the MRA.
- Finally, there should be regular opportunities for the professional staff of pharmacovigilance centres to upgrade their knowledge and experience through training, study and research and ideally in conjunction with colleagues in public health.

Among the important issues are information, information sharing and broader communication. What we need is a continuing and dynamic development of modern professional practice. We must recognize that solutions to the challenges will come from those inspired and committed individuals and institutions round the world with a vision of improved public health and patient safety. Most important in this venture is the need for a new spirit

of sharing of information and intelligence in line with the vision and aspirations of the Erice Declaration.

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