A REVIEW : PHARMACOVIGILANCE IMPORTANCE AND CURRENT REGULATIONS

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Summary

An increase in drug safety concerns in recent years with some high profile drug withdrawals have led to raising the bar by various stakeholders more importantly by the regulatory authorities. The number of Adverse Drug Reactions (ADRs) reported have also resulted in an increase in the volume of data handled and to understand pharmacovigilance a high level of expertise is required to rapidly detect drug risks as well as to defend the product against an inappropriate removal. [4]

Keywords:- Pharmacovigilance, Adverse Drug Reaction, National Pharmacovigilance Programme,

Introduction

Pharmacovigilance (abbreviated **PV** or **PhV**) is the pharmacological science relating to the detection, assessment, understanding and prevention of effects, particularly long term and short term side effects of medicines.[5]

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to:

- identifying new information about hazards associated with medicines
- preventing harm to patients. [5]

Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs). The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health. [1]

Pharmacovigilance is a new discipline to the students of India which provides newer and better opportunities to aspirants across the country who wish to build their career in the field of pharmacological science. [6]

Pharmacovigilance is a discipline which is concerned with identifying, validating, quantifying, evaluating and minimizing the adverse effects of medicine thereby increasing the safety of drugs in use. It is a study of drug related adverse effect carried out by pharmaceutical industries to suggest warnings and recommendation for product withdrawal. [6]

Pharmacovigilance is not only an academic necessity but also a need to ensure security of human beings. It is an accepted opinion of the mass to scrutinize the adverse effects of medicines which have been released in the market. [6]

The Pharmaceutical industry in India is valued at Rs. 90,000 Crore and is growing at the rate of 12 – 14 % per annum. Exports are growing at 25 % Compound Annual Growth Rate (CAGR) every year. The total export of Pharma products is to the extent of Rs. 40,000 Crore. India is now being recognized as the 'Global pharmacy of Generic Drugs' & has distinction of providing generic quality drugs at affordable cost. India is also emerging rapidly as a hub of Global Clinical trials & a destination for Drug Discovery & Development. [2]

The Government also puts forward a supportive hand and takes immediate actions for the implementation of such a course so that people become aware of the adverse effects of drugs which can be reduced by a discipline like pharmacovigilance.

Pharmacovigilance is important to implement quality systems in all pharmaceutical companies which produce huge amount of medicines that are marketed in India and Western Countries.

The process of collection of such information about a drug begins in phase I of the 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.

Brief history of Pharmacovigilance in India

Even though pharmacovigilance is still in its infancy, it is not new to India. It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India. [2] However, nothing much happened until a decade later when in 1997, India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centers for ADR monitoring were identified, mainly based in teaching hospitals: a National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs to medicines marketed in India. However, they hardly functioned as information about the need to report ADRs and about the functions of these monitoring centers was yet to reach the prescribers and there was lack of funding from the government. This attempt was unsuccessful and hence, again from the 1 st of January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational. [4]

The National Pharmacovigilance Program established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi. Two zonal centers-the South-West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi), were to collate information from all over the country and send it to the Committee as well as to the Uppsala Monitoring centre in Sweden. Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center in turn would have several peripheral centers reporting to it. Presently there are 24 peripheral centers. The program has three broad objectives: the short-term objective is to foster a reporting culture, the intermediate objective is to involve a large number of healthcare professionals in the systems in information dissemination and the long-term objective is for the program to be a benchmark for global drug monitoring. [4]

Risks of medical treatment

While 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.

1. While 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.
2. There are risks in any intrusion into the human body, whether chemical or surgical. Nothing in this field is entirely predictable as the interaction between chemicals and the human body may produce surprises.
3. Terms commonly works under real world circumstances, i.e., clinical practice (not clinical trials).
4. *Efficacy* is used to express the extent to which a drug works under ideal circumstances (i.e., in clinical trials). [5]

Pharmaceutical companies are required by law in all countries to perform clinical trials, testing new drugs on people before they are made generally available. The manufacturers or their agents usually select a representative sample of patients for whom the drug is designed — at most a few thousand — along with a comparable control group. The control group may receive a placebo and/or another drug that is already marketed for the disease. [5]

The purpose of clinical trials is to discover:

- if a drug works and how well
- if it has any harmful effects, and
- its benefit-harm-risk profile - does it do more good than harm, and how much more? If it has a potential for harm, how probable and how serious is the harm? [5]

Clinical trials do, in general, tell us a good deal about how well a drug works and what potential harm it may cause. They provide information which should be reliable for larger populations with the same characteristics as the trial group - age, gender, state of health, ethnic origin, and so on. [5]

The variables in a clinical trial are specified and controlled and the results relate only to the population of which the trial group is a representative sample. A clinical trial can

never tell you the whole story of the effects of a drug in all situations. In fact, there is nothing that could tell you the whole story, but a clinical trial must tell you enough; "enough" being determined by legislation and by contemporary judgements about the acceptable balance of benefit and harm. [5]

Importance of pharmacovigilance

When a medicine is released onto the market there is still a great deal that is unknown about the safety of the product. Once marketed the medicines are used by patients who have many different diseases, who are using several other drugs and who have different traditions and diets which may affect the way in which they react to a medicine. Different brands of medicines may differ in the manner in which they are produced and the ingredients that are used. The adverse drug reactions and poisonings associated with traditional and herbal remedies also need to be monitored in each country. The information we receive on the adverse effects of drugs in other countries may not be relevant or applicable to *{Country}'s* citizens. In some cases, adverse effects to certain drugs may only occur in *{Country}'s* citizens.

In order to prevent unnecessary suffering by patients and to decrease the financial loss sustained by the patient due to the inappropriate or unsafe use of medicines, it is essential that a monitoring system for the safety of medicines in *{Country}* is supported by doctors, pharmacists, nurses and other health professionals in the country. [3]

The *{Drug Regulatory Authority}* and the Department of Health's Essential Drug Programme are committed to improving drug safety through adverse drug reaction monitoring in *{Country}*. Through the *{Drug Regulatory Authority}'s* national pharmacovigilance programme, adverse reactions should be reported on a daily basis. [3]

Adverse Drug Reactions

The {Drug Regulatory Authority} defines an Adverse Drug Reactions (ADR) or adverse reaction as a response to a medicine used in humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine. [1]

While no studies have comprehensively assessed the burden of adverse drug reactions on health care, it is likely that the problem is considerable in *{Country}*. Studies conducted in developed countries have consistently shown that approximately 5% of hospitalised patients are admitted into hospital as a result of an ADR and 6-10% of in-patients will experience a serious ADR during hospitalisation. Even these startling figures don't represent the whole picture. These studies generally excluded ADRs caused by overdose, drug abuse, or therapeutic failures. The cost to most countries for managing adverse drug reactions is considerable. [1

Reporting of Adverse Drug Reactions

All health care workers, including doctors, dentists, pharmacists, nurses and other health professionals are requested to report all suspected adverse reactions to drugs (including vaccines, X-ray contrast media, traditional and herbal remedies), especially when the reaction is unusual, potentially serious or clinically significant. It is vital to report an adverse drug reaction to the *{Drug Regulatory Authority}'s* Pharmacovigilance programme **even if you do not have all the facts or are uncertain that the medicine is definitely responsible for causing the reaction**. [1]

The information obtained from the reported reactions promotes the safe use of

medicines on a local and national level. The reported case will be entered into the national adverse drug reaction database and analysed by expert reviewers. A well completed adverse drug reaction/product quality form submitted by you could result in any of the following:

• additional investigations into the use of the medication in *{Country}*
• educational initiatives to improve the safe use of the medication.
• appropriate package insert changes to include the potential for the reaction reported by you.
• changes in the scheduling or manufacture of the medicine to make the medicine Safer.

Therefore, the purpose of ADR reporting is to reduce the risks associated with drug prescribing and administration and to ultimately improve patient care and safety. [1]

Pharmacovigilance – Current Regulations and Guidelines

According to the WHO pharmacovigilance is defined as "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (WHO 2002 "Importance of pharmacovigilance", WHO/EDM/QSM/2002.2). It is a key public health system. [7]

European Union

In the European Union Regulation (EC) No 726/2004 with respect to centrally and Directive 2001/83/EC with respect to nationally authorised medicinal products provide the legal framework for pharmacovigilance. 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). [7]

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. [7]

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. [7]

Pharmacovigilance system comprises the following key elements:

- QPPV and the back-up procedure to apply in their absence.
- Organisation of the pharmacovigilance system describing the names, location and internal connections of the departments involved in pharmacovigilance activities within the company. A charter of the organisational structure should also illustrate the cooperation with external partners.
- Databases, listing of the data bases used for pharmacovigilance services, registration with the Eudravigilance system and description of processes used for electronic reporting.

- Contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations.
- Training, recording regular education and further training of the staff involved in pharmacovigilance activities.
- Documentation, description of the locations of the different types of pharmacovigilance source documents, including archiving arrangements.
- Quality Management System.
- Supporting Documentation.

Roles and responsibilities with regard to the tasks and responsibilities of the Marketing Authorisation Holder, the competent authority of the member states, the CHMP.

- Transparency and communication.
- Pharmacovigilance obligations by the marketing authorisation holder
- Risk management planning and non-interventional safety studies
- Adverse drug reaction case reports
- Periodic safety update reports and other safety related assessments

The proposals (EU-Pharmacovigilance Systems) focus on the update of the two main legal framework texts the Directive 2001/83/EC and the Regulation (EC) No 726/2004. Furthermore, the procedures of reporting of safety issues will be streamlined with the target to reduce duplication of efforts. The aim is to implement a centralised, efficient, co-ordinated EU procedure that supports a faster assessment of the product safety and a faster updating of the product information. [7]

United States

The FDA has a long history of pharmacovigilance activities. Already 20 years ago measures to minimise the risks of marketed drugs were applied (see Mitchell et al. 1995). In 1996 the FDA implemented the ICH guidance E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. [7]

In the recent years the FDA has developed several guidance documents related to safety of drug and biological products. Based on reauthorisation of the Prescription Drug User Fee Act (PDUFA III) by the Congress in 2002 and the associated goals with regard to guidance for industry on risk management activities for drug and biological products the FDA issued three concept papers focusing on

(1) conducting premarketing risk assessment,

(2) developing and implementing risk minimization tools,

(3) performing post-marketing pharmacovigilance and pharmacoepidemiologic assessments for public consultation. [7]

The Premarketing Guidance focuses on risk assessment during late stage clinical development, i.e. phase III. The document provides recommendations with regard to safety database size and characteristics like patient population, terminology, assessment methods, use of standard terms, dose to ensure quality and completeness. It offers considerations concerning detecting unanticipated interactions (drug-drug, product-demographic relationships, product-disease, product-dietary supplement interactions), developing comparative safety data, assessing and minimizing the potential for medication errors, addressing safety aspects during product development, data analysis and presentation. [7]

The RiskMAP Guidance provides recommendations regarding risk minimization and RiskMAP in risk management. RiskMAP is a strategic safety programme that is designed to meet specific goals and objectives in minimising known risks through the use of the following measures [7]

- product labelling,
- education and outreach to communicate risks and appropriate safety behaviours to healthcare practitioners or patients,
- reminder prompting systems, processes, or forms to foster reduced-risk prescribing and use,
- performance-linked access systems that guide prescribing, dispensing, and use of the product to target the population and conditions of use most likely to confer benefits and to minimise particular risks.

The pharmacovigilance guidance document gives recommendation about identifying and describing safety signals, investigating a signal through observational studies, interpreting safety signals and developing a pharmacovigilance plan.

Pharmacovigilance Programme of India (PvPI)

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in *collaboration with Indian Pharmacopeia commission, Ghaziabad* is initiating a nation-wide Pharmacovigilance programme for protecting the health of the patients by assuring drug safety. The programme shall be coordinated by the *Indian Pharmacopeia commission, Ghaziabad* as a National Coordinating Centre (NCC). The centre will operate under the supervision of a Steering Committee. [2]

Steering Committee Pharmacovigilance Programme of India[2]

Pharmacovigilance Programme of India
Chairman Drugs Controller General (India), New Delhi, *ex- officio*
Members 1. Scientific Director, Indian Pharmacopoeia Commission, Ghaziabad, ex-officio 2. Head of Department, Pharmacology, AIIMS, ex - officio 3. Nominee of Director General, ICMR, ex-officio 4. Assistant Director General (Extended Programme of Immunization [ADG(EPI)] as representative of Directorate General Health Services 5. Under Secretary (Drugs Control) as representative of The Ministry of Health & family Welfare. 6. Nominee of Vice Chancellor of Medical/Pharmacy University, ex-officio 7. Nominee of the Medical Council of India, ex-officio 8. Nominee of Pharmacy Council of India, ex-officio
Member Secretary Officer-in-Charge (New Drugs), CDSCO, New Delhi, *ex-officio*

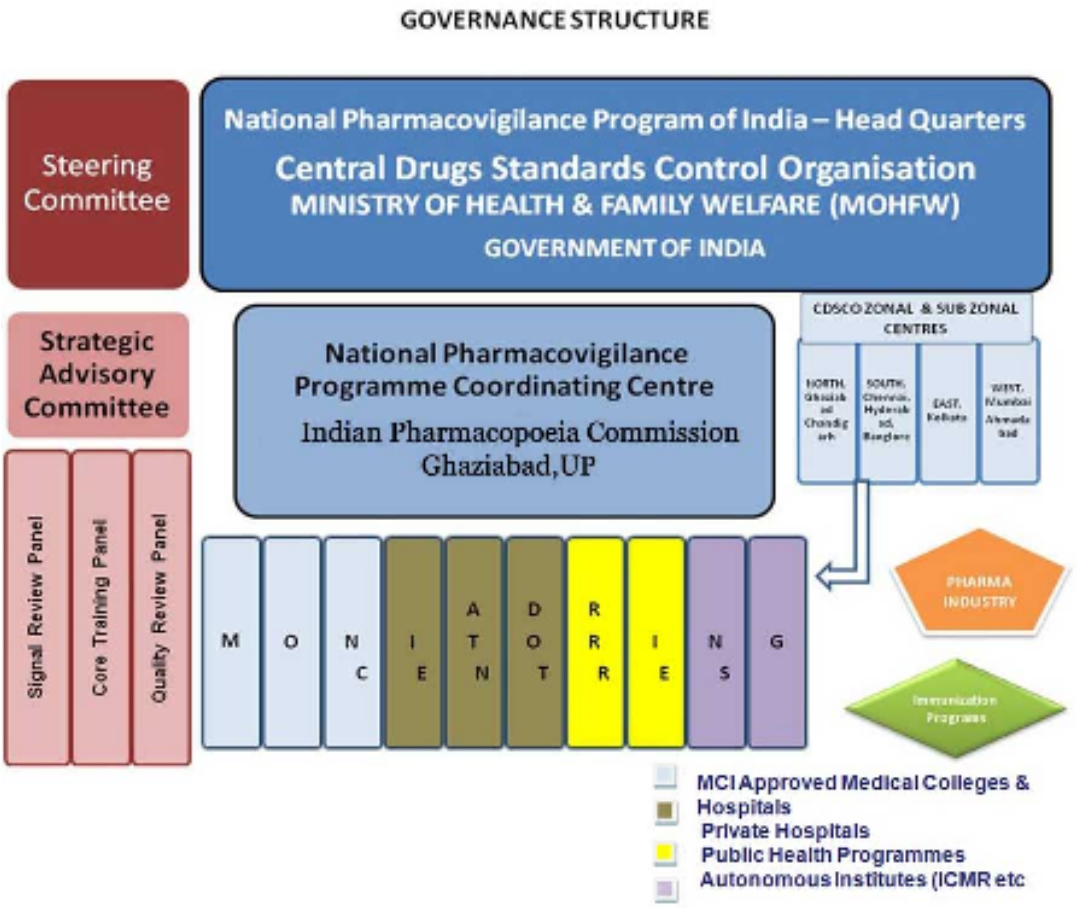

Diagram 1:- Governance Structure Of National Pharmacovigilance Programme

Monitoring & Evaluation:

To ensure the PvPI operates effectively and achieves its objectives, the centre will establish key indicators to measure the efficiency of (i) process (ii) outcome and (iii) impact of the PvPI. [2]

i. Process Indicators:

The following indicators will be measured:

a. Number of ADR monitoring centers participating in the PvPI
b. Number of AMC personnel trained in a year
c. Funds budgeted for PvPI and funds spent
d. AMC Personnel working full-time for PvPI [2]

ii. Outcome Indicators:

a. Software platform established
b. Number of ADR reports received in a year
c. Number of ADR reports processed in a year
d. Number of ADR reports submitted to Vigiflow

iii. Impact Indicators:

a. Number of signals generated and confirmed
b. Number of safety related alerts issued by CDSCO [2]

Conclusion

Pharmacovigilance is a complex process and robust systems are essential to undertake the activity.

Impact of pharmacovigilance is increasing day by day in pharmaceutical industries and analysis of adverse drug reaction is increasing patient compliance and safety.

Regulations and guidelines are helping to companies to follow a statistical and monotonous way of keeping patient safety.

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