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Review Article

LATEST REGULATORY GUIDELINES AND THE PROCESS OF ADR REPORTING IN INDIA

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ABSTRACT

Drug regulatory authorities are a key to establish the safety, efficacy and quality of marketed products**.** Regulatory authorities take a wide range of actions in response to a reported adverse drug reactions (ADR). ADR are a significant cause of morbidity and mortality, primarily identified in post-marketing surveillance. Improvement in current ADR reporting scenario in India, including utility of innovative methods like Pharmacovigilance, is crucial to improve patient safety and public health. Drug event monitoring, adverse events and spontaneous adverse event reporting is a method of active pharmacovigilance surveillance. Pharmacovigilance plays a consequential role in the surveillance of adverse drug reactions, which starts from the pre-marketing of new drugs and continues through the post-marketing of drugs. There is a need for robust pharmacovigilance programmes in India, considering its large population with various disease prevalence patterns, indigenous way of medication and practice. All the regulatory authorities, institutions even clinicians and physicians are initiating nation-wide pharmacovigilance programmes to collect, collate, analyse data on adverse drug reactions for protecting the health of the patients by assuring drug safety with well defined goal with predestined road map to ensure its future growth and progress. Ultimate goal of the program is to ensure that the benefits of use of medicine outweigh the risks and thus safeguard the health of the Indian population.

Keywords: *Pharmacovigilance, Drug Safety, ADR reporting*

INTRODUCTION

Indian Pharmaceutical Industry is one of the industry which is highly regulated by stringent guidelines.The government has laid regulatory guidelines as the pharma industry is responsible for health of the population. In India a well-defined Drugs and Cosmetics Act 1940 is established to control the regulatory guidelines o Pharmaceutical Industry. Rapid growth of Pharmaceutical Industry has revamped and modernized the regulatory set-up of the country. Many areas including the production and distribution of healthcare products are brought under the same umbrella of regulatory framework. Bio products, food additives and medical devices are all been regulated by regulating committee [1].

The prime objective of Regulatory authorities is to ensure the safety and quality of drugs. The regulatory guidelines ensure the standard of new drugs. It has been observed that an unsafe medicine can cause severe damage to the patient. Tragedies or accidents are unavoidable irrespective of sincere efforts by R&D for approval and introduction of the

drug; the regulatory agencies are answerable in cases of tragedies. Thus it is important for the government to make sure that all pharmaceutical companies abide the regulatory guidelines stated under the Drug Act .It is also mandatory for the government to create a robust regulating system to ensure the quality and safety of drugs for the use of human and animal [2].

PHARMACOVIGILANCE

Detecting, assessing and preventing adverse drug reaction is the major area on which pharmacovigilance department works on**.**

Each country has set their own set of guidelines on pharmacovigilance for detection, collection, assessment of adverse events in their corresponding regions. The ultimate goal of pharmacovigilance is to ensure safe and rational use of medications [1, 2].

The important concern of pharmacovigilance is to:

- Collect latest information on health hazards due to drugs.
- Prevention from such hazards.

WHO DEFINITION:

WHO defines the Pharmacovigilance (PV) as the pharmacological science relating to the detection, evaluation, understanding and prevention of adverse effects, particularly long term and short term side effects of medicine.

ADVERSE DRUG REACTION

At a normal dose sometimes the given medications may harm the patients which are called as an adverse drug reaction (ADR). Meaning of adverse drug reaction is different from side effect. The evaluation of ADRs is most critical in the field of pharmacovigilance. Concerning marketed remedies, a suitable definition of an adverse drug reaction is as follows: In patient at normal doses harmful and unpleasant reaction of drug for treatment and medication of disease or for changes of biological utility. Mainly two types of adverse drug reaction which are as follows:

Unlisted / Unexpected Adverse Drug Reaction

An adverse reaction is the nature or harshness of drug which is not reliable with the proper product data which available at the time of the clinical trials. Company is needed help during investigators brochure for an unapproved drug.

- **Listed / Expected Adverse Drug Reaction**

ADR contains an overall summary of the nature, severity and specificity of the drug product and is already been recorded**.**

ADVERSE EVENT

An adverse event is not having any casual relationship with patient treatment but it's one of the medical incidences with patient. So an adverse event (AE) can be any critical or Unintentional indication of disease which is temporally related with the use of a medication.

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ADVERSE DRUG REACTIONS REPORTING

When the adverse reaction to drugs is curious, potentially serious or clinically important, all health care workers, including doctors, pharmacists, nurses and other health experts are requested to clarify it. It is necessary to report an adverse drug reaction to the pharmacovigilance program even if you do not have all the facts or you are unsure that the medicine is definitely responsible for causing the adverse reaction [3].

SPONTANEOUS REPORTING SYSTEMS

- Regionalization.
- Repossession of further data.
- Access to all important pre- and post-marketing information.
- Detailed drug utilization data.
- Standardized evaluation of causality and significance.
- Encouragement.

PHARMACOVIGILANCE: INDIAN PERSPECTIVE

India with more than 1.2 billion population and it is the fourth largest producer of pharmaceuticals in the world & is emerging as an important Clinical trial hub in the world. So pharmacovigilance system protects the population from the potential harm that may be caused by drugs.

The Drug Controller General of India (DCGI) is responsible for the regulation of pharmaceuticals and medical devices The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC).

Adverse drug reaction (ADR) monitoring is one of the most important parts of pharmacovigilance.

The DCGI in the year 1982 established five centres for nationwide monitoring of adverse drug reaction (ADR) and hence its not a new concept. In 1987, ICMR had collected about 5,8000 ADR cases through its multi institutional study but they all stopped functioning reason being many but two of the primary reasons were meagre funding and unenthusiastic skills. Current programme have high chances of success as the foundation is based on corrective measures taken from the past experiences. The success of this programme depends on the continuous active support by Central Drugs Standard Control Organization CDSCO and the dedicated work of pharmacovigilance centres [3].

AIM AND OBJECTIVES

• To engage several healthcare professionals and public to participate in pharmacovigilance programme in India.

• To gain knowledge about the function of centre in India.

• To achieve such operational efficiencies that would make Indian National Pharmacovigilance Programme a benchmark for global drug monitoring endeavours.

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India's Central Drugs Standard Control Organization (CDSCO)

The supreme regulatory body in india for pharmaceuticals and medical devices is CDSCO with its headquarter in new delhi.
The Central Drugs Standard Control Organization (CDSCO) under Ministry of Health & Family Welfare, in collaboration with eminent bodies like Department of Pharmacology, All India Institute of Medical Science (AIIMS), New Delhi has initiated a nation-wide pharmacovigilance programme for protecting the health of the patients by assuring drug safety which will include data for drugs, biological, vaccines, diagnostics and medical devices covering public and private sector as well. In accordance with department of pharmacology, AIIMS this national programme is being run [3, 4].

NATIONAL PHARMACOVIGILANCE PROGRAM

The Indian agency has launched a Pharmacovigilance Programme of India for Assuring Drug Safety ,its mission being comparing the risk and benefit ratio of the medicines in use thereby protecting the helath of indian population in the coming 5 years.[4] Central Drugs Standard Control Organization (CDSCO) has initiated a well structured and highly participative National Pharmacovigilance Programme based on the recommendations made in the WHO document titled guidelines for setting and running a strong pharmacovigilance system "-medicinal products safety monitoring". More than five lakhs qualified doctors are a part of National Pharmacovigilance Program in India and 15,000 hospitals having bed strength of 6, 24 ,000 and has for key objectives:

- Adverse Drug reaction monitoring in india.
- Campaign for awreness on ADR reporting to the health care professionals.
- Assessing benefit risk ratio of medicines.
- To provide support to CDSCO on matters related to regulatory guidelines for safety of medicines.
- A single centre for pharmacovigilance should be created on a national level to communicate globally on matters related to safety monitoring of medicines.

The Programme aims to foster the culture of ADE notification in its first year of operation and subsequently aims to generate broad based ADR data on the Indian population and share the information with global health-care community through WHO-UMC (UPPASALA monitoring centre).The Pharmacovigilance Program of India will be administered and monitored by two committees, a

- Steering committee: Headed by DCGI (india) and also includes ex-officio members and pharmacopoeia members. Also members from ministry of health and family welfare and director general health services. 2) strategic advisory committee.

The program comprises of establishing 26 peripheral centres, 2 zonal centres and 5 regional centres wherein National pharmacovigilance advisory committee (NPAC) proposes the regulatory guidelines and coordinates and assesses the performance of all the centres [4].

NATIONAL PHARMACOVIGILANCE POLICY

This programme basically works by collecting , analyzing and using the outcomes to propose on regulatory measures, besides communicating risks to healthcare professionals and the public

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PHARMACOVIGILANCE SET UP IN INDIA

The Central Drugs Standard Control Organization (CDSCO) has initiated a country-wide Pharmacovigilance programme under the aegis of Directorate general of health services (DGHS), under health and family welfare ministry .national pharmacovigilance centre operating at CDSCO is actively involved in running the program and it is headed by national pharmacovigilance advisory committee which establishes the required procedures and guidelines. [4].

Regulations relating to Indian Pharmacovigilance Programme

Marketing license when acquired by a pharmaceutical company in India shall have well organized (PV) pharmacovigilance system which should ensure the authenticity of the marketed product as mentioned in schedule Y.

Schedule Y

Schedule Y of drug and cosmetics acts 1945 establishes the requirements of PV in India on a legislative level. Schedule Y establishes regulations for drug development including pre clinical and clinical stages. The requirements for clinical trial to import manufacture and obtain market approval for new drug in India is also established by schedule Y. Latest review and amendment for schedule Y was made in January 20, 2005. The amendments have laid special emphasis on reporting of adverse reactions during clinical trials .section of schedule Y dealing with post marketing surveillance emphasizes on PSUR submission requirements, PSUR's template and cycle and timelines for reporting.

PHARMACOVIGILANCE TASKS

Pharmacovigilance set up in companies perform an overall activity of spontaneous adverse reaction reporting and also serious unexpected reporting of adverse events .They follow a stepwise process of collecting, monitoring and reporting these events. PSUR preparation being an important activity wherein well set up system for literature survey, benefit-risk ratio assessment and managing safety data are important aspects. [4]

EVENT CONCERNING SPONTANEOUS ADVERSE REACTIONS REPORTING

Although not a tool of highest quality but can be used for benefit –risk assessment of new drugs and collection of safety information at an early stage. The cases wherein serious unexpected adverse events occur should be reported to the licensing authority within 15 days of information report submitted by the applicant. Further periodic safety update report should contain individual adverse reaction reports.[3,4]. ICH,ICH E2D are the documents which serves as guidelines and describes in detail about the procedures and criterias for validation of adverse reaction reports, handling and follow up of reports for spontaneous adverse events. Monitoring, documenting and reporting of adverse events during a clinical trial should be reported and notified to the authorities in a timely manner and as per the latest amendments in schedule Y. The responsibilities for these reporting tasks are taken by the sponsor. The communication for unexpected SAE reporting should be done to the licensing authority and investigator within 14 days of occurrence of such events.

An important part of the report is the covering letter which is prepared following the

template as a reference. A follow up report is to be framed and produced when there is lack of information at the time of report submission example compensation in case of death or serious injury.

According to schedule Y, in case of any serious or adverse event an investigator should take the responsibility and report the unexpected adverse event to the sponsor within time duration of 24 hrs also the ethics committee should be informed within seven days of the occurrence of adverse event.

An assessment report is prepared which describes about the adverse effect whether it is related or not to the study. Compensation details in case of serious injury or death also in situations where compensation is not paid then reason for it should be mentioned.

Specifications regarding multinational trials, foreign case reporting and detailed procedure on unbinding, safety reports on annual basis and adverse event handling in case of placebo are not mentioned in schedule Y [5].

KEY REQUIREMENTS TO REPORT SAE DURING A CLINICAL TRIAL

A) Details of the subjevt in terms of gender, date of birth,height and weight.

B) detailes description of tested drug for example generic name, usage ,daily dosage regimen , dosage form ,administration route,time from when tratment was started and then stopped thet is duration of treatment.

C) other treatments if any provided along with suspected drug it can be OTC drugs or any non drug therapies.

D) Description and providing details about SAE example reaction describing its severity and site , categorization of case into serious, its signs and symptoms along with diagnostic method used for detecting the reaction and final assessment by the investigator on basis of date and time for event to occur, duration of treatment during which causality was observed, hospital layout and its setting, specific test results or any treatment if conducted.

E) The cause of death or the relation between cause and reaction to be presented in the form of comments also if any findings during post-mortem should be mentioned along with details as any history of allergy, drug abuse, alcoholism, family history of any disease etc.

F) Investigator details including name, address, contact number, signature and reporting date to the ethics committee and licensing authority should be mentioned.

AMC's are responsible to collect the ADR reports and the PV employees at AMC's keep a check on the reports validity also sometimes causality assessment is performed. The forms are then forwarded to the coordinating centre wherein AMC staff keep a check on all centre activities by maintaining a log and perform ADR monitoring through a watch list. Causality assessment then performed by the coordinating centre and uploading of reports to PV software is done. Finally, a full-fledged report of ADR's is prepared by coordinating centre and collected at suitable time intervals [5].

CONCLUSION

Amendments to schedule Y has given Indian regulatory authorities a reason to establish a strong foundation for pharmacovigilance system as not long before there was no vision to have a well set up system for pharmacovigilance. The fatal incidences occurring during clinical trials must have drawn the attention with steps being taken by authorities who are visible enough in the form of seminars and trainings conducted at several places in India in association association with

WHO and time to time notifications from DCGI for establishment of a solid pharmacovigilance system.

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