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PHARMACOVIGILANCE MONITORING AT DIFFERENT STAGES OF DRUG DEVELOPMENT: IN INDIA

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ABSTRACT

Pharmacovigilance (PV) is an exclusive research-based activity that keeps a persistent observation on the drug and certain or uncommon Adverse Drug Reactions (ADRs) that were undiscovered throughout the clinical trial. The drugs are discovered to cure the human beings or living beings but still after the administration of drugs, sometime serious harmful effects are monitored which is known as Adverse Effects. The monitoring of Adverse Effect depend on determining about the harmful effect or adverse effect of an isolated drug and also to prevent its further existence. **AIM:** The aim of this review article is to aware the Patients and the Healthcare Professionals about the crucial steps taken by the Indian Pharmacopoeia Commission in collaboration with World Health Organization (WHO) to frame the structure of Pharmacovigilance Programme of India (PvPI) which is actively participating in Collection and Reporting of various ADRs, ICSR, AE by Patients, Doctors and the Industries which are playing a key role in development and marketing of Drugs in the global market.

KEYWORDS: Pharmacovigilance (Pv), Central Drug Standard Control Organization (CDSCO), National Coordination Committee (NCC), Adverse Drug Reactions (ADRs), Indian Pharmacopoeia Commission (IPC), World Health Organisation (WHO), Pharmacovigilance Programme of India (PvPI), Individual Case Safety Report (ICSR), Adverse Event (AE).

INTRODUCTION

Pharmacovigilance: Defined by WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[1]

Adverse Event (AE): An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.[2]

Adverse Drug Reaction (ADR): ADRs, which are defined as any response to a drug which is noxious and unintended, including lack of efficacy (the condition that this definition only applies with the doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological disorder function was excluded with the latest amendment of the applicable legislation).[3]

Spontaneous Reports: A spontaneous report is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional Centre, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products.[4]

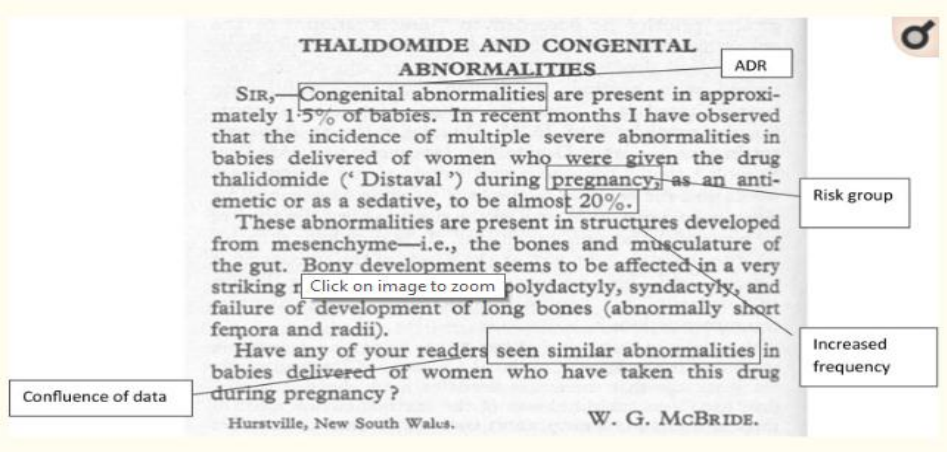
Pharmacovigilance is useful in assuring the efficacy of medicines and to secure the consumers from their adverse effects. Thus, for the safety of medication ADRs monitoring need for each medicine throughout its life cycle, during evolution of drug such as pre-marketing inclusive initial phase of drug design, clinical trials, and post-marketing surveillance. In India, Indian Pharmacopoeia Commission (IPC) and National Coordination Committee (NCC) along with the Central Drug Standard Control Organization (CDSCO) together regulate the PV activity. Since 2010, the program has been restructured as Pharmacovigilance Programme of India (PvPI) in participation with Indian Pharmacopoeia Commission, Ghaziabad. Hence for the effortless and effectual reporting of ADR IPC had taken several measures to execute the reporting centres at various regional, district and state levels. The recorded ADRs are collected and processed at the centres through Vigi-flow software. These centres perceives ADRs which were reported to CDSCO and World Health Organisation (WHO) for further evaluation and processing of

Regulatory actions. CDSCO-WHO by mutual understanding and constraint further publish the information through several social communication centres for the wellness and awareness of public health. The zonal centre for North is Ghaziabad; for East it is Kolkata; for South it is Chennai and for West it is Mumbai. Under the MOHFW, IPC is an autonomous body located in Ghaziabad was formed as an NCC for PvPI since 2011.

Origin of Pharmacovigilance

In 1961, Pharmacovigilance was reported when a causal link was built between serious foetal deformities (Phocomelia) and Thalidomide. Dr. McBride, an Australian doctor, wrote a letter to the editor of the Lancet Journal, in which he first suspected the cause of phocomelia to be thalidomide. A drug used as an anti-emetic in pregnant women introduced in the market in 1957. In fact, he observed that the incidence of congenital malformations of babies (1.5%) had increased up to 20% in women who had taken thalidomide during pregnancy.[5] At the same time, during a Paediatric Convention in Germany Dr. Lenz suggested a correlation between malformations and thalidomide and his suspect was published in a German Journal (Welt am Sonnatag).[6] In USA, the tragedy of thalidomide was not observed, because Dr. Kelsey showed strong doubts about the safety of thalidomide during pregnancy.[7] Due to the disaster tragedy of Thalidomide the serious adverse effect of the drug came into existence due to which the patients, healthcare professionals, Pharmaceutical Industry, and other Particulars who deals with the medicines understands the Importance of Monitoring the Safety and Efficacy Data of the Drugs products. This Tragedy bring the revolution in the Pharmaceutical / medicinal field which helped the professionals to understand the Pharmacovigilance system because the spontaneous reporting of adverse drug reactions became systematic, organized, and regulated. The letter which is mentioned below contains all the important terms which need to monitor spontaneous reporting and to establish a cause-effect relationship between the adverse event and the drug.[8]

McBride's letter and important elements for generating spontaneous reporting



Critical Pharmacovigilance Processes

The following processes should be considered as critical include:

- Continuous safety profile monitoring and benefit-risk evaluation of authorized pharmaceutical products;
- Establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimization;
- Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of ICSRs from any source;
- Signal management;
- Scheduling, preparation (including data evaluation and quality control), submission and assessment of PSURs;
- Meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
- Interaction between the Pharmacovigilance and product quality defect systems;
- Communication about safety concerns between MAHs and licensing authority in particular notifying changes to the benefit-risk balance of pharmaceutical products;
- Communicating information to patients and healthcare professionals about changes to the benefit-risk balance of pharmaceutical products for the aim of safe and effective use of pharmaceutical products;
- Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the regulatory authority;
- Implementation of variations to marketing authorizations for safety reasons according to the urgency required.[9]

How to Report ADR

- ADR shall be filled in the format approved by the PvPI
- One can download the ADR Reporting form from the official website of IPC and PvPI through ipc.gov.in and www. cdsco.nic.in
- Whenever the ADR shall be monitored the same shall be filed in the ADR reporting form.
- For each and every Patient separate ADR Form shall be filled to report the AE/ ADR with the completed information about the earlier Patient History or the drugs which the patient is taking.
- The filled ADR Form can be submitted directly to the official website of IPC i.e pvpi@ipcindia.net; pvpi.ipcindia@gmail.com or else the information can be shared with the nearest Adverse Drug Reaction Monitoring Centre (AMC) or to National Coordinating Centre.
- The AMC's staff maintains a record of all the activities of the centres and carries out ADR monitoring of drugs as per the standard procedure set by the Pharmacovigilance Team.
- These AMCs then finally evaluate the reported casualties and after preparation of final report keep the record in their PV database. The collected ADR reports by AMCs are communicated to NCC-PvPI through the provided VigiFlow tool of AMCs.
- The detection of ADR Reporting is finally processed and sifted through vigiflow database to the UMC Database. Further UMC team will submit the final report to the CDSCO with the help of NCC-PvPI to stop the use of marketing and administration of the drugs in India.
- After confirmation of Reported ADR further Drug Alerts are circulated by NCC-PvPI to all the MAH (Marketing Authorization Holders of Pharmaceutical Products). Stakeholders/Partners along with the AMCs where the patients are treated for the illness. The Drug-ADR relationship are mentioned as a alert in the regulatory authorities official sites. Any ADR among the drug alerts of PvPI are notified, especially on the follow-up.[10,11,12]

Regulatory Authorities Responsible for Conducting Clinical Research in India

In India there are various Regulatory Authorities which are having the key Role in organizing and approving the Clinical Researches which assures that the drug are safe to consume if taken up to the dose approved by the below mentioned authorities shown in the table[13]

Sr. No	Regulatory Authorities	Role
1.	Drug Controller General of India (DCGI)	Execution of National Pharmacovigilance Programme (NPP) in India.
2.	Central Drugs Standard Control Organization (CDSCO)	Execute under the supervision of National Pharmacovigilance Advisory Committee
3.	Indian Council of Medical Research (ICMR)	Finalize the Nutrient Requirements and Recommended Dietary Allowances For Indians.
4.	National Pharmacovigilance Advisory Committee (NPAC)	Collects, Monitor and Report the Adverse Drug Reaction to aware the Healthcare Professionals and Consumer regarding the ADR if reported by any of the drug marketed in India.
5.	Ministry of Health and Family Welfare (MHFW)	It is an autonomous body for finalizing the standards for all categories of Drug Manufactured and Marketed in India.
6.	Central Bureau of Narcotics (CBN)	It executes the clinical trials that are performed on Narcotics Drugs along with the compliance of Manufacturing, storage import and export of the Narcotics Drugs.

Importance of Pharmacovigilance at different stages of Drug Development

The development of Drug since from the initial stage till commercialization is a long a costly process.[14,15] The detailed study of the Product is done during the clinical trials to ensure that the complete safety studies of the participant molecule/ products are completed and ADR if any monitored it shall be collected and reported. By performing this activity according to the randomized designed plan helps to understand the Merits and Demerits of a New Medicinal Product which help to intensify the difference between the new product and the innovator w.r.t report the safety and efficacy of the product.[16]

Preclinical Trials

Before conducting the clinical studied directly in human being, the drug shall undergo through the process of Preclinical Studies which are done in Animals to monitor the Therapeutic and Adverse Effect of the Drug Product/molecule. The Preclinical Studies are done in detailed to investigate about the pharmacokinetics and pharmacodynamics of the drug, including absorption, distribution, metabolism, excretion, and persistence of pharmacological effects. For first in Human studies the dose should be calculated carefully based on non-clinical pharmacological, toxicological data generated.

Clinical Trials

As per the guideline to conduct Clinical Studies, the detailed studies of the Medicinal Product will be

proceeded in Phases. After completion and approval of Preclinical Studies on Animal now the clinical studies will be conducted in the human being which generally consist of four phases (I-IV Phases).

Phase I Studies: The objective of conducting the studies of this phase is to estimate the safety and tolerability with the initial administration of an investigational new drug into humans. This phase involve a small number of participant i.e. between 20 to 100.

- Studies conducted in Phase I, usually intended to involve one or more combination of following objective:
- Maximum Tolerated Dose
- Pharmacokinetics; i.e., Characterization of a drug absorption, distribution, metabolism and excretion.
- Pharmacodynamics.
- Early measurement of drug activity.

Phase II Studies: This studies are conducted with two objectives:

- The primary objective is to evaluate the effectiveness of the drug for a particular indication and to determine the common short term side effect and risk associated with the drug which results in requirement of larger number of participant (100 to 500). An important goal for this phase is to determine the dose and regimen for Phase III trials.
- Additional objective of this phase II studies can be included evaluation of potential study endpoints, therapeutic regimens and target population for further studies in Phase III

Phase III Studies: Phase III Studies have primarily objective of demonstration or confirmation of therapeutic benefits. Studies in Phase III are designed to confirm the preliminary evidence accumulate in Phase II that a drug is safe and effective for use in the intended indication and receipt population. These studies should be intended to provide an adequate basis for marketing approval.

- For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III. These studies carried out to complete the information need to support adequate instruction for use of the drug (prescribing information).
- For new drugs approved outside India, Prior to conduct of Phase III studies in Indian subjects. Central Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

Phase IV Studies: Phase IV or post marketing trial of new drugs are performed after the approval of the drug and related to the approval indication.

Phase IV trials include additional drug-drug interaction, dose response or safety studies and trials design to support use under the approved indication e.g. mortality studies, epidemiological studies etc.[17,18,19]

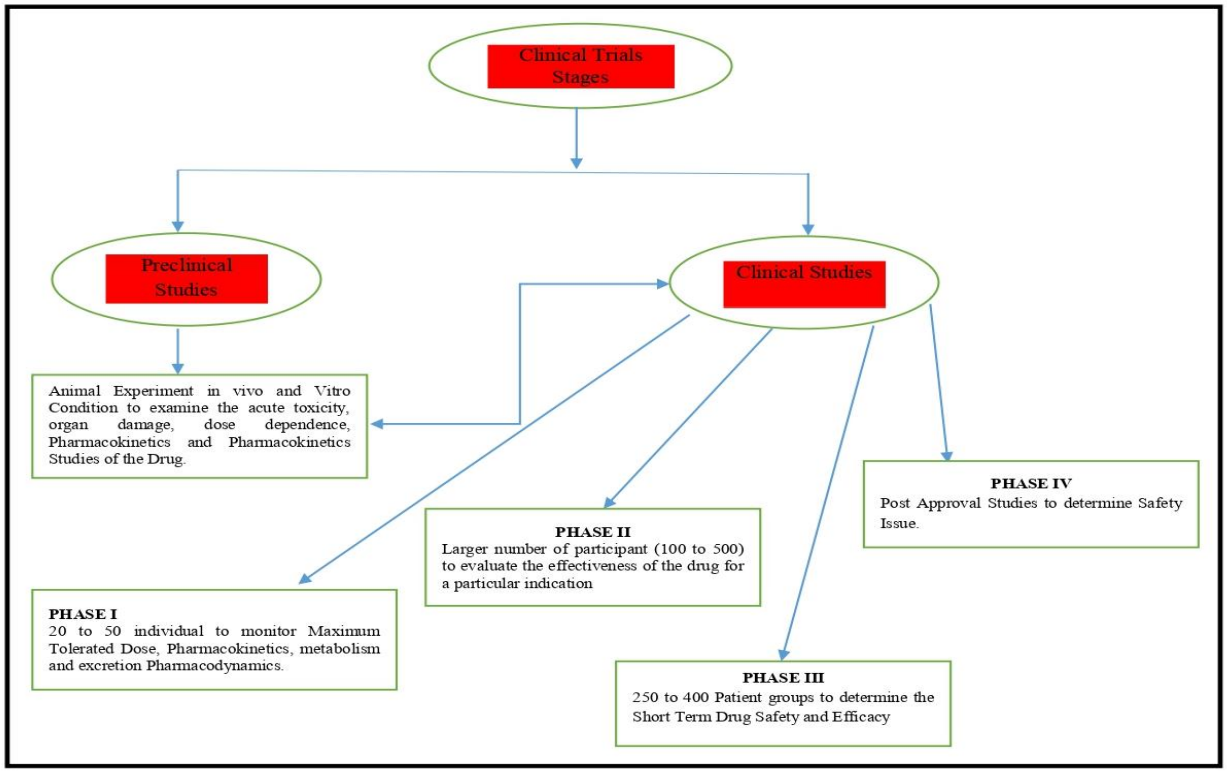


Figure 2: Stating the various stages of Preclinical and clinical Studies.

A Spontaneous Report

A spontaneous report is an unsolicited communication by health care professionals or consumers to a company, regulatory authority, or other organization that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme. Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies.[20, 21]

Spontaneous reporting of ADRs and adverse events is an important tool for gathering the safety information for early detection. Case reports collected by such a system represent the source of information providing the lowest level of evidence and highest level of uncertainty regarding causality. Spontaneous reporting has advantages in that it is available immediately after a new product is marketed, continues indefinitely and covers all patients receiving the drug. It is the most likely method of detecting new, rare ADRs and frequently generates safety signals which need to be examined further.[22] The main limitations are the difficulty in recognizing previously unknown reactions, particularly events that are not usually thought of as being ADRs, and under-reporting, which is variable and sensitive to reporting stimuli and difficult to quantify. It usually does not confirm hypotheses; although situations exist where spontaneous reporting data alone allow conclusions that a signal indeed represents a true ADR.[23]

CONCLUSION

Pharmacovigilance Programme of India plays an important role to ensure that the drug which are prescribed by the Healthcare Professionals are safe to administer. Pharmacovigilance come into existence with the objective of monitoring the ADR reported for those drugs which are marketed in India. India is the biggest player for manufacturing and developing of Generic Pharmaceutical Product along with the sophisticated Clinical Trials centre for conducting the Clinical Trials for all over the world. We need to construct the more efficacious Pharmacovigilance Team with addition of more number of AMCs. Also concluded to build the separate PV cell at each and every hospitals either Government or private to monitor the Pharmacovigilance activities.

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