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Review Article

PAST, PRESENT AND FUTURE OF PHARMACOVIGILANCE IN INDIA

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ABSTRACT

While major advancements in the discipline of pharmacovigilance have taken place in the West, not much has been achieved in India. However, with more clinical trials and clinical research activity being conducted in India, there is an immense need to understand and implement pharmacovigilance. Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines. As a means of pooling existing data on adverse drug reactions (ADRs), the World Health Organization (WHO) Programme for International Drug Monitoring was started in 1968. Currently, 86 countries participate in the programme, which is coordinated by WHO together with its collaborating centre in Uppsala, Sweden. The origin of pharmacovigilance in India goes back to 1986, when a formal ADR monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India. 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. This article gives a systematic review of the pharmacovigilance in India from its

origin to the current scenario and also discusses the various strategies and proposals to build, maintain and implement a robust pharmacovigilance system for India in the coming years.

INTRODUCTION

Pharmacovigilance is defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines.[1] Pharmacovigilance is an important and integral part of clinical research. Both, safety of clinical trials and post-marketing pharmacovigilance are critical throughout the product lifecycle. With a number of recent high-profile drug withdrawals, like Cerivastatin, the pharmaceutical industry and regulatory agencies have raised the issue of pharmacovigilance. Early detection of signals from both clinical trials and post- marketing surveillance studies have now been adapted by major pharmaceutical companies in order to identify the risks associated with the medicinal product and effectively manage the risks by applying robust risk management plans throughout the lifecycle of the product. Signal detection and risk management has added a new dimension to the field of pharmacovigilance and as an evolving discipline, it requires ongoing refinement in order to increase its applicability and value to public health.

While major advancements in the discipline of pharmacovigilance have taken place in the West, not much has been achieved in India. However, with more clinical trials and clinical research activity being conducted in India, there is an immense need to understand the importance of pharmacovigilance and how it impacts the lifecycle of the product. This will enable integration of good pharmacovigilance practice in the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post-marketing surveillance.

Origin of pharmacovigilance

A new breakthrough in this field only happened after an episode occurring in 1937. In that year, Sulfanilamide (Prontosil), used since 1932 for treatment of streptococcal infections, was launched as a syrup, containing diethyleneglycol as solvent. Although tested regarding aspect, taste and odor, its safety was not evaluated before launching. It was responsible for the death of 105 individuals (34children and 71 adults) and diethyleneglycol was incriminated. This tragedy caused the American Congress to approve in 1938 the Food Drug and Cosmetic Act, under which pharmaceutical product manufacturers would have to show scientific evidences of the safety of the drugs before releasing themfor sale.

The thalidomide tragedy is a milestone in the origin and development of pharmacovigilance. Thalidomide was introduced in 1957 and widely prescribed as an allegedly harmless treatment for morning sickness and nausea. It was tested in approximately 300 patients without toxicity. It was soon linked to a congenital abnormality phocomelia, which caused severe birth defects in children of women who had been prescribed

this medicine during pregnancy. In 1962, after reports of numerous cases of phocomelia, it was discontinued. In the same year, the Kefauver-Harris amendment was approved, requiring scientific evidences of efficacy and safety before drug tests in humans.[2]

As a means of pooling existing data on ADRs, WHO's Programme for International Drug Monitoring was started in 1968. Initially a pilot project in 10 countries with established national reporting systems for ADRs, the network has since expanded significantly as more countries worldwide developed national pharmacovigilance centers for the recording of ADRs. Currently, 86 countries participate in the programme, which is coordinated by WHO together with its collaborating centre in Uppsala, Sweden. The collaborating center is responsible for maintaining the global ADR database, Vigibase. At present the database contains more than four million ADR reports.

History of pharmacovigilance in India

The origin of pharmacovigilance in India goes back to 1986, when a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India.[3] However, nothing much happened until a decade later when in 1997, India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. This attempt was unsuccessful and hence, from 1January 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 26 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 system in information dissemination and the long-term objective is for the program to be a benchmark for global drug monitoring.

Given this background on pharmacovigilance in India to date, things have definitely changed for the better but at a very slow pace. The Regulatory Authority for India should be commended for introducing and implementing the Schedule Y and for reporting of all serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARS) from clinical trials. However, there is a need of spontaneous adverse event reporting from post-marketed medicines to the zonal centers and in turn to the

National Pharmacovigilance Centers to the WHO Uppsala Monitoring Center, which at the moment is woefully lacking. Therefore, in these circumstances, the questions that arise are whether the strategy should be changed and if so, how?

The immensity of the problem of ADRs

A number of studies conducted throughout the world have demonstrated that ADRs significantly decrease the quality of life, increase hospitalizations, prolong hospital stay and increase mortality. A landmark study by Lazarou in 1998 described ADRs to be the fourth to sixth largest cause of death in the USA and ADRs are estimated to cause 3-7% of all hospital admissions.[5] More than half of these ADRs are not recognized by the physicians on admission and ADRs may be responsible for the death of 15 out of 1000 patients admitted.[6] Furthermore, the financial cost of ADRs to the healthcare system is also huge. With more new medicines being approved for marketing more quickly without long-term safety studies by the regulatory authorities and switching of prescription-only medicines (POM) to over-the-counter (OTC) to be used more widely by patients for self-medication, the general public is at risk of exposing itself to ADRs.

Current scenario of pharmacovigilance in India

India is a vast country and there is a surfeit of drug brands—more than 6,000 licensed drug manufacturers and over 60,000 branded formulations. India is the fourth largest producer of pharmaceuticals in the world and is also emerging as a hub for clinical trials. Many new drugs are being introduced in the country, so there is an immense need to improve the pharmacovigilance system to protect the Indian population from potential harm that may be caused by some of the new drugs.

In the past, India’s regulatory agencies and drug companies based their safety assessments on experiences derived from long-term drug use in the Western markets and there was no real urgency for the government to establish a strong pharmacovigilance system of its own. In recent years, however, the lag between when a drug is placed in the market and its subsequent availability in India has decreased considerably so that the much needed longer-term safety data is no longer available. In addition, India-based drug companies have increased their capacity to develop and launch new drugs through their own research efforts and this has heightened the importance of developing adequate internal pharmacovigilance standards to detect adverse drug events.[7]

However, what needs to be more important along with the funding is a focused vision and effective strategy for developing the pharmacovigilance systems, especially in the Drug Controller General Ofof India Office, which is lacking. Traditionally, pharmacovigilance was never done in India in pharmaceutical companies, be it Indian or multinational companies (MNCs), so there is an immense shortage of knowledgeable people who will be able to advice the DCGI on this matter, as pharmacovigilance is a very complex subject,

intertwined with regulations and complex systems. The need is therefore to engage a completely independent adviser who has extensive and practical knowledge on pharmacovigilance, who can act as a Pharmacovigilance Advisor to the Government of India to effectively implement the systems and policies on pharmacovigilance. This will help the DCGI to spearhead the activities and implementation of pharmacovigilance.

The information obtained to date in the zonal centers from various peripheral centers is often poor and not well-analyzed. There is insufficient research on ADRs in India, so the exact incidence of specific ADRs is unknown. The reporting forms used by many people engaged in various pharmacovigilance work are different from the reporting form used by the National Pharmacovigilance Program, which makes it extremely difficult to transfer data to the national database, even if this has been shared by the various parties.

Understanding by healthcare professionals (both in rural areas and urban cities and hospitals) and knowledge and motivation for pharmacovigilance is almost negligible. There is hardly any encouragement from the department of health to provide more training and create more awareness amongst them for better reporting.

In India, there are several consumer groups who encourage patients to report any adverse reactions encountered by them, although there is no information for patients on how to report ADRs directly to the regulatory authority. Direct reports from the patients, the ones who actually experience ADRs, are not accepted by the monitoring centers and by regulatory authorities. To add to this is the total lack of any awareness about ADRs in the general population.

With more and more clinical trials and other clinical research activities being conducted in India, there is an immense need to understand the importance of pharmacovigilance and how it impacts the lifecycle of the product. Given this situation at present, the DCGI should act quickly to improve pharmacovigilance so as to integrate Good Pharmacovigilance Practice into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post-marketing surveillance.

Strategies and proposals: The way forward in India

A properly working pharmacovigilance system is essential if medicines are to be used safely. It will benefit all parties including healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk and to devise and implement effective risk management plans to save their drugs in difficult circumstances.

Having considered the problems and challenges facing the development of a robust pharmacovigilance system for India, we would like to make the following proposals:

1. Building and maintaining a robust pharmacovigilance system.
   The DCGI should invite experienced private firms to help, train and set up the pharmacovigilance system to combat the problems of inexperience and shortage of trained personnel.
2. Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections.
   The Government of India's Health Ministry will need to pass a law and make pharmacovigilance reporting mandatory. This should be valid not only for the MNCs operating within India but also for the Indian pharmaceutical companies. A department for Pharmacovigilance Inspections should be incorporated within the DCGI with the view of starting inspections in all pharmaceutical companies operating in India. All pharmaceutical companies should be instructed to maintain and submit to the DCGI the Summary of Pharmacovigilance System document operating within the company, which would serve as the base for future pharmacovigilance inspections.

3. High-level discussions with various stakeholders.
   A high-level discussion with various stakeholders, i.e., Ministry of Health and Family Welfare (MHW), Indian Council of Medical Research (ICMR), Medical Council of India (MCI), Pharmacy Council, Nursing Council, Dental Council, Pharmaceutical Companies, Consumer Associations, Nongovernmental Organizations (NGOs) and Patient Groups should be initiated in order to make them aware of how the DCGI is planning to improve and develop a robust system in pharmacovigilance

4. Strengthen the DCGI office with trained scientific and medical assessors for pharmacovigilance.
   Intensive training should be given in all aspects of pharmacovigilance to officials working within the pharmacovigilance department of the DCGI and in the peripheral, regional and zonal centers. This should be an ongoing activity with training scheduled twice a year.

5. Creating a single countrywide specific adverse event reporting form to be used by all.
   A single countrywide specific adverse event reporting form needs to be designed, which should not only be used by the National Pharmacovigilance Centers, but also by all registered hospitals (both private and government), teaching hospitals, Drug Information Centers and pharmacies throughout the country. It should also be made available to all primary healthcare centers (PHCs) in rural areas and all practicing general practitioners and physicians.

6. Creating a clinical trial and post-marketing database for SAEs / SUSARs and ADRs for signal detection and access to all relevant data from various stakeholders.
   Full complete data should be made available to the DCGI and to the various stakeholders from the date of first registration of the clinical trial in the India. This data should comply with consolidated standards of reporting trials (CONSORT) guidelines including overall benefit-risk profile of the product.

Current standards of safety reporting as outlined in Schedule Y and information about all AEs and ADRs per study arm should be systematically included as well as detailed description of cases with previously unknown AEs/ADRs and the reasons for study withdrawals.

For drugs already in the market, type and frequency of all adverse events (serious and non-serious) should be submitted in periodic safety update reports (PSURs) and also added to the summary of product characteristics (SPCs).

7. List all new drugs/indications by maintaining a standard database for every pharmaceutical company
   A list should be maintained by the regulatory authorities and pharmaceutical companies for all new drugs/indications in the database. All new issues need to be put under heightened surveillance. Pharmaceutical companies in these circumstances should have meetings set up with the DCGI to outline their risk management plan (RMP) for the safety issues in question and describe how they would put effective strategies in place to mitigate them.

8. Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance.
   There are several courses conducted by various organizations focusing in clinical research, but to date there is no course relevant to pharmacovigilance in the country. The various stakeholders including the MCI should incorporate a pharmacovigilance syllabus within the pharmacology and medicine curricula so that proper theoretical and practical training can be imparted to physicians. Similarly, nurses and pharmacists should also be trained in pharmacovigilance so that they are able to recognize ADRs and develop a culture of reporting ADRs in the future.

   An awareness program and a training schedule (both by distance education and face-to-face learning) covering all aspects of pharmacovigilance have now been designed by Symogen Ltd. These are meant for the research and development (R and D)-based pharmaceutical companies, particularly those involved in new drug research, the medical profession, the pharmacists and chemist-druggist trades and the patients, to be alert in detecting ADRs and reporting them to the Indian regulatory agencies, who in turn will investigate and take timely corrective action.

9. Collaborating with pharmacovigilance organizations in enhancing drug safety.
   With advancements in information technology (IT), there has been the emergence of new opportunities for national[8] and international[9] collaborations that can enhance post-marketing surveillance programs and increase drug safety. The Uppsala Monitoring Center (UMC) is an example of an international collaboration to establish a harmonized post-marketing surveillance database.[9] The system is based on the exchange of adverse reaction information among national drug monitoring centers in 80 countries. The information is transferred, stored and retrieved in a timely and secure way through the internet. The UMC database collectively contains over four million records with a large number of data fields.

A similar database can be built for the DCGI with the help of experienced private firms from the safety data received from clinical trials and post-marketing surveillance.

10. Building a network of pharmacovigilance and pharmacopeidemiologists in India.

    A core group of experts will need to be formed which will have representatives from MNCs, Indian pharmaceutical companies and personnel from the regulatory authority (DCGI).

11. Interaction with the IT sector in building a robust pharmacovigilance system for India.

    Software programs developed can be used for collection and analyses of data sets, determining trends of drug usage in various disease areas, compliance, medication errors and drug interactions leading to ADRs.

CONCLUSION

India is now considered to be a hub for clinical research. The DCGI has shown its commitment to ensure safe use of drugs by establishing the National Pharmacovigilance Program. More and more clinical trials are now being conducted in India and business process outsourcing (BPOs) based in India are now also undertaking pharmacovigilance projects from MNCs. Healthcare professionals, consumer groups, NGOs and hospitals should appreciate that there is now a system in place to collect and analyze adverse event data. They should start reporting adverse events actively and participate in the National Pharmacovigilance Program to help ensure that people in India receive safe drugs. With the help and proper coordination of all stakeholders, we can definitely build a world-class pharmacovigilance system in India.

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