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LEADING ARTICLE

Pharmacovigilance in India: Present Scenario and Future Challenges

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Abstract
Pharmacovigilance in India was initiated way back in 1986 with a formal adverse drug reaction (ADR) monitoring system, under supervision of the drug controller of India. India joined the World Health Organization (WHO) Programme for International Drug Monitoring in 1998, but was not successful. Later, the National Programme of Pharmacovigilance was launched in 2005, and was renamed as the Pharmacovigilance Programme of India (PvPI) in 2010. In consideration of having a robust pharmacovigilance system in India, steps were taken. The National Coordination Centre was shifted from New Delhi to the Indian Pharmacopoeia Commission (IPC) in Ghaziabad. The PvPI works to safeguard the health of the Indian population by ensuring that the benefit of medicines outweighs the risks associated with their use. The culture of reporting of ADRs has achieved remarkable success, with 250 PvPI-established adverse drug monitoring centres all over India and provision of training to healthcare professionals. The programme is striving hard to build trust between the physician and the patient, thereby increasing patient safety and the confidence of people in the country's health system, in addition to the detection of substandard medicines and prescribing, dispensing and administration errors. The IPC-PvPI has now become a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services. In spite of these achievements, several challenges are faced by the PvPI, like the monitoring of generic drugs, biosimilars, and disease-specific ADRs of antidiabetic, cardiovascular and antipsychotic drugs and, above all, creating awareness, which is a continual process. At the same time, the PvPI is trying to address other challenges like counterfeit drugs, antimicrobial resistance, and surveillance during mass vaccinations and other national programmes.

Key Points

India now has a stable and robust pharmacovigilance system; this enables the global community to ensure the safety of medicines.

As a World Health Organization (WHO) Collaborating Centre, the Pharmacovigilance Programme of India provides technical support to the WHO member countries participating in the international drug monitoring programme.

1 Overview

The tragedy of thalidomide in the 1960s compelled health agencies and regulators worldwide to deliberate on drug safety issues [1–3]. Thousands of babies were born without limbs because of exposure to thalidomide consumed by the pregnant mothers for morning sickness. Little did the world know about its adverse effect on babies in utero. Consequently, for the first time, systematic efforts were made globally to deal with the adverse effects of drugs and patient safety. In 1963, the 16th World Health Assembly adopted a resolution (WHA 16.36) [4] for rapid dissemination of

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information on adverse drug reactions (ADRs), and later on, this formed the basis of the World Health Organization (WHO) Pilot Research Project for International Drug Monitoring in 1968. The project aimed to develop an international system that could detect previously unknown or poorly understood adverse effects of drugs. The WHO initiated the project with the cooperation of ten countries, which had their own pharmacovigilance systems. These countries had well established national drug monitoring centres receiving adverse drug reports from healthcare professionals (HCPs). The reports received by the centres were analysed locally and then forwarded to the WHO database, which since 1978 has been maintained by the WHO Collaborating Centre for International Drug Monitoring, located in Uppsala, Sweden [5]. These member countries provided the essential information required for the database. Thus the science of pharmacovigilance or drug safety emerged. Gradually, more and more countries joined the WHO Programme for International Drug Monitoring (PIDM). The Uppsala Monitoring Centre (UMC) supports the PIDM by collecting, assessing and communicating information from member countries' national pharmacovigilance programmes with regard to the benefits, harms, effectiveness and risks of drugs.

At present, more than 150 countries are members of the PIDM. India, too, joined the programme in 1998, with three centres involved in ADR monitoring, but was not successful because of a lack of manpower and a lack of funding from the government, providing insufficient information for the contribution to the database.

The functions of pharmacovigilance are to detect and study ADRs, measure risk and effectiveness of drug use, disseminate this information and educate people and HCPs. The term "pharmacovigilance" is now familiar to most healthcare providers. In the year 1986, pharmacovigilance activities were initiated with a proposal of a formal ADR monitoring system with 12 regional centres for a population of 50 million each, and in 1989, six regional centres were set up in Mumbai, New Delhi, Kolkata, Lucknow, Pondicherry and Chandigarh, under the supervision of the drug controller of India [6].

2 The National Pharmacovigilance Programme

Pharmacovigilance in India was reinitiated by the Government of India by launching the National Programme of Pharmacovigilance (NPP) with the support of the World Bank in November 2004, and started functioning 1 January 2005. The National Pharmacovigilance Center (NPC) at the Central Drugs Standard Control Organization (CDSCO) coordinated the countrywide pharmacovigilance programme under the aegis of the Ministry of Health and Family Welfare, New Delhi, and the programme was directed by the National Pharmacovigilance Advisory Committee (NPAC). The programme had three main objectives: to foster a reporting culture, to involve a large number of HCPs in the system for the dissemination of information, and to be a benchmark for global drug monitoring [7]. Two zonal, 26 peripheral and five regional centres were established. These centres were responsible for collating the information about adverse drug events from all over the country. The zonal centres submitted these reports to the CDSCO as well as to the UMC in Sweden [8]. However, the programme did not meet expectations, and in 2009, it was temporarily suspended, as the support from the World Bank was discontinued [9].

3 The Pharmacovigilance Programme of India (PvPI)

The need for a robust pharmacovigilance system for safeguarding public health was soon realized by the regulatory authorities, and the NPP was renamed the Pharmacovigilance Programme of India (PvPI), which started functioning 14 July 2010, with the All India Institute of Medical Sciences (AIIMS), New Delhi, as the National Coordination Centre (NCC). In order to monitor ADRs all over India, the programme had 22 ADR monitoring centres (AMCs), including AIIMS, New Delhi. The NCC was later shifted from AIIMS to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, on 15 April 2011, for effective implementation of the programme, with the main aim of generating independent data on the safety of drugs to match the global drug safety monitoring standards. Because pharmacovigilance was considered to be a programme that monitors prescriptions for adverse drug events and medication errors, some clinicians were apprehensive about it, as they felt that their capabilities were being doubted [10]. The PvPI is striving hard to overcome this challenge of apprehension and to eliminate the reasons for underreporting [11] by way of conducting several continued medical education, awareness and training programmes for HCPs on a regular basis to educate them on and inculcate the habit of reporting of ADRs. The HCPs have been made aware that no legal action is implicated in reporting ADRs.

The programme intended to build trust between the physician and the patient, thereby increasing patient safety and the confidence of people in the health system of the country. The PvPI works with the mission to safeguard the health of the Indian population by ensuring that the benefit of medicines outweighs the risks associated with their use [12].

The PvPI collates the information received in the form of Individual Case Safety Reports (ICSRs) from the AMCs, HCPs, pharmacists and other non-HCPs (medical colleges and hospitals, medical/central/autonomous

institutes or corporate hospitals not enrolled under the PvPI) (Fig. 1), and analyses the data and uses the conclusions to recommend informed regulatory interventions. Simultaneously, it informs the HCPs and consumers about the risks associated with the medicines. Apart from this, the PvPI also aims to detect substandard medicines and prescribing, dispensing and administration errors to achieve better patient safety. At the same time, the PvPI is trying to address other challenges like counterfeit drugs, antimicrobial resistance, and surveillance during mass vaccinations and other national programmes. The following are the objectives of the programme [12]:

- To create a nationwide system for patient safety reporting
- To identify and analyse new signals from the reported cases
- To analyse the benefit–risk balance of marketed medications
- To generate evidence-based information on the safety of medicines
- To support regulatory agencies in the decision-making process on the use of medications
- To communicate safety information on the use of medicines to various stakeholders to minimize the risk
- To emerge as a national centre of excellence for pharmacovigilance activities
- To collaborate with other national centres for the exchange of information and data management
- To provide training and consultancy support to other national pharmacovigilance centres across the globe
- To promote rational use of medicines

The programme resurged within a span of 5 years and exhibited impressive performance at the international level, including ADR reporting and providing skill development. During 2017, the PvPI conducted six skill development programmes; around 276 HCPs have acquired basic knowledge and adequate skills in pharmacovigilance. The participants were pharmacists (70%), doctors (10%) and regulators and nurses (20%). At present, about 250 AMCs have been established in government and private hospitals, medical colleges and pharmacy colleges all over India, establishing a framework of pharmacovigilance and developing a culture of reporting in India [13].

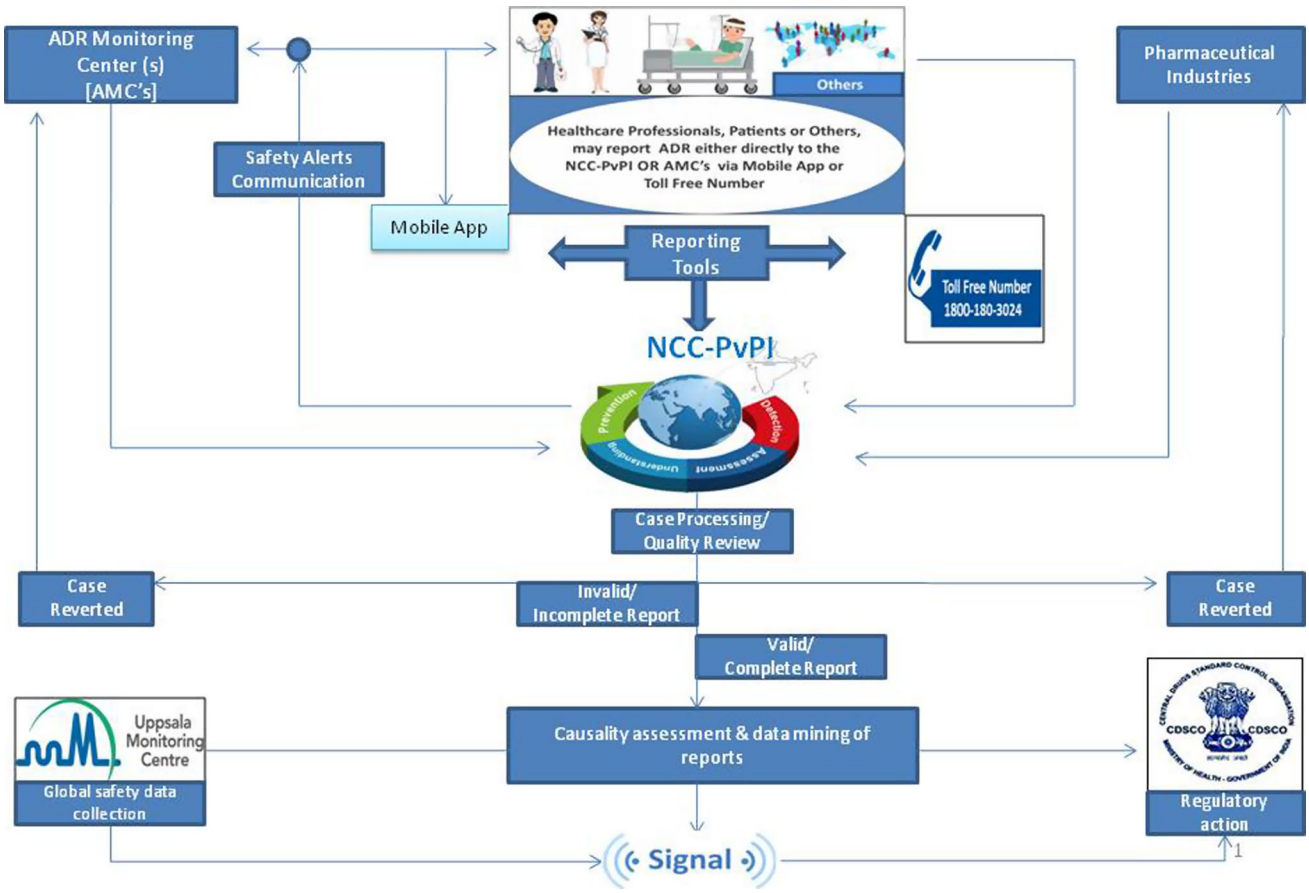

Fig. 1 System and procedure for adverse drug reporting in PvPI

For public outreach, several awareness programmes have been conducted by the AMCs. The PvPI organized interactive sessions for market authorization holders in April 2015 and 2016 and nursing staff to improve the quality of reports [14]. The reporting forms have been made available in ten vernacular languages, and also, separate forms for HCPs and consumers are available on the CDSCO website.

The NCC-PvPI identifies potential signals from India-specific ICSRs from the national ICSR database management system, i.e. VigiFlow. Over the period of 7 years, the PvPI database has grown exponentially; all the reported ICSRs are collated and analysed for relatedness and causality assessment. The HCPs at the AMCs are trained on ADR prevention and management. The causality assessment of the ICSRs is a joint activity of the AMC and the NCC. Around 3% of ICSRs fall under the category of "certain", around 47% of cases are "probable", 20% of cases are "possible" and the rest fall under the category of "unlikely/unassessible".

The programme has a signal review panel (SRP), which provides technical assistance by scrutinizing the data for any new signal. A signal is, "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously", as defined by the WHO [15]. The PvPI identifies signals from the ICSRs by applying methods such as the proportionality reporting ratio (PRR) and information component (IC) value. At present, the PvPI shares the information about the identified signals with the AMCs, regulatory authority staff and their advisers participating in the PvPI [12]. So far, the PvPI has generated five India-specific signals and 71 alerts, and 24 cases were recommended to the CDSCO regarding changes to package inserts. The PvPI sends alerts time to time to HCPs.

Good Pharmacovigilance Practices (GPPs) and applicable regulations compel pharmaceutical companies to always be vigilant about their products regarding the benefits and risks associated with them.

The NCC-PvPI is actively involved in providing training to existing professionals in pharmacovigilance along with young pharmacy, medical and paramedical professionals regarding the basics and regulatory aspects of pharmacovigilance round the year.

The NCC-PvPI IPC was also launched as a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services on 30 October 2017, at the IPC in Ghaziabad.

4 The Haemovigilance Programme of India

The Haemovigilance Programme of India (HvPI) was launched on 10 December 2012 by the NCC-PvPI with the National Institute of Biologicals, Noida, Uttar Pradesh, under the Ministry of Health and Family Welfare, Government of India, as the NCC [16], keeping in view the monitoring of blood quality and blood products in transfusion. The programme was initiated in 60 medical colleges in the country that were already enrolled under the PvPI. The programme collates and analyses information about haemovigilance and adverse events concerning biologicals [17], and is constantly working toward the advancement of the quality and safety of blood products and the transfusion process to ensure patient care and safety [18, 19].

5 The Materiovigilance Programme of India

The Materiovigilance Programme of India (MvPI) is responsible for monitoring and reporting adverse events associated with the use of in vitro diagnostics.

To monitor medical device-related adverse events, the MvPI was launched by the Drugs Controller General of India (DCGI) at the IPC on 6 July 2015. Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, is the National Collaboration Centre, and the National Health System Resource Centre (NHSRC), New Delhi, provides technical support.

However, on 21 March 2017, the NCC-PvPI IPC was urged to bear the responsibilities of the MvPI. Recently, a circular was sent to all AMCs under the PvPI highlighting the requirement to report all adverse events due to use of medical devices in duly filled Medical Device Adverse Event Reporting Forms. It also emphasized the need for coordination by the PvPI with the cardiology, orthopaedic and dentistry departments of all AMCs to ensure urgent reporting, and simultaneously urged the PvPI to develop relationships with biomedical engineers, technical partners and HCPs [20]. To date, about 850 adverse events due to invasive and non-invasive devices have been reported using the Medical Device Adverse Event Reporting Form. These reports were associated with the use of hip implants, intrauterine contraceptive devices, cardiac stents and others. All the reports were analysed for a causal relationship between the device and the events; it was concluded that in most of the cases, devices were not responsible for causing the events. Certain cases were referred back to the reporter to obtain more information.

6 Achievements of the PvPI

- Establishment of 250 AMCs that create a framework of pharmacovigilance and the culture of reporting all over India.
- For public outreach, several awareness programmes have been conducted by the AMCs. The ADR reporting culture, needed to strengthen the system, is improving throughout the country, including within groups such as defence personnel, nursing staff, and market authorization holders [21]. The reporting forms have been made available in ten vernacular languages, and also, separate forms for HCPs and consumers are available on the CDSCO website.
- The PvPI has contributed in national health programmes such as those for tuberculosis, neglected tropical diseases, vector borne diseases, HIV-AIDS, and immunization. The drug alerts/signals generated with respect to the drugs/vaccines have been communicated to their respective programmes for better patient safety outcomes. Post-alignment with the adverse event following immunization (AEFI) benefitted at large in the National Regulatory Authority Assessment 2017, as the vigilance benchmarking tool reached the highest maturity level of 4.
- The PvPI initiated a skill development programme on "Basic & Regulatory Aspects of Pharmacovigilance" to train young professionals in pharmacovigilance. The course was attended by HCPs from all over India.
- Antimicrobial resistance in the country is increasing, and the PvPI acts by all possible means of interventions to check the danger of antimicrobial resistance. Pharmacovigilance activities are being strengthened at national, regional and district levels to safeguard public health. The National Health Policy 2017, launched by the Ministry of Health and Family Welfare, addresses antimicrobial resistance and pharmacovigilance. This policy-level amendment shall provide the scope for better reporting and preventing ADRs wherever possible.
- The PvPI under the aegis of the IPC, Ministry of Health and Family Welfare, was successfully assessed by the World Health Organization–National Regulatory Authority (WHO-NRA) 2017 Global Benchmarking Tool (GBT). As an outcome, vigilance achieved a maturity level of 4 out of 5 [22, 23].
- In view of the quantity and quality of the work conducted by the NCC-PvPI during the past 6 years and its significant contribution to the WHO PIDM, the IPC is now recognized as a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services.

7 Future Challenges

7.1 Comparison and Monitoring of Original/Reference Products and Generic Products/Biosimilars

Unlike developing countries, the majority of developed countries have the fundamental institutions and processes of a pharmacovigilance framework in place, with robust systems of pharmacovigilance, but still, they face challenges in monitoring ADRs due to generic drugs or biosimilars.

A large number of generic pharmaceuticals enter the market once the exclusivity of its innovator product is over. The cost effectiveness of these generic products helps regarding the affordability and accessibility of these drugs. Generic drugs are similar to the original product in all respects except for the excipients used by the different manufacturers. These excipients are inactive substances and have no effect on the drug action, but have also been reported to cause instability and adverse effects [24, 25].

However, because biosimilars are structurally similar, though not identical, to the originator biological product, there is concern about the occurrence of adverse events related to immunogenicity [19]. It has been reported that even if the patient has switched over from a branded drug to a generic version, the adverse effect due to the generic version is attributed to the branded drug. This needs careful pharmacovigilance monitoring. The nomenclature of the generic/biosimilar drugs also plays a vital role in the monitoring of marketed products [25–28]. Therefore, in order to ensure seamless and rigorous pharmacovigilance practices for biosimilars, harmonization of Council for International Organizations of Medical Sciences (CIOMS), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and other guidelines is necessary.

7.2 Monitoring of Disease-Specific Adverse Drug Reactions

7.2.1 Cardiovascular Drugs

Hypertension and cardiovascular disease (CVD) are leading causes of mortality and morbidity all over the world [29, 30]. India, with an estimated population of 1.27 billion, has about 30 million coronary artery disease (CAD) patients [31], with 14 million in urban and 16 million in rural areas, and by 2020, the load of CVD in India will exceed other regions of the world [18]. Every year, more than 30% of the deaths are due to CVD [32]. The mortality

due to CVD is projected to rise to 4.2 million by 2030 [31]. The mortality and morbidity due to CVD are increasing at an alarming rate. Since the patients are on polypharmacy for a longer duration, the risk of ADRs always exists. Studies have reported an ADR prevalence of 18–24% in CVD patients [30–35].

7.2.2 Antidiabetic Drugs

Similar to CVD, diabetes is another disease which is gripping a large number of people globally [36]. Worldwide, 415 million people have diabetes, and the number of people with the disease is set to rise beyond 642 million by 2040 [37]. In India, more than 65.1 million individuals have been diagnosed with the disease [38], and the estimates suggest 89 million patients by 2030 and about 56% of patients will be from urban regions [39].

7.2.3 Antipsychotic Drugs

An increased incidence and prevalence of psychiatric disorders has led to increased use of antipsychotic drugs in India. Since antipsychotic drugs affect the multiple dopaminergic pathways, several ADRs have been observed in hospital-based, retrospective, prospective and community-based studies in India and abroad [40–45], such as gastrointestinal, reproductive and neurological disorders impairing the quality of life of patients. The researchers of the studies recommend caution in prescribing antipsychotic drugs. Nonetheless, data are lacking on the exact prevalence and magnitude of the problem in India.

7.3 Awareness Among Medical and Paramedical Staff

Studies have shown that a large percentage of the paramedical staff and even HCPs lack awareness about the pharmacovigilance system of the country [46–51]. Medical interns and post-graduates had better awareness compared to the medical graduate students because of their clinical association. It is advisable to induct pharmacovigilance courses in the undergraduate curriculum, and training should be given to paramedical and medical staff to eliminate the deterrents for reporting [49–51].

7.4 Combination Products

In India, adverse event reporting associated with the use of combination products such as fixed-dose combinations (FDCs) has remained a challenge. Because FDC formulations may have up to five (or even more) drugs, it is very difficult to establish a temporal relationship between any one drug and an event. However, in the present scenario, the causality of adverse events associated with FDCs is assessed on the basis of the clinical experience and expertise of the HCPs.

7.5 Adverse Events Reporting with the Use of Diagnostics

Another emerging challenge is adverse event reporting with the use of diagnostics. Since, medical device adverse event reporting through the MvPI is in the initial stage, it may be a few years down the line until facts will be established for root-cause analysis.

8 Conclusion

The PvPI has strived tirelessly to achieve its goals. These continued efforts have resulted in remarkable achievements within a period of 6 years. Despite its achievements, the programme intends to continue with the same fervour to meet its challenges, like creating awareness and inculcating the reporting habit in the country's population, with special attention to disease-specific ADRs. It is noteworthy that monitoring of generic drugs and biosimilars is becoming a major challenge. The regulatory authorities must address these challenges in a harmonized manner with the best pharmacovigilance practices.

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Compliance with Ethical Standards

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