

Safety of medicines

Pharmacovigilance Programme of India

The journey travelled and the way forward

Pharmacovigilance is important in assuring the safety of medicines and protecting patients from harm. The Pharmacovigilance Programme of India (PvPI) is a robust scientific platform that provides valuable information on the safety of medicinal products and contributes to regulatory decisions. Recent changes in the regulation of the drug approval processes and pre- and post-approval vigilance of undesired effects have strengthened pharmacovigilance in India. This article gives an overview of pharmacovigilance structures and practices, their integration into public health programmes, the regulatory context, recent initiatives undertaken by PvPI, challenges to overcome, and the way forward.

Introduction

All medicines carry some risk of harm. It is therefore important to monitor their effects, both intended and unwanted, to get an evidence-based assessment of risk versus benefit. Today it is well recognized that a reliable pharmacovigilance system is essential for rational, safe and cost-effective use of medicines and therefore has clear advantages in relation to cost for public health.⁽¹⁾

Pharmacovigilance in India has huge socio-economic implications. The total size of the Indian pharmaceutical industry was about US\$ 33 billion in 2016, making it the world's third largest in terms of volume.⁽²⁾

An increasing part of the medicines on the Indian market are novel products. Their available baseline safety data often do not reflect the social, economic, epidemiological or health conditions of India, and their safety in everyday use still has to be proven. Establishing a standardized and robust pharmacovigilance system in India is therefore of paramount importance.

Pharmacovigilance in India

The concept of pharmacovigilance in India was first proposed in 1986 with a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centres.

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In 1989, six regional centres were set up under the aegis of the Drug Controller General of India. In 1997, India joined the WHO Programme for International Drug Monitoring. In 2004, the Central Drugs Standard Control Organization (CDSCO) established the National Pharmacovigilance Programme (NPVP); however in mid-2009 the World Bank funding for the NPVP ended and the programme was suspended. Recognizing the need for improved ADR monitoring in India, the Government of India proposed to work on a new framework of the programme. The Pharmacovigilance Programme for India (PvPI) was launched on a national footing in 2010 by the Ministry of Health & Family Welfare (MoHFW) of the Government of India.⁽³⁾

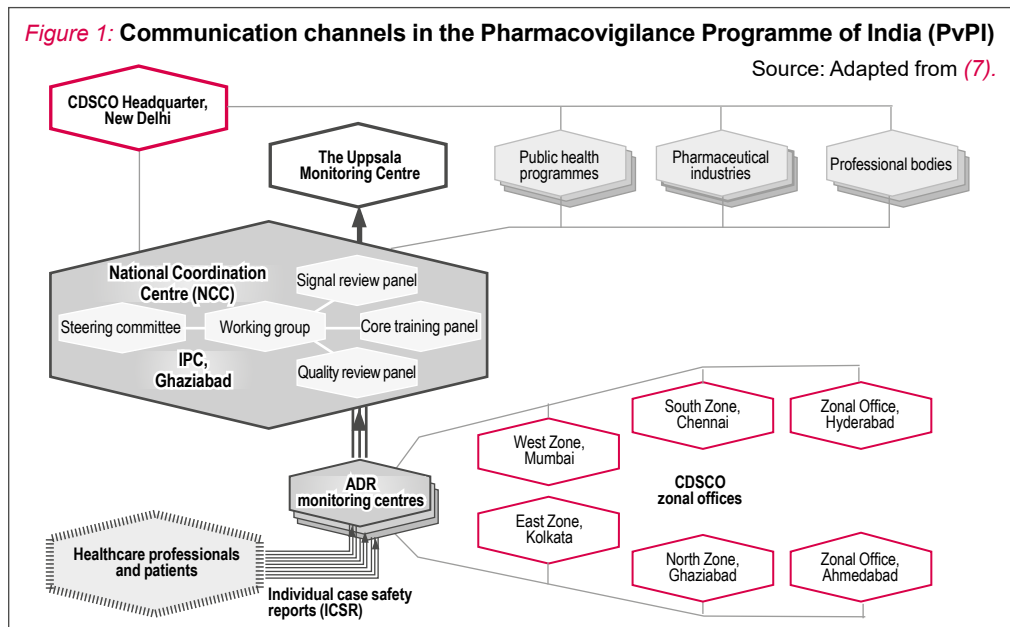
In 2016 pharmacovigilance became a mandatory requirement under the Drugs & Cosmetics Act,⁽⁴⁾ which was amended to require all manufacturers and importers of medicines to set up pharmacovigilance systems within their company. Periodic

safety update reports (PSUR) and post-marketing surveillance are described in Schedule Y of the Act. Pharmacovigilance guidelines for marketing authorization holders of pharmaceutical products were released in October 2017, together with the National Strategic Plan for Scale up of Pharmacovigilance in India, which aims to establish pharmacovigilance systems at District Hospitals, Community Health Centres (CHCs) and Primary Health centres (PHCs) under the umbrella of the national health mission, to support the existing pharmacovigilance systems in public health programmes.

The Pharmacovigilance Programme of India (PvPI)

Structure

Since 2011 PvPI is coordinated by the Indian Pharmacopoeia Commission (IPC) as the National Coordination Centre (NCC) (*Figure 1*).



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ADR monitoring centres across the country collect reports from healthcare professionals and patients and submit them as individual case safety reports (ICSR) to NCC. The number of centres has increased more than tenfold from 22 in 2010 to 250 in August 2017, with many more to follow.

PvPI has a steering committee, a working group that gives technical input to CDSCO, and three expert panels to advise on technical issues. The Quality Review Panel reviews the quality and completeness of ICSRs, makes recommendations to the PvPI working group after data analysis and devises formats and guidance documents for follow-up actions. The Signal Review Panel identifies and evaluates signals from the ICSRs submitted to NCC, defines biostatistical methods for analysis and actionable indicators, and proposes appropriate regulatory interventions to CDSCO. The Core Training Panel identifies trainers, training needs and training content, and interacts with international agencies on participation and implementation of pharmacovigilance training programmes.

NCC sends the ICSRs to the WHO ICSR database, [VigiBase](#), which is managed by the [Uppsala Monitoring Centre \(UMC\)](#), the WHO Collaborating Centre for International Drug Monitoring in Sweden. UMC supports the PvPI with tools such as [VigiFlow](#), [VigiMine](#), [VigiMed](#), [VigiSearch](#), [VigiLyze](#) and [VigiAccess](#). Currently, India's total contribution to [VigiBase](#) is more than 280 000 ICSRs. The process of ADR reporting in India has been streamlined and is supported by feedback, circulars and newsletters. Data quality has increased since 2011 and is far above the average for reporting countries globally.⁽⁵⁾ In 2016 the completeness score for the Indian ICSRs as per the UMC documentation grading was 0.82 out of 1.

Capacity building

Four regional resource centres provide training and technical support to AMCs of their respective regions¹. In addition, NCC regularly organizes national and regional programmes for training, consumer awareness and Continuing Medical Education. A [Guidance document for spontaneous ADR reporting for medicines, vaccines and blood products](#) was published in 2014. In January 2017 PvPI started a nationwide [skills development programme](#) on basic and regulatory aspects of pharmacovigilance for healthcare professionals.

Pharmacovigilance tools

PvPI, in collaboration with WHO India, has developed the PvPI toolkit, a package of simple pharmacovigilance tools in line with WHO guidelines and current best practice. The toolkit includes an [ADR reporting form](#), which is available in Hindi and nine other regional languages to encourage direct patient reporting. There is also a [feedback form for stakeholders](#).

To extend the outreach of PvPI to remote areas a toll-free helpline (1800 180 3024) with SMS feedback facility has been launched. The helpline is manned during working hours, missed calls are followed up the next day. The ADR reporter information is communicated to the nearby monitoring centres to allow any follow-up.

An android mobile application for reporting ADRs was launched in May 2015 by PvPI in collaboration with NSCB Medical College, Jabalpur. The application has built-in functionality for customization

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of reporter details, auto-entry of drug details and WHO algorithm-based causality assessment. In October 2017, NCC developed an advanced version of the application with features that support source document and image attachment, XML generation and auto-filling of report details.

PvPI also uses social media including LinkedIn (NCC PvPI), WhatsApp (7042343309), Facebook (Ncc-PvPI Ipc) and Twitter (@IPCNCPPvPI).

Catalysts

Three recent initiatives have acted as catalysts for vigilance strengthening in India:

Firstly, at the end of a comprehensive review conducted from 13-17 February 2017, WHO experts concluded that the national regulatory authority (NRA) and affiliated institutions in India continue to meet the requirements for a functional vaccine regulatory system as defined in the WHO global benchmarking tool (GBT). Pharmacovigilance is one of the core functions in the GBT and was assessed at Maturity Level 4 – the highest level – during the benchmarking exercise in India.

Secondly, in 2017 the NCC became a [WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services](#). This is the first WHO Collaborating Centre on this theme. Its tasks are to develop tools and guidelines for enhancing pharmacovigilance practice in low- and middle-income countries (LMIC), to contribute to capacity building in WHO Member States, and to provide scientific support to countries for pharmacovigilance in public health programmes and regulation.

Thirdly, India is actively engaged in the [South East Asia Regulatory Network \(SEARN\)](#) in a move to increase access to high quality medical products in

WHO Member States. Vigilance of medical products is one of the four core priority areas of SEARN.

Collaboration with public health programmes

Optimizing the safety of medicines used in public health programme is essential to maximize the benefits of these programmes and maintain public confidence. The WHO Country Office for India has been engaged in providing pivotal strategic and technical support to the PvPI in setting up pharmacovigilance systems in the national immunization programme and in treatment programmes for tuberculosis, HIV/AIDS and vector-borne diseases.

Universal Immunization Programme (UIP)

An adverse event following immunization (AEFI) is “any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of vaccine”.⁽⁶⁾ Adverse reactions to vaccines are rare but may become apparent when a large cohort is vaccinated. It is important to report and investigate each AEFI in order to determine whether it is causally linked to a vaccine and to take appropriate action.

The AEFI surveillance system in India was initiated in 1988. Reports on AEFIs are collected by monitoring centres throughout the country. AEFI committees have been constituted at state and district levels to regularly review and analyze AEFI reports. The support of the WHO National Polio Surveillance Project network is being leveraged at state and district levels.

At the national level the system is handled by three partner entities, namely CDSCO, MoHFW, and NCC. The Pharmacovigilance Division (Human vaccine) of CDSCO's

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Biological Division monitors all post-licensure activities of vaccines for regulatory decision-making. The AEFI Secretariat at the MoHFW's Immunization Technical Support Unit (ITSU) collects and collates AEFI data for the National AEFI Committee to review. The NCC's Signal Review Panel analyzes AEFI reports and forwards its observations to the National AEFI Committee, to recommend regulatory actions to CDSCO.

The achievements of the AEFI division at the MoHFW, with WHO support, have strengthened pharmacovigilance of vaccines in India. Communication Guidelines for Building Vaccine Confidence around AEFI were released in 2013, and training has been undertaken in 8 states. quality management system, AEFI surveillance and response operational guidelines, standard operating procedures, training and a pilot online reporting project have also been established. As a result, AEFI reporting has increased from 398 in 2012 to 1393 in 2016. However, considering the large number of vaccine doses given to children in India there is scope for further improvement.

WHO has also provided technical, operational and financial support to the follow up of a landmark study on the potential association of all-cause death and hospitalization with routine UIP vaccinations administered to a cohort of infants in Kerala and Tamil Nadu states of India, in line with the government's commitment to scale up the pentavalent vaccine in India. The study has provided some interesting learnings for countries in the region on pentavalent vaccine and routine UIP vaccines.

HIV and tuberculosis programmes

Treatment for HIV and tuberculosis often involves a significant pill burden. A patient diagnosed with tuberculosis may

take 4–14 medicines concurrently, with regimens lasting from six months to two years or more, increasing the likelihood of ADRs. Adverse events can cause patients to interrupt their treatment prematurely, which can contribute to avoidable morbidity, drug resistance, treatment failure, reduced quality of life, or death. It is important that ADRs, especially serious ones, be routinely monitored. WHO has produced handbooks on pharmacovigilance for anti-tuberculosis and antiretroviral medicines.

A memorandum of understanding (MOU) was signed between IPC as the NCC for pharmacovigilance and the National AIDS Control Organization (NACO) in September 2014 for setting up systems and processes for reporting, analysis and monitoring of ADRs due to antiretroviral medicines. In a first phase, 37 ART centres were identified among the existing PvPI monitoring centres, and focal personnel were trained.

A similar MOU was facilitated between IPC and the Revised National Tuberculosis Programme (RNTCP), one of the largest public health programmes in India. In December 2014 WHO, IPC, RNTCP and NACO, in collaboration with PvPI, organized a joint workshop on ADR monitoring, reporting and causality assessment for medical and statistical officers from treatment centres all over India.

A focus is on monitoring of bedaquiline, which was launched in March 2016 for the treatment of multidrug-resistant tuberculosis under RNTCP's Conditional Access Programme (CAP), together with guidelines on the Prevention and management of ADRs associated with antitubercular drugs. Currently there are 19 sites where at least one patient has been initiated on bedaquiline, and training has been conducted to expand

the programme to additional sites across India. WHO is supporting PvPI in setting up systems for reporting of adverse events in patients treated with bedaquiline. A prospective, observational Cohort Event Monitoring (CEM) of adverse events with bedaquiline is being implemented as part of CAP. Data are recorded upon treatment initiation and at every follow-up visit or whenever an event is reported. The data from CEM are entered into Nikshay, the electronic database used by the tuberculosis programme in India, from where they are automatically transmitted through a bridge application to the VigiFlow database used by PvPI to record ICSRs. A Drug Safety Monitoring Committee will review the use of bedaquiline and provide recommendations on its scale-up in India based on the analysis of the data from CEM.

Vector-borne diseases programme

PvPI (with WHO support) is collaborating with the National Vector Borne Disease Control Programme (NVBDCP) to set up focused pharmacovigilance systems for medicines used in vector-borne diseases. An MOU was signed in August 2016. In February 2017 WHO, in collaboration with NVBDCP and PvPI, organized a national meeting to accelerate Kala-azar elimination, in conjunction with a national pharmacovigilance workshop. This was followed by five regional workshops which reached a total of 530 participants in all endemic districts of four Indian states. Reporting of ADRs to Kala-azar medicines started in April 2017.

Deworming programme

Once a year, on national deworming day, all enrolled and out-of-school children aged 1 to 19 in schools and child care

centres are given albendazole deworming tablets. This is followed by a “mop-up day” to deworm children who could not be treated on national deworming day. Two ADR reporting forms – one for healthcare professionals and one for consumers – have been included in the protocol and made available as annexure to the [National Guidelines for Deworming Day](#).

Collaboration with medical organizations

IPC has identified six institutions affiliated to the [Indian Council for Medical Research \(ICMR\)](#)² for focused pharmacovigilance research to ensure the safety of vulnerable populations exposed to different drug regimens. This collaborative effort aims to synergize experience in pharmacovigilance and pharmacoepidemiology to bolster the country's PvPI initiative.

The [Indian Medical Association \(IMA\)](#) and IPC have agreed to work together to enhance ADR reporting by clinicians. A patient safety monitoring cell equipped with skilled manpower and a dedicated helpline for ADR reporting and other logistics has been set up at the IMA headquarters in New Delhi. There will be regular training and advocacy to doctors on pharmacovigilance. IMA has also declared a “National Patient Safety Day”.

In January 2017 IPC signed an MoU with the [National Accreditation Board for Hospitals and Healthcare providers \(NABH\)](#) to promote monitoring and reporting of ADRs by NABH-accredited hospitals.

² National AIDS Research Institution (NARI), Pune; Institute of Research in Reproductive Health (IRRH), Mumbai; National Institute of Cholera & Enteric Diseases (NICED), Kolkata; National Institute of Nutrition (NIN), Hyderabad; National Institute of Epidemiology (NIE), Chennai; National Institute of Malaria Research (NIMR), New Delhi

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Vigilance for medical devices

The Materiovigilance Programme of India (MvPI) was launched on 6 July 2015 to monitor adverse events occurring with the use of medical devices. IPC is collaborating with the National Health System Resource Centre (NHSRC), the Sree Chitra Tirunal Institute for Medical Sciences & Technology (SCTIMST) and CDSCO to provide technical support for regulatory actions for safe use of medical devices based on data generated in India.

Under MvPI a wide range of professionals including clinicians, biomedical engineers, clinical engineers, hospital technology managers, pharmacists, nurses and technicians can report adverse events experienced with medical devices, using the Medical Device Adverse Event (MDAE) reporting form. Medical device manufacturers, importers and traders can report adverse events specific to their products to SCTIMST. There are 10 medical device monitoring centres that accept MDAE forms for onward submission to NCC. The toll free PvPI helpline also provides assistance in reporting.

NHSRC's Division of Health Care Technology is India's first [WHO Collaborating Centre for Priority Medical Devices & Health Technology Policy](#). In this role the centre frames technical specifications for medical devices, develops best practices for technology life cycle management and maintenance, assesses innovations for uptake into public health systems, and conducts health technology assessments in collaboration with WHO. Assessments of over 50 technologies have been completed and published in a compendium. NHSRC and WHO have been jointly offering Health Technology Assessment Fellowships once every six months. Over 300 professionals from across

India have been trained in the past five such programmes.

Vigilance for blood products

Tracking adverse events occurring after administration of blood products is important to ensure that blood transfusions and other uses of blood products are safe and have the intended benefits in the health care system. Haemovigilance is the set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through to their provision and transfusion to patients, and including their follow-up. It is intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of blood products and to prevent their occurrence and recurrence. Haemovigilance enhances patient safety by learning from failures.

The Haemovigilance Programme of India (HvPI) was launched under the umbrella of PvPI on 10 December 2012. Currently 154 centres are enrolled in this programme. The [National Institute of Biologicals](#) (NIB) is the coordinating centre for HvPI.

Challenges

Setting up a national pharmacovigilance system in India presents some formidable challenges. The health sector caters for a population of over 1.3 billion with vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines and different socioeconomic status. There has been a rising disease burden with an increasing incidence of non-communicable diseases such as cardiovascular conditions and diabetes. And the country's production and use of medical products is growing fast,

with many new and complex technologies coming to market.

One of the biggest issues, as stated by Dr Kalaiselvan, Principal Scientific Officer of PvPI in an [interview with UMC](#), is under-reporting of ADRs. The heavy workload of healthcare professionals does not leave much time for reporting. PvPI staff at the monitoring centres – which are mostly hospitals – therefore actively solicit ADR reports from doctors and nurses. Another challenge for PvPI is that pharmacists need to be empowered to enhance ADR reporting.

Running a pharmacovigilance programme in India, with its 28 states and more than 600 districts governed by a complex public administration, is no easy task. Previous pharmacovigilance programmes in India suffered from a lack of communication and coordination. The government and policymakers in India have now recognized the importance of pharmacovigilance. This has enabled PvPI to establish the good management and working relationships needed to make it effective.

Way forward

Patient safety is a fundamental principle of health care. Delivering safer care and preventing harm, particularly “avoidable harm”, is one of the greatest challenges in today’s complex, pressurized and fast-moving environments.

As a next step, PvPI activities will be expanded to other levels of the health system in line with the national scale-up plan for pharmacovigilance in India. More district hospitals will be set up as monitoring centres. The expansion of pharmacovigilance activities will strengthen the agenda of patient safety in India, which is in line with WHO’s Third Global Patient Safety Challenge: [Medication without Harm](#).

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