



REVIEW ARTICLE

An overview of the worldwide master key for pharmacovigilance and its role in India

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Introduction: Pharmacovigilance (PV) is defined as the science and activities related to the detection, assessment, understanding, and prevention of Adverse Drug Reactions (ADRs) and related conditions.

Methods: In the 1970s, several significant cases of ADR aided the advancement of the discipline. Between 1989 and 2004, several attempts were made to implement such a program in India, but the scheme was eventually launched in 2010 and is now operating successfully and producing positive results.

Results: The pharmacovigilance Program of India (PvPI) contributed different data to the World Health Organization (WHO) Uppsala Monitoring Center (UMC) based on the data gathered from this process. Indian regulatory have sent several alerts to stakeholders and provided the Central Drugs Standard Control Organization (CDSCO) with several recommendations. CDSCO has since advised Marketing Authorisation Holders (MAHs) to follow the same guidelines and has amended the Drugs and Cosmetics Act and Regulations to reflect this.

Conclusions: The time has come for Indian regulatory authorities to take the required action based on data generated in our country rather than data generated in several other countries.

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Introduction

Pharmacovigilance (PV) The word Pharmacovigilance was derived from the two Greek words “Pharmakon”-drug and “vigilare”-to keep observe.

According to WHO, PV is explained as the science and actions connecting to the detection, evaluation, understanding, and prevention of ADRs or associated conditions (WHO, 2006).

As usual, PV is post-market observation. It is important to track medications after they are placed on the market. The factors of consideration can be widely categorized into two groups: (Mandal *et al.*, 2017)

Human factor

Among human factors that are of consideration are:

Inadequate confirmation of safety in the clinical study when it is short-time, mostly lasting just a few weeks. Animal



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tests often do not represent human pharmacodynamics and pharmacokinetics throughout drug development.

In drug development, the size of the population is restricted and not more than 5000, and sometimes as minimal as 500 participants.

The demographic group is small and age-specific and gender-specific.

The studies include narrow guidelines, as only the underlying illness is examined.

Post marketing

Several criteria are significant for post-marketing issues. They may be described as follows:

Post-marketing monitoring provides a diversity of evidence and displays of the effect of the drug, provided that the drug is used on a broad population scale, with many and complex individual differences playing a role.

Unwanted adverse effects are frequently observed in Phase IV tests.

Certain drug-drug interactions, drug-food interactions, intolerance responses, hypersensitivity, severe ADRs such as anaphylaxis that might not be identified in Phase I-III trials are also identified in phase IV trials.

Patient quality of life control is only feasible in phase IV trials because it is a long-term analysis. Feedback is also relevant for doctors as well as for the formulating and promoting organization.

The long-term effectiveness of the medication can be assessed only in the PV research, as all studies up to phase III are short-term studies in which the long-term efficacy of the drug is impossible to estimate.

The cost-benefit ratio of the treatment can be determined only after phase IV studies. If the drug is to be pulled from the sales due to serious ADRs, the economic strain on the company is immense. In the context of expensive drugs, the influence of medication costs on consumers can only be measured in long-term trials, as with evidence from PV (Mandal et al., 2017).

Necessity of Pharmacovigilance

Medicines are meant to save lives, not steal down. Mortality from cancer is always possible, but mortality from a drug is not appropriate. In the United States of America (USA), ADRs are some of the 10 largest reasons for death (Lazarou et al., 1998) and in the United Kingdom, it is proposed that ADRs may trigger 5,700 fatalities per year. The number of hospital referrals attributed to drug-related incidents in certain nations is about 10 % (Mandal et al., 2017). A variety of ADR linked to medications has led to the establishment of the "Pharmacovigilance" science. The thalidomide tragedy of 1961 is one of the events where

thousands of congenitally deformed children were born. This inspired the WHO to carry out a rigorous review of ADR medicines, which is the origin of PV. Several ADRs have been identified thereafter, and some of those are presented in below **Table 1** (Mandal et al., 2017)

Table 1: Some severe and unpredictable adverse events leading to the withdrawal of the medicine

S. No.	Drugs	Examples of severe and unpredictable adverse effects leading to the withdrawal of the medicine	Year
1.	Veralipride	Anxiety, Depression and Movement disorders	2007
2.	Rofecoxib	Cardiovascular effects	2004
3.	Terfenadine	Torsade de pointes	1997
4.	Benoxaprofen	Nephrotoxicity and Cholestatic jaundice	1982
5.	Practolol	Sclerosing peritonitis	1975
6.	Clioquinol	Subacute nephropathy	1970
7.	Thalidomide	Phocomelia	1961

Rational behind ADR monitoring in India

In addition to cultural, dietary, disease prevalence, and genetic distinctions, changes in prescription patterns influence the benefit-risk ratio, e.g. Pioglitazone is prohibited in certain emerging regions due to increased incidence of bladder carcinoma, while it is not prohibited in India due to low incidence of bladder carcinoma (Mandal et al., 2017).

History of pharmacovigilance in India

In the before independence age of pharmacovigilance

In the year 1880, the opinion of the Glasgow board formed by the British Medical Association considered that 'Chloroform was hazardous for cardiovascular and in contrast, much harmful co ether'. Then after the counterargument was given after 8-years by Surgeon-Major Laurie, head of state Hyderabad Medical School in the year 1888, who demonstrated the effectiveness of chloroform in approximate 40 000 patients with no single mortality in Hyderabad City (Thomas et al., 1971). They have never seen the cardiovascular disorder or critically damaged by it. This was possibly the first implementation of a systemic technique for the identification of ADRs in the world (Thatte et al., 2018).

Post freedom, pharmacovigilance

The first PubMed nation indexed case report on ADRs emerged in 1975 when 336 individuals underwent to the general medical unit were prospective study screened for ADRs and 20 percent of them were observed to acquire ADRs (Vakil *et al.*, 1975).

Pharmacovigilance program progression in India

ADR surveillance service head to Dr. Molly Thomas, a pioneering clinical pharmacologist at Christian Medical College, Vellore, South India, who developed the program in the year 1983 (World Health Organisation, 2003). They trained 1,650 doctors and set up a spontaneous tracking plan in the institute. In one year, they got 600–900 data and issued 4 yearly newsletters. They were the first to recognize weak monitoring frequency and clinicians' propensity to record only significant and not small responses (Thatte *et al.*, 2018).

Unlike developing countries, many of them adopted structured PV programs in year 1960s after the Thalidomide tragedy, India's PV Policy launched in the year 1986. That was the first effort by the regulatory agency in India to officially create PV in the nation. The system has foreseen the development of knowledge on ADR by monitoring randomly and had an aggregate of 12 major centers (several they based in Chandigarh, Delhi, Kolkata, Lucknow, Mumbai, and Pondicherry) distributed throughout India. Primary health facilities and hospitals had to be connected to such major hubs. It was projected that each major center will have a demographic of 50 000 000 (Kulkarni *et al.*, 1986).

In the year 1997, the program underwent a major amendment, with India being a section of the WHO International Drug Surveillance System organized by the UMC in Sweden. That was the second effort by the agency to reinvigorate PV in the nation. That model of the service had 6 centers around the country Aligarh, Chandigarh, Kolkata, Lucknow, Mumbai, New Delhi, and Pondicherry (Protocol for National Pharmacovigilance Program., 2004). None of the 2 try in the year 1980s and year 1990s truly gave some substantial boost to the country's discipline development, with most of the documentation being both limited and intermittent.

Those 2 efforts, the Indian Medical Research Council, India's leading research organization, conducted its Adverse Reaction Control System, which was monitored by the working group. The independent system has a separate set of 12 clinics around India which reported 4490 adverse effects in 82,761 patients shown in the centers (Rahmanet *et al.*, 2021; Dikshit *et al.*, 2008). When the initiative was ongoing, the working group identified crucial areas that required change if the initiative were to be implemented. This included the required choice of centers involved in the project, the requirement for specialized submission and

maintenance of data personnel, consistent recognition of the coordination center, and instruction in analysis and interpretation of data (Thatte *et al.*, 2018).

A massive shift towards keeping India a major key in PV around the world came in the year 2004 to the year 2005, with aid by the world-bank and WHO seeking to lay its support beneath India. The Indian PV Programme was formally christened India's national PV program (NPP) on Nov 23, 2004, and World Bank committed USD 100 000 a year for 5-years (Adithan *et al.*, 2005). This system is supervised through the National PV Advisory Committee, a central agency body in India. India's adverse reaction cases flowed to 2 major zones – the South West Zonal Centre and the North East Zonal. The southwest zonal center will be gathering its self-data and will have 3 regional centers monitoring it. Likewise, the North-East Zonal Centre will gather its self-data and have 2 territorial centers to report to it. In exchange, every regional center will have branch centers reporting data (Biswas *et al.*, 2007).

The initiative has 3 broad objectives: to promote an environment of monitoring in the brief, to disseminate data and to engage a wide number of health providers in meantime, and to set universal targets as a long-duration goal. Although that revived initiative was with its share of obstacles. Funding by the World Bank alone without agency help implied that the program stayed in 'project mode,' there was no governance at the peak, there was no clear interaction between the centers collaborating with the agency, and there was no effect on legislative decision-making. Investment by the World Bank ended in the year 2009 (Pharmacovigilance Programme of India., 2018).

Pharmacovigilance Programme in India

On Jul 14, 2010, the regulatory made a deliberate attempt to formalize PV in the nation (Kalaiselvan *et al.*, 2012). There was a secure structure with the agency at the forefront, official regulations in effect to sustain the initiative, a national center based at the Pharmacology Department, the All India Institute of Medical Sciences (AIIMS), New Delhi, and government resources to build the long-term program. The aims of this program were multiplier to produce knowledge on ADR in the community of Indians; to increase understanding between medical services practitioners of the importance for PV; to actively track the profit risks of medicinal products; to establish unbiased, impartial, evidence-based guidelines on the protection of medicinal products; to urge regulators to pursue safety-related judgments; Convey results to all relevant investor and set up a National Centre of Excellence under national wide guidelines for drug safety surveillance. Four stages of the initiative were already Emergence has foreseen (the year 2010 to the year 2011);

- growth and restructuring (the year 2011 to the year 2012);
- expansion and maintenance (the year 2012 to the year 2013);
- expansion and optimization (2013–2014); and
- Perfection (2014–2015).

The program has an advisory group and a task force providing strategic guidance to the regulatory and 3 specialist committees (quality analysis, signal evaluation, and key training panels) for recommendations on difficulties:

The Committee of Quality Control regularly evaluates the performance and accuracy of the ICSRs, suggests decisions to the PvPI the participating committee's further information processing, and develops frameworks and policy records for follow-up activities. The Committee of Signal understanding and analyze the signals provided by ICSRs for interpretation and actionable measures and recommends relevant regulatory actions to CDSCO. The Core Training Council evaluates coaches, requirements practicing, and practicing material and communicates with global organizations on the involvement and execution of PV practicing programs.

Legislation in India pharmacovigilance

Schedule Y

The legal criteria in India for PV are regulated through the provisions of Schedule Y of the Drugs and Cosmetics Act 1945. Schedule Y includes laws covering preclinical and clinical trials for the production of developing medicines, specifications for clinical trials for the production and of new drugs in India. Schedule Y was modified and updated on Jan 20, 2005, as the proceed pledge of the Drug Controller General of India to verify that the PV responsibilities of pharmaceutical firms are sufficiently complied with (CDSCO, 2005). An effort was created in revised Schedule Y to further describe the functions and obligations of pharma firms concerning their drugs and also the monitoring of adverse effects from clinical trials (Biswas P, 2014).

Unexpected responses of drug

Schedule Y states that any cases with significant unintended adverse reactions should be notified to the licensing agency within 15 days of the individual's primary reception of data, with follow-up data given. Individual ADR data should be required in the next annual safety summary report, and not generally as a matter of urgency. However, more information on the identification, analysis, and ADR follow-up was not discussed in Schedule Y. Accordingly, medical firms in India follow International Conference on Harmonisation (ICH) E2D guidelines for the management of spontaneous data on goods (Biswas P, 2014).

Pharmacovigilance system workflow as per Indian scenario

Pharmacovigilance Programme of India

The regulatory agencies soon recognized the need for a comprehensive PV program to protect community welfare, and the NPP was changed its title India's Pharmacovigilance Program (PvPI), which began running on Jul 14, 2010, with the AIIMS, New Delhi, as the National Coordinating Center (NCC). In track ADRs across the nation, the system had 22 ADR Monitoring Centers (AMCs), along with AIIMS. Subsequently, the NCC was moved from AIIMS to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, on Apr 15, 2011, for the successful execution of the initiative, with the key objective of producing empirical data on drug safety in line with global drug safety surveillance requirements. Since PV was perceived to be a service that tracks medications for harmful drug events and dosage mistakes, some physicians became worried about it and they thought that their skills were being challenged (Dhamija *et al.*, 2017). The PvPI is working hard to address this obstacle of uncertainty and to minimize the causes for undercounting by implementing a variety of clinical practices, awareness-raising, and practicing activities for Health Care Professionals (HCPs) on a continuous justification to teach and remind them of the practice of reporting ADRs. HCPs have been made clear that no disciplinary action is taken with the monitoring of ADRs (Rakesh *et al.*, 2012).

The purpose of the program was to create faith comparison between the practitioner and the patient, thus improving care and enhancing people's interest in the nation's health system. The PvPI partners with the project to promote the safety of the Indian people by maintaining that the pros of drugs outweigh the risk related to their use (Pharmacovigilance Programme of India., 2017).

The PvPI gathers data obtained in the shape of ICSRs from AMCs, HCPs, and other non-HCPs. PvPI assesses the evidence and uses the findings to suggest educated regulatory interventions.

Around the same time, it reminds HCPs and customers of the risks associated with pharmaceutical drugs. In addition, the PvPI also seeks to detect under-standard drugs and prescribe, dispense and distribute errors to increase consumer health. Around the same period, the PvPI aims to solve other issues such as illicit medicines, antimicrobial tolerance, and monitoring during vaccines and other regional programs.

PVPI's aims and strategies

The main PVPI goals are as follows: (Pharmacovigilance Programme of India., 2017):

- Build a strategic plan for patient care monitoring
- Recognize and interpret new emerging data from documented cases
- Evaluating the benefit-risk balance of products on the market
- Produce Scientific proof research on the efficacy of pharmaceutical products
- To assist governing bodies in Strategic thinking mechanism on the utilize of medicines
- Convey safety data on the utilize of pharmaceutical products to different stakeholders to reduce risk
- To develop as a regional area of competence for PV practices
- Cooperation with other regional knowledge sharing and data processing centers;
- Offer educational and advisory services to individuals' regional PV centers around the globe (*Kalaiselvan et al., 2019*).

Framework and structure of the PVPI

At the period of its establishment, the PVPI was planned to be done in 3 stages. The first Phase enabled the development of 40 AMC's and launched in 2010. Eventually, 140 Medical Council of India approved medical academics were connected to initiative such branch of the second Phase in the year 2011. Eventually, the third Phase will include the whole healthcare system by the year 2013. The first phase also consisted of 2 stages, first a phase and first b phase (*Dylan et al., 2019*). These all were meant to improve AMC's concerning new facilities. Logistic and technical assistance from the CDSCO zoning centers based in Ghaziabad, Mumbai, Kolkata, and Chennai are provided to the AMC (*Rama et al., 2011*). The CDSCO Zonal Centers are under the execution of the CDSCO Headquarters. The data has been presented in **Figure 1** (*Dylan et al., 2019*).

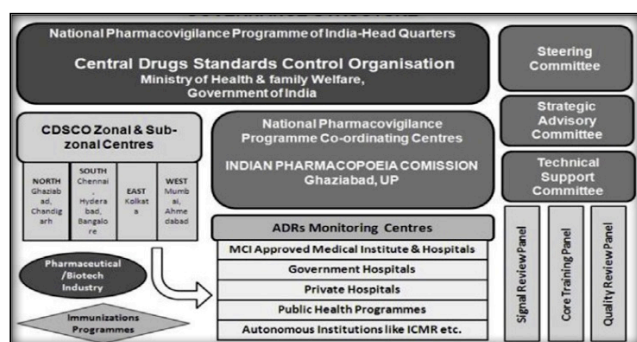


Figure 1. The framework of the management of the Drug safety program of India

Adverse drug reaction data flow

The ADR information sent to ADR Monitoring Center (AMC's) to be subject to primary review by the PV personnel. AMC personnel will hold a list of each operation executed. Upon receipt of the ADR forms, a causal assessment will be carried out by the coordinating center before the records are submitted to the PV database. The consolidated ADR report will be compiled by the coordinating center at pre-planned periods. The combined data will then be transferred via the Vigiflow database to the UMC ADR portal and the signal analysis to be performed (*Suke et al., 2016*). The ADR communication channel can be schematically depicted according to the below presented in **Figure 2** and **Figure 3**.

Unpredictable ADR Monitoring and ADR monitoring form could be reporting in 2 ways.

1. Active Surveillance Monitoring
2. Passive Surveillance Monitoring

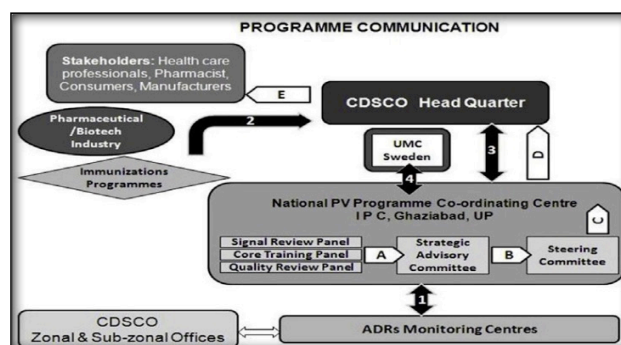


Figure 2. Program Coordination of ADR information processing

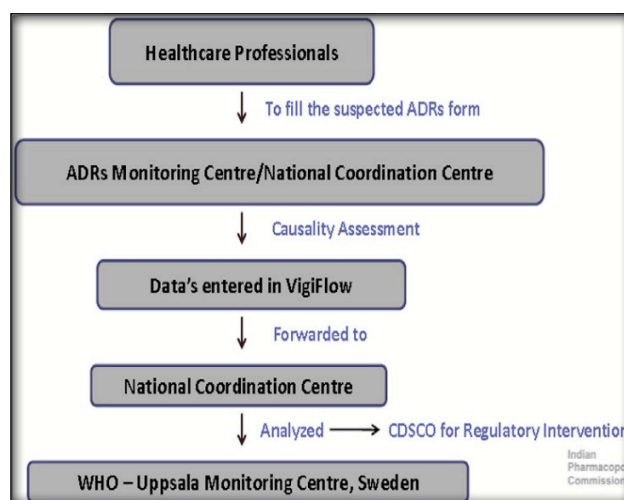


Figure 3: Information gathering, review, and assessment of ADRs

Achievements of the PvPI

Development of 250 AMCs which provide a platform for PV and monitoring environment across India. A variety of AMC awareness campaigns have been initiated for public outreach. The ADR monitoring environment required to develop the framework is growing around the world, even within categories such as nursing workers and MAH (PvPI, 2016). Monitoring forms have been accessible in 10 vernacular languages and different templates for HCPs and customers are also accessible on the CDSCO website.

PvPI applied to regional wellbeing services like measles, neglected tropical infections, vector-borne illness, Acquired immunodeficiency syndrome, and immunization. Product warnings produced for medications have been transmitted to their respective platforms for enhanced public health results. Post-compatibility with the post-immunization ADR gained greatly in the National Regulatory Authority's Assessment of 2017 when the surveillance benchmarking method hit the maximum maturity stage of IV (Kalaiselvan et al., 2019). PvPI has introduced a 'Basic and Regulatory Dimensions of PV' skill learning initiative to educate young PV practitioners. HCPs from across India joined the program. Resistance of antimicrobial in the nation is growing and the PvPI works by any indicate necessary to monitor the possibility of resistant bacteria. PV measures are also being enhanced at the state, local, and country-level to maintain patient care. The 2017 regional healthcare agenda, initiated by the Ministry of Health and Family Welfare (MoHFW), examines infectious diseases and PV. This regulation amendment would have scope for effective monitoring and avoidance of ADRs whenever possible (Kalaiselvan et al., 2019).

The PvPI under the auspices of the IPC, MoHFW, was thoroughly investigated by the WHO – National Regulatory Authority (NRA) 2017 Global Benchmarking Tool (GBT). As a result, diligence reached a maturity growth of 4 out of 5 (Singh et al., 2017; WHO, 2017).

In consideration of performance and nature of employ carried out by the NCC-PvPI period the last 6-year and it is an important support to WHO Programme for International Drug Monitoring, the IPC currently known as the WHO Coordinating Centre for PV in Public Health agencies and Regulatory Systems (Kalaiselvan et al., 2019).

The contrast between USA, EU, and Indian PV

PV is also in its development stage in India relative to the PV program in each the EU and the US. Both the EU and the USA need mandatory oversight of all significant ADR, while in India there have been no clear requirements for monitoring of ADRs apart from Schedule Y before PvPI was welcomed into force (Postigo et al., 2018). It has officially become mandatory for MAHs to register ADRs into PvPI in 2018. MedWatch and EudraVigilance are the

US and EU web-based ADR monitoring functions, Although India works on Vigiflow based on the WHO framework. ADR forms are not categorized in 2 distinct categories, as in the US and EU schemes (Jose et al., 2019; Bhargavi et al., 2015; Miller et al., 2012).

Advice about reporting

What to report

Report serious ADR: There is a serious reaction once the patient's result is

- Mortality
- Frightful for life
- Primary and long-term hospitalization
- Minor, recurrent, or long-lasting disability
- Congenital anomaly
- Needed action to avoid permanent injury
- Document non-serious, not known repeated, or unusual ADRs related to pharmaceutical drugs, vaccines, and herbal products.

Who can report

All health care practitioners can report ADRs.

Where to report

The thoroughly completed Suspicion ADR notification form could be submitted to the neighboring AMC or individually to National Coordinating Center (NCC).

To notify ADRs, dial Helpline (Toll-Free) 1800 180 3024.

Or mail completed form directly to pvpi@ipcindia.net or pvpi.ipcindia@gmail.com

There are several AMCs in India is accessible at: <http://www.ipc.gov.in>, http://www.ipc.gov.in/pvpi/pv_home.html

What happens to the submitted information

The details contained in the template are treated in absolute assurance. The usefulness determination is conducted on AMCs utilizing the WHO-UMC metric. The evaluated form is sent to the NCC via the ADR database.

Eventually, the information is processed and sent to the Global PV Database maintained by the WHO. The documents are routinely checked by NCC-PvPI. The knowledge produced depends on these observations, it improves the formative evaluation of the benefit-risk ratio of medicinal products. The data shall be forwarded to the PVPI Advisory Board established by the MoHFW. The Commission shall be responsible for analyzing results and recommending any measures that could be needed (Kalaisevan et al., 2016).

The mandatory field for suspected ADR monitoring form

Patient initial, age at the start of the response, term of reaction, data of start of reaction details, Suspicion of medication(s), and reporter details (Kalaisevan et al., 2016).

Management of the safety database

No detailed guidelines on the monitoring of safety records or the preservation and upgrading of Company Core Data Sheet or Company Core Safety Information are available from Indian regulators. Usually, all evidence gathered during the literature review, spontaneous adverse case events, clinical and non-clinical studies, or from all other sources are recorded and stored in the drug safety file (Arora et al., 2008).

Discussion

PV proceeds to play a vital role in overcoming the threats raised by the ever-enhancing variety and efficacy of drugs, many of which have an inherent and often uncertain possibility for badness. When side effects and risks occur, particularly during newly identified, they must be recorded, examined, and accurately conveyed to the public with awareness of the understanding of the facts. There is an exchange between the benefits and the possibility for risk for all pharmaceutical goods. Damage will be reduced by confirming that drugs of high consistency, protection, and effectiveness are used rationally and that the customer's needs and interests are taken into consideration when making clinical judgments. To do this is to promote global welfare and to promote a sense of faith among patients in the medications they use that will raise faith in the healthcare service in usual, confirm that risks in the usage of drugs are expected and handled, provide authorities with the necessary evidence to update the guidelines on the use of medicines, and increase collaboration among health practitioners and educating the public and health practitioners to consider the usefulness or harm of the medications they recommend.

Conclusions

When compared to other nations, India's PV systems are also in their infancy. The two recent developments in this area in India are the NPP and the PvPI. Because of technological advancement and other tools, the United States and Europe have well-established PV networks. India is the world's largest pharmaceutical manufacturer and a major clinical research center, necessitating a more rigorous PV setup. With India's population and the introduction of new drugs daily, an efficient PV system is needed.

Conflicting Interests

No potential conflicts were declared.

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